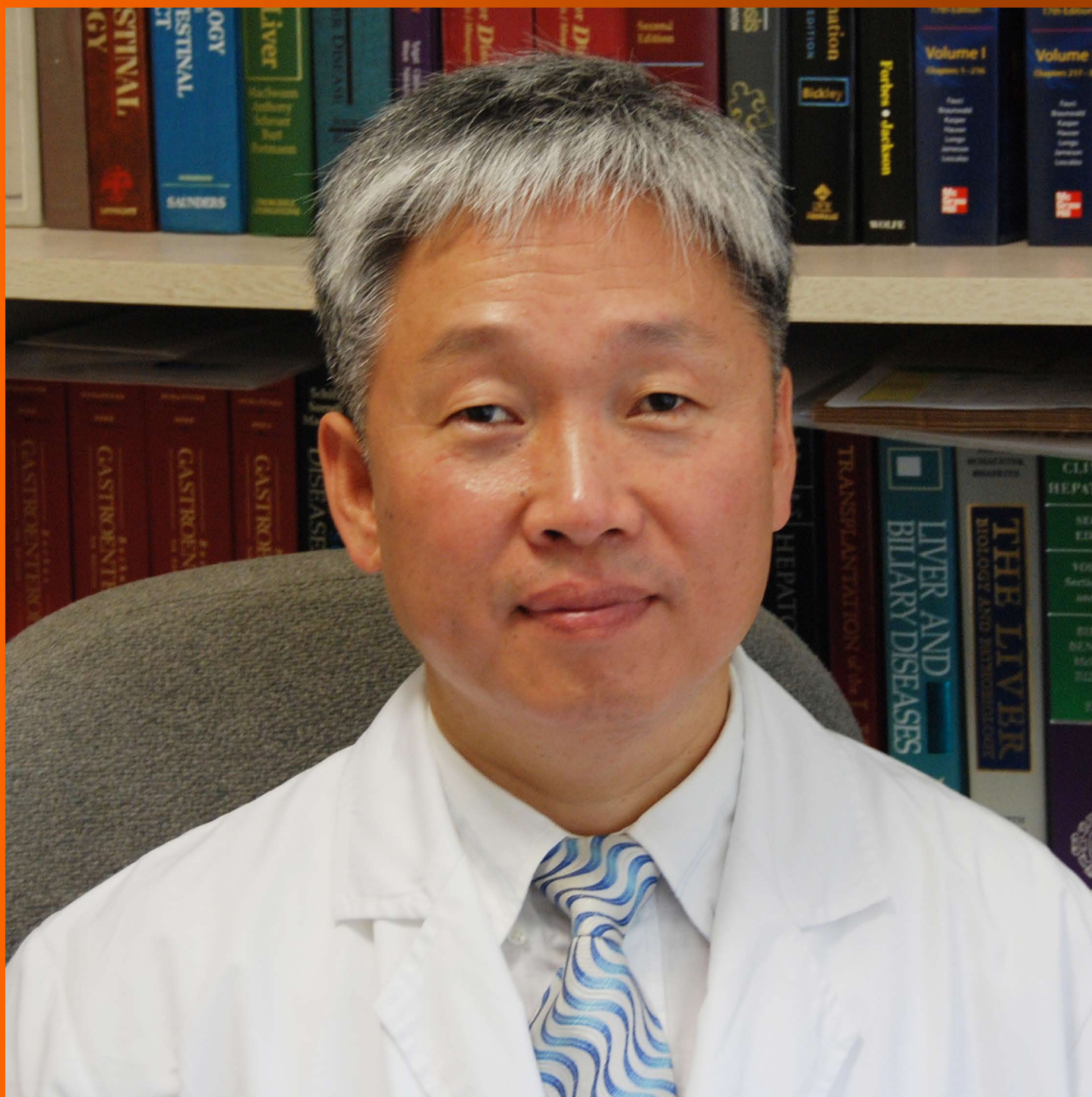


World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2017 May 6; 8(2): 90-154





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World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN

ISSN 2150-5349 (online)

LAUNCH DATE

May 6, 2010

FREQUENCY

Quarterly

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PUBLICATION DATE

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Management of esophageal caustic injury

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Author contributions: All authors gathered the available literature; Tuazon DJS made the initial draft; Timbol ABG added the tables, figures, and algorithm and made revisions on the article; De Lusong MAA made critical revisions and final approval of the version to be published.

Conflict-of-interest statement: All authors have no conflict of interest to declare. All authors have seen and approved the manuscript submitted. The article has not received prior publication and is not under consideration for publication elsewhere.

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Received: October 15, 2016

Peer-review started: October 19, 2016

First decision: November 14, 2016

Revised: February 25, 2017

Accepted: March 12, 2017

Article in press: March 14, 2017

Published online: May 6, 2017

Abstract

Ingestion of caustic substances and its long-term effect

on the gastrointestinal system maintain its place as an important public health issue in spite of the multiple efforts to educate the public and contain its growing number. This is due to the ready availability of caustic agents and the loose regulatory control on its production. Substances with extremes of pH are very corrosive and can create severe injury in the upper gastrointestinal tract. The severity of injury depends on several aspects: Concentration of the substance, amount ingested, length of time of tissue contact, and pH of the agent. Solid materials easily adhere to the mouth and pharynx, causing greatest damage to these regions while liquids pass through the mouth and pharynx more quickly consequently producing its maximum damage in the esophagus and stomach. Esophagogastroduodenoscopy is therefore a highly recommended diagnostic tool in the evaluation of caustic injury. It is considered the cornerstone not only in the diagnosis but also in the prognostication and guide to management of caustic ingestions. The degree of esophageal injury at endoscopy is a predictor of systemic complication and death with a 9-fold increase in morbidity and mortality for every increased injury grade. Because of this high rate of complication, prompt evaluation cannot be overemphasized in order to halt development and prevent progression of complications.

Key words: Caustic ingestion; Esophageal caustic; Caustic injury; Corrosive ingestion; Esophageal injury

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Core tip: Caustic ingestion maintains its place as an important public health issue in spite of the multiple efforts to educate the public. This is due to the ready availability of caustic agents and the loose regulatory control on its production. Substances with extremes of pH are very corrosive and can create severe injury in the upper gastrointestinal tract. Locations most seriously affected are in the esophagus and stomach and may lead to chronic complications like stricture formation, gastric outlet obstruction, and malignant transformation. Prompt evaluation is therefore emphasized in order to halt development and prevent progression of these

complications.

De Lusong MAA, Timbol ABG, Tuazon DJS. Management of esophageal caustic injury. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 90-98 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/90.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.90>

INTRODUCTION

Ingestion of caustic substances and its long-term effect on the gastrointestinal system maintain its place as an important public health issue in spite of the multiple efforts to educate the public and contain its growing number. This is due to the ready availability of these caustic agents as items of household use and loose regulatory control on its production. According to the American Association of Poison Control (AAPCC), there were approximately two hundred thousand cases of cleaning substance exposure since 2000^[1]. Data from developing countries, however, are sparse given that cases are largely underreported.

The age of occurrence presents in a bimodal fashion. The first peak is in the 1 to 5-year-old age group. Compared to adults, children are more likely to ingest caustic substances either accidentally or out of curiosity. Their higher exposure rate, however, is usually offset by a lower overall rate of complicated caustic injury because children often spit out the corrosive material immediately. The second peak is in the adolescent and young adult (21 years and older) age group. Majority of ingestions at this age group are intentional suicide attempts resulting in a greater and more extensive injury^[2,3].

SUBSTANCES CAUSING CAUSTIC INJURY

Caustic agents can be acidic or alkaline in nature. Common alkali-containing caustic agents are household bleaches, drain openers, toilet bowl cleaners, dish-washing agents and detergents. Acid-containing agents implicated in caustic ingestion include toilet bowl cleaners, anti-rust compound, swimming pool cleaners, vinegar, formic acid used in the rubber tanning industry and other similar acids^[3,4]. The type of caustic agent most commonly implicated in poisonings varies from country to country. In the annual report of the AAPCC in 2008, the most commonly implicated caustic agent was the alkali-sodium hypochlorite, which was found in bleaches, toilet bowl cleaners, drain cleaners and household disinfectants. Local experiences from Denmark, Israel, United Kingdom, Peru, Spain, Australia, Saudi Arabia and Turkey also showed that alkaline agents were more commonly involved in caustic injury^[4]. Most caustic substances were ingested in the

liquid form and events commonly occurred at home^[4]. Indian data, on the other hand, showed that majority of ingestions in their country were due to acids since these were cheaper and more readily available^[3,4].

PATHOPHYSIOLOGY

Substances with extremes of pH (less than 2 or greater than 12) are very corrosive and can create severe injury and burns in the upper gastrointestinal tract. Locations most seriously affected are in the esophagus and stomach since the corrosive material often remains in these areas for a longer period of time. However, injuries can also occur in any area in contact with the caustic agents such as the oral mucosa, pharyngeal area, upper airways, and duodenum^[5,6].

Acids and alkali agents have contrasting characteristics and differ in how they cause tissue damage. Alkaline agents are usually colorless, relatively tasteless, more viscous, and have a less marked odor. Hence, the amount ingested tends to be more^[4]. Once ingested, alkaline substances react with proteins and fats and are transformed into proteinases and soaps, resulting in liquefactive necrosis. This leads to deeper penetration into tissues with a greater likelihood of transmural injury^[6]. Acids, on the other hand, have a pungent odor and an unpleasant taste. It tends to be consumed in smaller amounts and are swallowed rapidly after ingestion^[4]. Once it reacts with tissue proteins, these substances are converted to acid proteins. The mode of tissue injury is coagulation necrosis^[6]. The coagulum prevents the corrosive agent from spreading transmurally, hence reducing the incidence of full thickness injury^[4]. This distinction, however, is not always the case. In the setting of strong acid or strong base ingestion, both these substances easily penetrate the esophageal or gastric mucosa and cause full-thickness injury^[7].

The traditional opinion is that acids preferentially damage the stomach. Its lower surface tension and the formation of protective esophageal eschar allow acids to bypass the esophagus rapidly without much damage while affecting the stomach more severely. Conversely, alkalis cause more injury to the esophagus. The higher surface tension of alkalis that permit a longer contact time with esophageal tissues and the acidic contents in the stomach that act to neutralize gastric injury explain the more severe damage to the esophagus.

Mucosal injury begins within minutes of caustic ingestion. It is characterized by necrosis and hemorrhagic congestion secondary to the formation of thrombosis in the small vessels. These events continue in the next several days until approximately 4 to 7 d later when mucosal sloughing, bacterial invasion, granulation tissue and collagen deposition occur. The healing process typically begins three weeks after ingestion. It is during this time (first 3 wk) that the tensile strength of esophageal and/or gastric tissues is the lowest. If the ulcerations extend well beyond the muscularis layer, the wall becomes vulnerable to perforation^[3,6].

It is for this reason that authorities advocate avoiding endoscopy between the 5th and the 15th day after caustic ingestion^[3,6]. By the 3rd week, scar retraction occurs and may continue for a few more months until stricture formation occurs. The lower esophageal sphincter pressure becomes also impaired in the process causing an increased frequency and severity of acid reflux that further aggravates existing mucosal injury and accelerates the stricture formation^[7].

The severity of injury depends on several aspects: concentration of the substance, amount ingested, length of time of tissue contact, and pH of the agent. Solid materials easily adhere to the mouth and pharynx, causing greatest damage to these regions. Liquids, on the other hand, pass through the mouth and pharynx more quickly consequently producing its maximum damage in the esophagus and stomach^[7,8].

CLINICAL PRESENTATION

The clinical presentation of caustic ingestion is diverse and do not always correlate with the degree of injury. Symptoms mainly depend on the location of damage. Hoarseness and stridor are signs that are highly suggestive of an upper respiratory tract involvement, particularly the epiglottis and larynx. Presence of these findings may signal a potentially life-threatening respiratory event^[7]. The upper gastrointestinal tract, on the other hand, may present as dysphagia or odynophagia for esophageal injury and hematemesis or epigastric pain for gastric involvement^[7,8].

Short-term complications include perforation and death. Perforation of the esophagus or stomach can occur at any time during the first 2 to 3 wk of ingestion. A sudden worsening of symptoms or an acute deterioration of a previously stable condition should warrant a thorough investigation to rule out the possibility of a perforated viscus^[7,8].

Chronic complications of caustic ingestion include stricture formation, gastric outlet obstruction and malignant transformation. Patients with esophageal strictures usually complain of dysphagia and substernal pressure, and may become symptomatic 3 wk or later after ingestion. Symptoms of early satiety, post-prandial nausea or vomiting, and extreme weight loss suggest gastric obstruction. The latter commonly occurs in the first 5 to 6 wk of ingestion^[6].

Carcinoma of the esophagus is a well-recognized consequence of caustic ingestion - partly due to the chronic inflammation from the initial burn, the trauma induced by repeated dilation, and the continuous tissue reaction from food stasis. Patients with a history of caustic ingestion often have a 1000-3000-fold increase in the incidence of esophageal carcinoma. Conversely, up to 3% of patients with carcinoma of the esophagus may have a history of caustic ingestion^[7,8]. For alkaline ingestion in particular, subsequent development of squamous cell carcinoma has been reported to occur approximately 40 years after injury. This is mainly

because of the liquefactive necrosis caused by alkali agents, which causes a deeper penetration of injury compared to the less severe and often limited mucosal injury of acidic substances. Periodic endoscopic evaluation is therefore suggested starting 20 years after the caustic ingestion with an interval of 1 to 3 years.

DIAGNOSIS AND STAGING

Laboratory tests

Laboratories were not found to directly correlate with the severity or the outcome of the injury. One study showed that age, an elevated white blood cell count (> 20000 cells/mm), and the presence of gastric deep ulcer or gastric necrosis are independent predictors of death^[9]. Basically, laboratory work-ups play a more important role in guiding patient management than in predicting morbidity or mortality^[7,8].

Traditional radiology

Plain chest radiography may show gas shadow in the mediastinum or below the diaphragm suggesting esophageal or gastric perforation, respectively. If perforation is suspected, an upper gastrointestinal series using a water-soluble agent can be performed.

Ultrasound

Endoscopic ultrasound can also be used to evaluate the esophageal wall. Though in comparison to the conventional endoscopy, no difference was achieved in predicting early complications. Reports show that destruction of the muscularis layer on EUS could be a reliable sign of stricture formation and a marker for decreased response to balloon dilatation. However, further studies are needed to establish the role of EUS in caustic injury^[7,8].

Computed tomography scan

In assessing the extent and boundary of injury, computed tomography (CT) scan has a slightly higher diagnostic contribution than upper endoscopy. It can show the depth of necrosis and even the presence of transmural damage, thereby allowing clinicians to assess threatened or established perforations^[7,8]. And because of its non-invasive quality, CT scan may prove to be a promising diagnostic in the early evaluation of caustic injury^[7].

Magnetic resonance imaging

Magnetic resonance imaging (MRI), in general, provides little advantage over CT scan in the assessment of caustic injury. Besides its obvious benefit of processing images without the use of ionizing radiation, it does not reliably distinguish the different layers of the esophageal wall, which is crucial for the initial assessment of the extent of mucosal involvement. In addition, some patients, particularly the acutely ill, may not be able to tolerate the slower throughput of MRI and may not be able to cooperate during the procedure resulting in movement artifacts.

Table 1 Zargar classification and its corresponding endoscopic description

Zargar classification	Description
Grade 0	Normal mucosa
Grade I	Edema and erythema of the mucosa
Grade II A	Hemorrhage, erosions, blisters, superficial ulcers
Grade II B	Circumferential lesions
Grade III A	Focal deep gray or brownish-black ulcers
Grade III B	Extensive deep gray or brownish-black ulcers
Grade IV	Perforation

Endoscopy

Esophagogastroduodenoscopy is an important and highly recommended diagnostic tool in the evaluation of caustic injury especially during the first 12 to 48 h of caustic ingestion, though several reports indicate that it can be safely performed up to 96 h post-ingestion. Gentle and cautious insufflation during the procedure cannot be sufficiently emphasized. Endoscopy is generally not advised 5 to 15 d after caustic ingestion due to tissue softening and friability during the healing stage. With findings of extensive damage and necrosis, aborting the procedure is not mandatory^[7,8]. However, endoscopy is usually contraindicated in several situations; such as hemodynamic instability, severe respiratory compromise, and suspected perforations^[8].

In the absence of symptoms and in the presence of accidental ingestions (especially those of less corrosive substances), significant lesions are usually not observed on upper endoscopy. As such, it is not required in some reports to perform endoscopy for asymptomatic patients with ingestion of low potency materials. This, however, is not applicable to patients with intentional ingestions since the substances they commonly consume are more potent. Therefore, emergent endoscopy among these patients is generally recommended^[7,8].

Ultimately, endoscopy is considered the cornerstone in the diagnosis, prognostication, and guide to management of caustic ingestions. Various endoscopic grading is available and Zargar's classification is one of the most commonly used (Table 1 and Figure 1). In his study, Zargar *et al.*^[10] found that early major complications and death were confined to patients with grade III injuries. All patients with grade 0, I and II A burns recovered without sequelae. Majority of grade II B and all survivors with grade III injury developed eventual esophageal or gastric cicatrization^[10]. In general, the degree of esophageal injury at endoscopy is a predictor of systemic complication and death with a 9-fold increase in morbidity and mortality for every increased injury grade^[10].

MANAGEMENT

General measures (Figure 2)

Management of caustic injury includes immediate resuscitation and evaluation of extent of damage. In general, correlation between symptomatology and en-

doscopic post-corrosive severity is still unproven. The patient's initial signs and symptoms are oftentimes unreliable to gauge the extent of involvement since 20% of caustic ingestions may not present with oropharyngeal injury^[11,12]. Nevertheless, for patients with a clear history of accidental ingestion of a low-volume, low-concentration caustic substance and with no signs and symptoms of oropharyngeal injury, endoscopy may be deferred. These patients may then be discharged after a 48-h observation period^[11]. For those with large volume of ingestions and with significant findings on endoscopy (at least grade IIB), in-patient observation for any immediate complications in the intensive care unit is generally advised^[13,14].

The cornerstone of all caustic ingestions is airway and hemodynamic stabilization. Since direct exposure of the upper respiratory tract by the corrosive substance may occur, patients should be evaluated for the need to do immediate intubation or tracheostomy. Intubation with direct visualization under fiberoptic laryngoscopy is most appropriate to avoid the risk of bleeding and further airway injury from "blind" airway access^[10,15,16]. If the epiglottis and larynx are edematous, tracheostomy should be performed.

Neutralizing agents

In previous protocols, neutralizing agents (weakly acidic or basic substances) for caustic ingestion was viewed as one of the first steps for treating caustic intoxications^[11]. However, it has now been emphasized that these substances should not be administered due to the additional thermal injury and chemical destruction of tissues these reactions produce^[14,17].

Nasogastric tube

Routine nasogastric intubation for the purpose of evacuating any remaining caustic material is no longer warranted prior to endoscopic assessment of mucosal injury. This is due to the possibility of inducing retching or vomiting leading to further esophageal exposure by reflux of the remaining intragastric caustic material. Moreover, insertion of a foreign body in the acute setting may act as a nidus for infection, which may subsequently delay mucosal healing^[16].

A preliminary survey of expert opinion from members of the world society of emergency surgery showed that 93% opted to use nasogastric tubes in patients with evidence of oropharyngeal injury while 7% avoided placement in any scenario. Among the 93%, more than two thirds opted to insert a nasogastric tube endoscopically. The theoretical advantage is said to provide a patent route for enteral feeding while serving as a stent to maintain luminal integrity and to decrease stricture formation^[18].

Gastric acid suppression and mucosal protection

Upon admission, the patient should be kept fasting. Gastric acid suppression with H₂ blockers or intravenous proton pump inhibitors are often initiated to allow faster

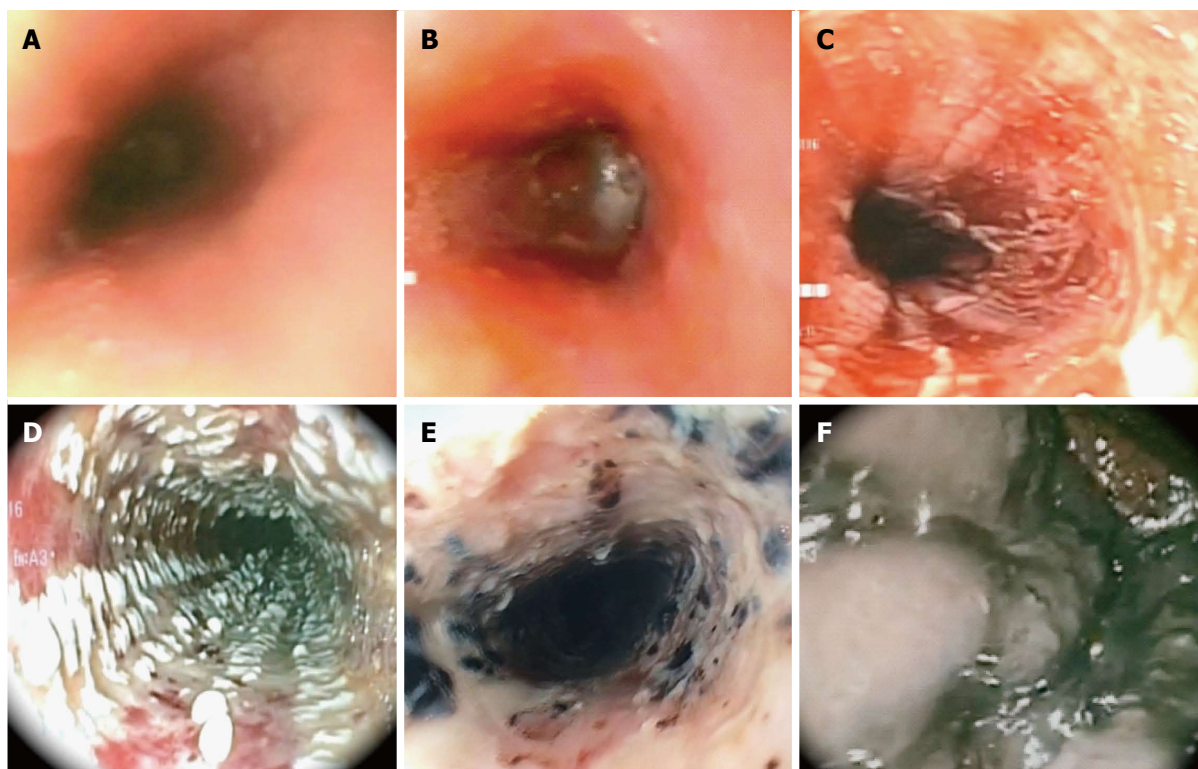


Figure 1 Endoscopic pictures of Zargar classification 0 to III B. A: Zargar Grade 0: Normal mucosa; B: Zargar Grade I: Edema and erythema of the mucosa; C: Zargar Grade II A: Hemorrhage, erosions, blisters, superficial ulcers; D: Zargar Grade II B: Circumferential bleeding, ulcers. Exudates; E: Zargar Grade III B: Focal necrosis, deep gray or brownish black ulcers; F: Zargar Grade III B: Extensive necrosis, deep gray or brownish black ulcers.

mucosal healing and to prevent stress ulcers. Efficacy of these agents for caustic ingestion has not yet been proven, although a small study done in 2013 has shown endoscopic healing after omeprazole infusion^[7,16,19].

Sucralfate is now a common adjunct in the management of acute ulcers. It achieves its therapeutic effect by maintaining mucosal vascular integrity and blood flow. In the setting of caustic ingestion, sucralfate is said to hasten mucosal healing by providing a physical barrier between the harmful effects of the corrosive substance and the gastroesophageal mucosa^[20-22]. Several small randomized controlled studies have assessed the efficacy of sucralfate in corrosive esophagitis. Results from these studies showed that sucralfate may decrease the frequency of stricture formation with advanced corrosive esophagitis. However, further research with a larger sample size is required to support its recommended use in this setting^[20,23].

Antibiotics

To date, evidence is still conflicting with regard the use of antibiotics. A study in 1992 analyzed the utility of antibiotic together with systemic steroid administration in caustic ingestion. It was concluded that antibiotics with steroids may be useful in preventing strictures in patients with extensive burns^[24]. But since it was not possible to separate the effect of the antibiotic from that of the possible effect of the steroid in this study, it may be difficult to support the use of antibiotic in preventing stricture formation with such limited data. Hence, the consensus

maintains that patients treated with steroids should also be treated with antibiotics^[16].

Steroids

Initial studies on corticosteroid administration to prevent stricture formation in caustic ingestion were mainly on children and results were conflicting. Methylprednisolone at a dose of 1 g/1.73 m² per day for 3 d showed benefit in reducing stricture development^[25]. Likewise, dexamethasone (1 mg/kg per day) was shown to be better than prednisolone (2 mg/kg per day) in preventing stricture formation (38.9% vs 66.7%) and severe stricture development (27.8% vs 55.6%)^[26].

However, another study showed that prednisolone at a dose of 2 mg/kg intravenous did not provide any benefit in preventing stricture development^[27]. A systematic pooled analysis of caustic ingestion supported this finding as it failed to show additional benefit with the use of steroid in patients with grade II esophageal burns^[28]. Based on the above evidence, it seems prudent to avoid systemic corticosteroids in caustic ingestion until further research confirms its efficacy.

Triamcinolone and mitomycin-C

Intralesional steroid such as triamcinolone (40-100 mg/session) has long been known to augment the dilatation of caustic-induced esophageal strictures although results from most studies are still conflicting^[29,30].

Recently, mitomycin C has been shown to decrease

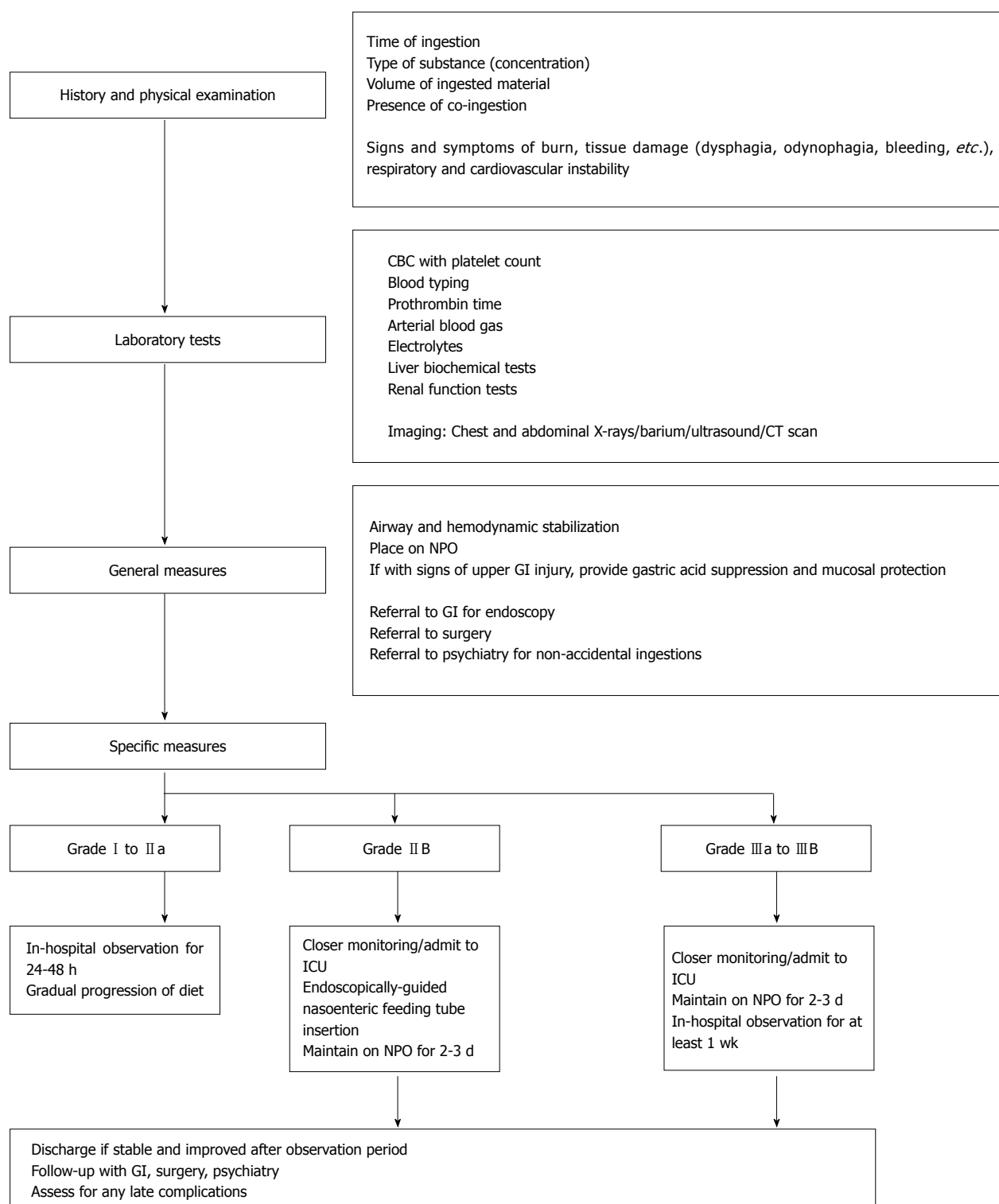


Figure 2 Management algorithm for caustic substance ingestion. CT: Computed tomography; GI: Gastroenterology; ICU: Intensive care unit.

the rate of caustic stricture formation in animals due to its antifibroblastic properties^[31]. It has been used as an adjunct^[32-34] after dilatation of caustic strictures in humans (including those with long strictures) by applying mitomycin-C topically at a dose of 0.4 mg/mL^[34,35]. In a study of 16 patients treated with endoscopic topical application of mitomycin-C, a decrease in the number of dilatations and apparent relief of dysphagia were

achieved compared to triamcinolone^[35].

ENDOSCOPY

Endoscopy is important not only in the diagnosis of corrosive ingestion but also in determining subsequent management. In general, patients with normal looking mucosa or those with very mild injury may be dischar-

ged. For those with Zargar grade I or II A, in-hospital observation is advised and gradual progression of diet from liquids is done in the next 24 to 48 h. Patients with at least grade II B are monitored more closely. An endoscopically-guided nasoenteric feeding tube may be placed with caution, bypassing the areas of necrosis, to facilitate feeding while initiating trial of per oral feeding. For grade III injuries, the patient's response to treatment and feeding is usually observed for at least a week^[14]. Prophylactic esophageal stenting in the acute setting is generally not recommended^[36] due to a high perforation rate.

LATE COMPLICATIONS AND MANAGEMENT

Esophageal stricture is one of the most common sequelae of caustic injury. Up to 70% of patients with grade II B and more than 90% of patients with grade III injury are likely to develop esophageal stricture^[37].

Peak development of strictures commonly starts on the 8th week post-ingestion, although it has been reported to occur as early as 3 wk^[7,37,38]. The timing of management is crucial in achieving long-term functional effects.

Endoscopic dilatation

The primary non-surgical treatment of caustic esophageal stricture is endoscopic dilatation. This can be achieved with Bougies or balloon dilators. For tight and fibrotic strictures, bougies dilators are often more reliable than balloon dilators^[37]. A prospective study published in 2015 assessed a rigorous weekly schedule of bougie dilatation (Savary-Gilliard) along with intralesional triamcinolone in patients with refractory esophageal corrosive strictures. It was noted that this intervention was safe and effective in improving dysphagia, achieving clinically significant dilatation, reducing dilatation frequency, maintaining luminal patency of ≥ 14 mm^[14,39].

Using balloon dilators, a lower dilatation force should be used initially to avoid perforation^[40]. This may need to be repeated and advanced slowly to achieve effective and safe dilatation. The interval between dilatations varies from 1-3 wk among different studies^[16] but usually an interval of 3-4 wk is recommended.

For either technique, the goal is to achieve relief of symptoms (particularly dysphagia) and maintain efficient luminal diameter of up to 15 mm^[41].

Esophageal stents

Though endoscopic dilatation with balloon has been the standard of treatment for benign esophageal strictures, the recurrence rate still reaches 30%-40%. Approximately 10% of these patients fail to achieve clinical improvement and remain refractory to repeated dilatations. In such patients a good option is stent insertion. Recently, 3 types of stents are now available: Self expanding metal stents (SEMS), plastic sent, and

biodegradable (BD) stent - each with its own advantage and disadvantage.

SEMS are often discouraged in benign esophageal stenosis due to its high rate of necrosis and ulceration, tissue hyperplasia, new stricture or fistula formation, and the tendency for the metal portion to embed within the esophageal wall. Plastic stents are said to have lesser tissue hyperplasia but with higher rate of stent migration and lower tendency to sustain significant radial force. Both of these stents require repeated endoscopic intervention for stent retrieval. Recently, BD have been introduced in the hopes of avoiding the above complications and the need for re-intervention for stent extraction^[42].

A study in 2012 compared these 3 stents in patients with refractory benign esophageal stenoses. In this study, long-term resolution of dysphagia was highest in the metal stents group (40%) compared to BD stents (30%) and plastic stents (10%). Tissue migration was highest in the plastic stent group and lowest in the BD stent group^[43]. To date, there is still no ideal stent recommended for universal use among patients with benign esophageal strictures, the choice for each patient should be individualized^[44].

Surgery

Corrective surgery for esophageal strictures from caustic injury is done only in severe cases where endoscopic therapy fails or is deemed harmful. Surgical options include partial or total esophagectomy with gastric pull up or, preferably colonic interposition^[38]. Gastric pull-up in general, is quicker and requires only one anastomosis. However, the long-term functional outcome may decrease with development of complications such as recurrence of stricture, bothersome reflux, and subsequent metaplasia over the anastomotic site^[7,16,45-52]. On the other hand, colon interposition is a more complex procedure requiring 3 anastomoses, albeit with a more stable long-term functional outcome. It is often associated with a lower incidence of stricture formation than gastric pull-up hence its preferential use in the setting of a relatively spared and healthy stomach^[16]. Mortality rates of late reconstructive surgery depend on local surgical expertise.

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P- Reviewer: Hashimoto N, Hoff DAL, Imaeda H **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Lu YJ



5-Aminosalicylates to maintain remission in Crohn's disease: Interpreting conflicting systematic review evidence

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Author contributions: Gordon M was the sole author of this work.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

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Manuscript source: Invited manuscript

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Received: January 23, 2017

Peer-review started: January 28, 2017

First decision: March 8, 2017

Revised: March 15, 2017

Accepted: April 23, 2017

Article in press: April 25, 2017

Published online: May 6, 2017

Abstract

5-Aminosalicylates are a class of anti-inflammatory agents that have been used for decades in inflammatory bowel disease. Whilst they are first line for induction and an

option for maintenance of remission in ulcerative colitis, the picture in Crohn's disease is variable. For maintenance of remission, key Cochrane systematic reviews have found conflicting results between the medical and surgical induced contexts. In this piece, the possible reasons for this are considered. It is proposed that clinicians should consider 5-aminosalicylates agents an option to maintain remission post-surgery. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis and will guide policy makers in the future.

Key words: 5-Aminosalicylate; Systematic review; Crohn's disease; Inflammatory bowel disease; Cochrane

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Core tip: This paper proposes that the varying length of remission and disease activity of patients enrolled in studies for medically induced remission is different to surgical induced remission and may explain differences in findings. This guides future research proposals. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis.

Gordon M. 5-Aminosalicylates to maintain remission in Crohn's disease: Interpreting conflicting systematic review evidence. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 99-102 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/99.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.99>

INTRODUCTION

There are broadly three classes of treatment that are commonly used to induce and maintain remission in inflammatory bowel disease (IBD): Antinflammatory agents, immunosuppressive agents and biologic therapies. 5-aminosalicylates (5-ASAs) are a group of antiinflammatory compounds used for many years to treat IBD. The first 5-ASA used in clinical practice was to manage arthritis in the 1940s^[1]. It was noted that patients who had concomitant IBD had improvements in their bowel symptoms.

COCHRANE EVIDENCE IN IBD

In the 1970s and 80s, there was growing academic and clinical concern with varying quality of primary research evidence and in particular reviews summarising evidence^[2]. The concept of scientific medicine began to grow in response to this, which then became known as evidence based medicine^[3]. The Cochrane Collaboration was at the forefront of evidence based medicine, leading the way in producing systematic reviews and methodological guidance for authors of reviews^[4]. For 20 years, Cochrane has produced systematic reviews of primary research in human health care and health policy, and these are internationally recognized as the highest standard in evidence-based health care resources^[5]. Whilst there have been criticisms of Cochrane reviews, they often inform international guidance and practice and so consideration of these reviews is vital for practising gastroenterologists.

WIDER COCHRANE EVIDENCE FOR 5-ASA AGENTS IN IBD

This class of agents have been employed in a variety of formulations within the context of IBD. In ulcerative colitis, it is well excepted in international guidance^[6] and from Cochrane systematic reviews of the topic^[7] that 5-ASA preparations are effective in inducing remission. Similarly, they are shown to be effective within Cochrane systematic reviews for the maintenance of remission in ulcerative colitis^[8] and suggested as first line therapy for maintaining remission^[6].

Interestingly despite this widespread evidence for effectiveness in ulcerative colitis, in Crohn's disease the evidence has always been more capricious. Early research demonstrated 5-ASAs are more effective for inducing remission in ileal, ileocolic, or colonic disease^[9,10]. Due to this evidence, some 5-ASA agents have been frequently employed by gastroenterologists for mild Crohn's disease. However, a Cochrane review updated in 2016^[11] that highlights a small benefit over placebo, but inferiority to other agents for inducing remission and mixed findings in newer studies of higher 5-ASA dosing. Until further research is performed, the authors do not suggest their use. This is also reflected in international guidance that note the variability in the evidence and do not currently suggest their use^[12,13].

CONFLICTING COCHRANE EVIDENCE IN MAINTAINING REMISSION IN CROHN'S DISEASE

For maintaining remission in Crohn's disease, there is a significant difficulty in interpreting the Cochrane evidence. A recently published Cochrane review update^[14] has found no evidence for the use of 5-ASA in maintaining medically induced remission. However, a review considering 5-ASA agents in post-surgical remission highlighted very different results^[15]. 5-ASA was significantly more effective than placebo for averting relapses, with no statistical heterogeneity. A large number of subgroup analyses were completed to investigate length of follow up and dosage, with no change in the statistical significance of results, except when follow up was less than 12 mo. Clearly, this robust effectiveness result in the post-surgical setting^[15] is at odds with the results for medically induced remission^[14]. The only area of agreement between these two key reviews is related to occurrence of adverse events, with no statistical difference between 5-ASA and placebo.

The situation is further complicated in a complimentary review that investigates purine analogues for maintenance of post-surgical remission in Crohn's disease^[16]. Whilst these were effective against placebo, there were only two studies in this analysis. The majority of studies compared to 5-ASA, reflecting their widespread use in this context. Meta-analysis of five studies showed no difference in preventing clinically diagnosed relapse at 12-24 mo post-surgery between 5-ASA and purine analogues. In fact, the trend in the risk ratio was towards 5-ASAs, suggesting inferiority of purine analogues. When considering adverse events that led to withdrawal of patients from treatment, these were statistically more common in the purine analogue patients compared to 5-ASA.

RECENT IMPACT ON PRACTICE GUIDANCE

As these key reviews^[14-16] are reasonably contemporaneous, impact on international guidance is currently limited. However, UK guidance from the National Institute for Health and Care Excellence has recently reflected this evidence. Previous guidance clearly suggested the 5-ASA agents should not be recommended in the post-surgical settings^[17], but the 2016 update now proposes 5-ASA can be offered^[18] reflecting on this key Cochrane secondary evidence^[15]. It remains to be seen whether other guidelines will shift advice in line with this evolving Cochrane evidence base.

UNDERSTANDING CONFLICTING RESULTS

The primary issue this spectrum of systematic review evidence raises is why 5-ASA agents have clear evidence of effectiveness in the post-surgical setting, but no

evidence in medically induced remission. There is no published research to give insight into these results, but the existing evidence base may hold the answer and allow hypotheses to be made.

Early evidence in Crohn's disease suggested that more mild disease was susceptible to 5-ASA agents^[9,10], particularly in terms of the location of disease. Whilst surgery within Crohn's disease can be heterogeneous and is patient specific, it is long accepted that the most common indications relate to limited resections of particularly diseased areas with complications^[19]. It is therefore possible that in the post-surgical setting, the patient has been reverted to a more disease naïve state within the remaining bowel, which due to pre-surgical medical management, is most commonly in a remission state. In many of the medical remission studies, this has been defined using clinical criteria and so at an endoscopic or histological level, there may well be disease activity. A counter view may suggest that because surgical patients had more severe disease, they do not have more mild disease. However, the author maintains that given the combination of surgical resection of these diseased areas and pre-surgical medical management, it is still likely that they represent a group with a different level of disease activity to the medical induce remission cohort of patients. This issue of clinical heterogeneity between the patient groups may explain why post-surgery evidence demonstrates efficacy of 5-ASA agents.

This hypothesis also raises a related methodological issue. Whilst studies included in the Cochrane reviews^[14-16] in both medically and surgically induced remission had to define remission using accepted international rating scales, the timing of entry appears particularly capricious within the medically induced remission papers^[14]. A review of the characteristics of studies suggests that patients could have been in remission for up to two years on entry within these studies. This is in stark contrast to the post-surgical remission papers reviewed that required study entry within at the most 60 d of surgery^[15,16]. When this is combined with the accepted limitations of clinical disease activity scoring^[20] compared to endoscopic or histological scoring methods, it is entirely possible that patients entering both sets of studies were simply not at a similar state of disease activity. In terms of 5-ASA agents and the acceptance that they are particularly efficacious in mild disease, this is a vital issue to consider.

The final issue to be considered is in the context of the post-surgical setting when comparing 5-ASA to Purine analogues. For those who have considered the individual study data within the Cochrane review^[16] it will be apparent that there is clearly a contrast between primary study conclusions of purine analogue efficacy and the meta-analysis performed. This is due to the intention to treat analysis performed in the review. A per protocol analysis would suggest superiority of purine analogues, in line with the individual studies. This is not the method used in the review for several Cochrane methodological reasons related to risk of bias from incomplete outcome data. Given the clearly pervasive problem with over a quarter

of patients on purine analogues not able to continue due to side effects^[16] this clearly demonstrates the limitations of per protocol analysis and supports this approach from Cochrane. This was worth comment as readers may have found this discrepancy concerning. The wider relevance of this intention to treat finding is to once again suggest that 5-ASAs are not necessarily the most efficacious therapy in Crohn's disease for either induction or maintenance of remission, but there is universal agreement on their good safety profile^[7,8,11,14-16].

IMPLICATIONS FOR PRACTICE

Based on the current Cochrane systematic reviews, 5-ASA agents cannot be recommended for maintenance of medically induced remission. However, in the post-surgical remission setting they are safe and effective. Given the concerning safety profile of purine analogues, it is proposed that clinicians consider this when discussing options with patients for post-surgical medication to maintain remission.

IMPLICATIONS FOR RESEARCH

There are two key areas that require further work. The first is within the medically induced remission setting. Given the volume of work suggesting the safety and potential efficacy, future large randomised controlled trials could be considered that pay particular attention to the extent and state of disease when entering the trial. Certainly, it is proposed that the use of endoscopic or histological methods to ensure induction of remission and consideration of the extent of previous disease are noted to ensure analysis can consider these factors that may be key in selecting appropriate patients for such therapy.

Secondly, given the most recent evidence now finds a role for 5-ASA agents in maintaining remission post-surgery in Crohn's disease, it is key to consider its relative efficacy to other agents, including immunosuppressive and biologic therapies. In the past, such analysis was impossible without individual primary trials investigating each comparison, but network meta-analysis offers this possibility^[21]. This is a meta-analysis which allows multiple treatments to be compared directly and across trials using a common comparator, such as placebo. The end result of such analysis is to allow true conclusions to be drawn as to the relative efficacy and therefore shape future international guidance on such issues. The Cochrane Inflammatory Bowel Disease group is currently planning such a review.

CONCLUSION

It is proposed that clinicians should consider 5-ASA agents an option to maintain remission post-surgery, but evidence does not demonstrate similar efficacy in medically induced remission and so 5-ASA agents cannot be recommended in that context. Future primary research is needed in the medical induced remission setting which considers the length of remission on enrolment and endoscopic

or histological disease scores. Additionally, secondary research to rank the various treatment options in the post-surgical setting could be achieved through the use of network meta-analysis.

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P- Reviewer: Chiba T, Tsoulfas G S- Editor: Qi Y L- Editor: A
E- Editor: Lu YJ



Combination therapy for inflammatory bowel disease

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Author contributions: Sultan KS designed and composed this review; Berkowitz JC and Khan S contributed to the design and composition of this review.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

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Manuscript source: Invited manuscript

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Received: March 7, 2017

Peer-review started: March 10, 2017

First decision: March 29, 2017

Revised: April 7, 2017

Accepted: April 23, 2017

Article in press: April 25, 2017

Published online: May 6, 2017

Abstract

Biologic therapies such as infliximab and adalimumab

have become mainstays of treatment for inflammatory bowel disease. Early studies suggested that combination therapy (CT) with infliximab and an immunomodulator drug such as azathioprine may help optimize biologic pharmacokinetics, minimize immunogenicity, and improve outcomes. The landmark SONIC trial in Crohn's disease and the UC SUCCESS trial in ulcerative colitis demonstrated CT with infliximab and azathioprine to be superior to monotherapy with either agent alone at inducing clinical remission in treatment naïve patients with moderate to severe disease. However, many unanswered questions linger. The role of CT in non-naïve patients as well as the optimal duration of CT remains unknown. The effectiveness of CT with alternate biologics and/or alternate immunomodulators is not as clear, and it is unknown whether SONIC's conclusions can be extrapolated beyond infliximab and azathioprine. Also looming are the risks of CT including opportunistic infection and malignancy; specifically, lymphoma. This review lays out the evidence as it pertains to the risks and benefits of CT as well as the areas that require further research. With this information in hand, the practitioner may develop a treatment strategy that best suits each individual patient.

Key words: Crohn's disease; Adalimumab; Vedolizumab; Ulcerative colitis; Infliximab; Inflammatory bowel disease; Methotrexate; Azathioprine

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Core tip: The benefits of combination therapy (CT) with infliximab and azathioprine likely outweigh its risks in treatment naïve patients with moderate to severe Crohn's disease and ulcerative colitis. A similar benefit in patients already failing biologics or immunomodulators is not as well defined. There is a lack of strong prospective evidence demonstrating a benefit for CT with adalimumab and an immunomodulator. While expert guidelines emphasize the use of CT, its use should be preceded by a careful weighing of the risks and benefits by the physician and patient, especially in scenarios where the strongest

evidence for CT may not directly apply.

Sultan KS, Berkowitz JC, Khan S. Combination therapy for inflammatory bowel disease. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 103-113 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/103.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.103>

INTRODUCTION

Traditional management of inflammatory bowel disease (IBD), both Crohn's disease (CD) and ulcerative colitis (UC), involved the stepwise use of 5-aminosalicylate compounds, followed by steroids and then an immune modulator (IMM) such as 6-mercaptopurine (6MP), azathioprine (AZA) or methotrexate (MTX) in those individuals unable to successfully taper off steroids, or those with rapid disease recurrence once steroids were withdrawn. While the IMMs are generally ineffective agents for induction of response or remission in IBD^[1] the thiopurines 6MP/AZA have proven to be effective for the maintenance of response and remission in CD and UC^[1,2] while the purine analogue MTX appears to offer the same benefit for CD^[3]. Beginning in the 1990's, biologic therapies targeting tumor necrosis factor alpha (TNF- α) entered into this paradigm. The first in class medication infliximab (IFX) was initially shown to be effective both for induction and maintenance of remission for CD, and latter for UC. In the years that followed, IFX was followed by other TNF- α blockers including adalimumab (ADA) for CD and UC, certolizumab pegol for CD, and golimumab for UC. Even more recently we have seen the addition of biologics targeted at different points in the body's inflammatory response, such as the anti-integrins natalizumab and vedolizumab (VDZ) which inhibit the migration of white blood cells, mostly activated T cells to areas of bowel inflammation, as well ustekinumab which blocks the IL 12/23 pathway of inflammation.

Consistently, clinical trials of biologics have involved the use of these newer therapies in combination with IMMs. Initially, the use of this form of combination therapy (CT) was a natural outgrowth of the failure of IMMs to fully control disease in some of the clinical trial population, with the biologic therapy added on to continued IMM treatment. While the initial clinical trials of IFX did not show any improved response with the use of CT over monotherapy with biologic alone, there were some other findings which suggested that the use of both classes of medications together might be superior to one or the other alone. In a way, the potential benefit of CT would seem to be an answer to an obvious question: If one has access to two separate therapies with different mechanisms, each less than 100% effective, can the use of both in combination increase the rates of response over each individually?

In the following review we will address the basic

questions both the clinician and patient will need to have answered before considering the use of CT; (1) Does CT work, and why does it work? (2) Is CT effective for those with either CD or UC? (3) Is CT effective for different combinations of IMM and biologic? (4) Is CT effective at all stages of IBD therapy? (5) Is CT safe? (6) Is CT being utilized? and (7) What do the experts say about CT?

DOES CT WORK/WHY DOES IT WORK?

Though the earliest clinical trials of IFX were not designed to assess the efficacy of CT, study design permitting continued IMM use provided some early data on the effect of CT. Given the few options for alternate therapy available at the time, a majority of patients in the phase 3 trials of IFX for both CD and UC had experienced prior failure of IMM therapy with either 6MP/AZA or MTX. For many, this failure to achieve remission likely involved a partial response rather than a complete lack of efficacy. In either case, large numbers of patients entering these trials continued on prior IMM therapy. This "step up" approach to CT will be discussed in more detail in the following sections. In the case of the CD trials ACCENT 1 and ACCENT 2^[4,5] approximately 50% of study patients, well matched by active treatment and placebo arms, continued on IMMs. In the UC studies of IFX, ACT 1 and 2, approximately 33% of patients were on IMMs at study entry^[6].

Overall, the clinical trials of IFX did not show any improved clinical efficacy associated with the use of CT. These early trials did however give the first hints of how CT might provide a benefit to the IFX patient over monotherapy in the form of decreased immunogenicity. Overall, the development of antibodies to IFX (ATI) were significantly lower in the CT patients, with 4%-20% without CT developing ATI, compared to rates of 4%-6% among those using CT^[7]. This effect was noted to be greatest for those patients using the current standard 5 mg/kg dose of IFX. There was also no observed benefit in terms of higher IFX levels, but neither was there any increase in the rates of infections. Along with the lower ATI levels for those using IMM, were lower overall rates of infusion reactions at 12.5%, compared to 22.0% for those not using IMM.

Following up on these early observations, subsequent investigations began to take a closer look at the interplay between IFX, the development of anti-drug antibodies and possible impact on IFX drug levels, treatment reactions and clinical efficacy. In a prospective non-randomized trial, Baert *et al*^[8] followed 123 patients on IFX, with 47% receiving concurrent IMM. In this study, as was common at that time, patients with luminal disease were treated with episodic rather than scheduled IFX therapy, while those with fistulizing disease received a week 0, 2 and 6 induction regimen followed by episodic treatment. Overall, patients received a mean number of 3.9 infusions. In total, 61% developed ATI. Higher antibody

levels > 8.0 µg/mL predicted shortened clinical response, 35 d vs 71 d ($P < 0.001$), with higher levels of ATI in those without IMM usage ($P < 0.001$) and lower drug levels in those without IMM usage ($P < 0.001$). Infusion reactions were found to be more common among those not using IMM [relative risk (RR) = 2.40; 95%CI: 1.65-3.66; $P < 0.001$]. Vermeire *et al.*^[9] performed similar work using IFX on demand for both luminal and fistulizing CD. They enrolled 174 patients who received IMM (either MTX or AZA) or no IMM in a non-randomized fashion. MTX was given subcutaneously at 25 mg weekly for 12 wk followed by 15 mg weekly, while ASA was given at a weight-based dose of 2-2.5 mg/kg. ATI levels were checked at 4 wk following IFX doses. Again, episodic treatment with IFX resulted in high ATI levels, especially for patients not receiving concomitant IMM. Overall they observed 73% of patients without IMM developing ATI, compared to 46% with IMM, $P < 0.001$. This effect was consistent across IMM types, with 44% of MTX patients developing ATI vs 48% of AZA patients, $P = \text{NS}$. There was a trend towards higher average IFX drug levels with IMM, 2.22 µg/mL vs 6.45 µg/mL, $P = 0.065$, and significantly less infusion reactions with IMM, 16% vs 40%, $P = 0.04$.

Taking into account the two main observations of IFX immunogenicity at the time, the association of lower ATIs with scheduled treatment^[10,11] and concurrent use of IMM, the Study of Biologic and Immunomodulators Naïve Patients in Crohn's Disease (SONIC) trial was designed to answer the question of whether clinical response was superior with CT over monotherapy^[11]. Unlike the earlier clinical trials, patients entering SONIC were entered into one of three treatment arms and followed prospectively. Additionally, given the strong association between episodic dosing, antibody formation and decreasing effectiveness of treatment, all patients in SONIC and future trials of CT were given IFX on a fixed schedule rather than episodically, as is the current practice. In total, 508 patients were randomized to either IFX monotherapy (with oral placebo), AZA monotherapy at 2.5 mg/kg (with IV placebo), and CT with IFX and AZA. All patients in the study were naïve to both IMM and biologics, had a Crohn's Disease Activity Index (CDAI) > 220, and underwent ileocolonoscopy at baseline. The primary study endpoint was steroid free clinical remission at 26 wk, defined by a CDAI < 150. This endpoint was achieved by 30.0% of those on AZA monotherapy vs 44.4% on IFX monotherapy, ($P = 0.006$) and 56.8% of those on CT, which was significantly greater than either AZA ($P < 0.001$) or IFX monotherapy ($P = 0.02$). Though CT achieved higher rates of mucosal healing than IFX alone, 43.9% vs 30.1%, this result was not found to be statistically significant, $P = 0.06$, likely due to the large number of patients without active disease found on baseline ileocolonoscopy. Additional findings again mirrored those of earlier studies, showing higher week 30 IFX trough levels with CT vs IFX monotherapy, 3.5 µg/mL vs 1.6 µg/mL ($P < 0.001$), and lower incidence of ATI, 0.9% vs 14.6%. Notably, serious adverse events

(SAE) were actually lower with CT than IFX monotherapy (15.1% vs 23.9%, $P = 0.04$). Serious infections were similar across treatment groups, with 3.9% of patients on CT, 4.9% of those on IFX monotherapy, and 5.6% of those on AZA alone.

IS CT EFFECTIVE FOR UC?

Though SONIC was notable in regards to the generally short median disease duration of 2.3 years of participants, it did appear to provide an answer to the question of the superiority of CT over monotherapy with IFX, at least for the select group of treatment naïve patients with CD. Following up on these findings the UC SUCCESS trial was designed to answer the same question, and determine if CT with IFX and AZA was also more effective for UC^[12]. With a similar study, 239 patients with active UC confirmed by sigmoidoscopy were enrolled to treatment arms of IFX with oral placebo, AZA with IV placebo, and AZA. Again, all patients were biologic naïve, though prior AZA exposure (discontinued at least 3 mo earlier) was permitted. The primary study endpoint of steroid free remission at week 16, defined by a MAYO score ≤ 2 , was achieved by 39.7% of CT vs IFX monotherapy ($P = 0.017$). Mucosal healing, defined by a subscore of 0 or 1, showed a trend towards greater effect for CT vs IFX monotherapy 62.8% vs 54.6% ($P = \text{NS}$), and complete mucosal healing defined by an endoscopic subscore of 0 was significantly greater for those on CT vs IFX monotherapy, 29.5% vs 11.7%, $P = 0.006$. Again, no increased incidence of SAE was observed with CT. Serious infections were similar in all three groups, (0 in the CT group, 1 in the IFX monotherapy group, and 1 in the AZA monotherapy group).

IS CT EFFECTIVE FOR OTHER IMMS?

Of course thiopurines were not the only IMMs that had shown potential benefits when used with IFX. MTX had demonstrated similar effects of decreasing ATI and increasing IFX trough levels. With that in mind, a prospective study of MTX with IFX, the COMMIT trial, was preformed comparing IFX monotherapy and subcutaneous placebo to IFX with subcutaneous MTX for patients with CD^[13]. Like SONIC the study enrolled biologic naïve patients, but other inclusion criteria and study methods were notably different. There was no need for minimum baseline CDAI, and inclusion only required that patients had required steroids within 6 wk prior to enrollment. Additionally, all IFX infusions were given along with 200 mg of IV hydrocortisone as premedication. The primary study endpoint was failure to achieve steroid free remission at week 16 (defined by a CDAI < 150), or failure to maintain remission through week 50. In total 126 patients were enrolled, with an average disease duration of over 10 years in each treatment arm, as well as a relatively low CDAI of 207 for both CT and monotherapy groups. The week 14 primary endpoint of steroid free remission was not

found to be greater for CT vs monotherapy, 76% vs 78%, and neither was the week 50 endpoint, 56% vs 57%. Critiques of the trial have pointed at the overall low baseline levels of CDAI, suggesting that it is more difficult to detect a significant response to therapy when the disease is less severe. Also, the use of hydrocortisone along with all infusions may have offered additional clinical benefit, again obscuring any distinct MTX effect. Even so, the trial again demonstrated the ability of MTX to modify immune response to IFX, with lower ATI in the MTX arm vs placebo, 4% vs 20% ($P = 0.01$), and a trend towards higher IFX trough levels, 6.35 $\mu\text{g/mL}$ vs 3.75 $\mu\text{g/mL}$ ($P = \text{NS}$).

IS CT EFFECTIVE FOR OTHER BIOLOGICS WITH IMMS?

The next biologic, possessing a similar mechanism of action to IFX, was adalimumab (ADA). ADA differs from IFX not only by its subcutaneous route of delivery, but by its fully humanized protein structure. Given that the main benefit of IMM with IFX appeared to be linked to blunting an immune response, it could not be assumed that ADA would be as immunogenic, or that IMM with ADA would demonstrate the same benefits. In fact, early studies of ADA pharmacokinetics and clinical outcomes did demonstrate a correlation of clinical response to higher ADA trough levels and lower antibody to adalimumab, similar to prior observations with IFX. Unlike IFX however, early investigations did not find that IMM influenced these outcomes^[14]. A retrospective analysis of mixed IBD patients using IFX ($n = 108$) again showed increased drug levels ($P = 0.037$) and decreased antibodies to IFX ($P = 0.001$) among those using IMM. This benefit to IMM was not found among the 109 ADA treated patients, with CT showing similar drug trough levels ($P = 0.496$) and antibody levels ($P = 0.63$)^[15] to those on ADA monotherapy. A recent large meta-analysis of ADA pharmacokinetics of 14 studies included 1941 patients with mixed IBD diagnoses with available clinical outcome, drug trough and antibody data available. Once again, clinical response was associated with higher drug trough and low antibody to ADA, but CT did not appear to influence either antibody or drug trough levels^[16]. The study suggests that antibodies to ADA do occur, they do appear to cause low levels of trough ADA and lessened clinical effect, but there is a lack of evidence suggesting that IMM have the ability to prevent the development of these antibodies.

To the present time there has been no trial of ADA matching the designs of either SOINIC or UC SUCCESS. While not a substitute for a prospectively designed trial, there is still clinical data available addressing the issue of CT with ADA and IMM. Another meta-analysis designed to look specifically at clinical outcomes with ADA monotherapy vs CT among CD patients included 18 studies [randomized control trials (RCT), open-label

prospective, observational studies, cohort and case-control studies] with 2280 ADA monotherapy patients and 2014 CT patients^[17]. Of the 6 studies analyzing induction of remission (960 ADA, 997 CT), the use of CT was associated with greater clinical response OR = 0.79 (0.65-0.96); $P = 0.02$, though this was not found to be the case when the analysis was limited to the RCT, OR = 1.11 (0.72-1.73); $P = 0.64$. There was also no evidence of clinical benefit to CT for induction of response OR = 0.68 (0.37-1.25); $P = 0.22$, 12 mo remission OR = 1.08 (0.79-1.48); $P = 0.61$, or 12 mo response OR = 1.21 (0.74-1.99); $P = 0.44$. At present there is even less data specifically addressing the clinical impact of IMM with ADA for UC. As was the case with the early IFX trials, almost half of the patients in the initial clinical trials were using IMM at enrollment. Though the remission rates were higher with CT, the small absolute number of patients involved and the absence of a specific prospective trial design should caution against any definitive conclusions.

Since IFX and ADA were the first biologics approved for IBD treatment, most of the current data on CT deals with IFX and ADA. Of course, biologic development has continued beyond this class of medications, most recently with the addition of the new integrin inhibitor, VDZ. While not the first in class, with that distinction going to natalizumab, the updated mechanism of action targets $\alpha 4\beta 7$ on circulating white blood cells. Blockade of this gut specific integrin decreases WBC adherence to the vascular endothelial wall, and subsequent migration to areas of inflammation. As is the case for all non-IFX biologics, there is currently no prospectively designed study addressing CT of VDZ with IMM. Review of the results of the large phase 3 clinical trials offers some of the early immunologic data seen with earlier biologics. GEMINI 1, enrolling 895 patients with UC for induction and maintenance, included a third of patients with concurrent IMM use. Overall, antibodies to vedolizumab (AVA) were infrequent, found in 3.7% of patients at "any time" during testing, with a mere 1.0% testing positive on ≥ 2 samples^[18]. GEMINI 2, enrolling 1115 patients with CD for induction and maintenance also included a third with concurrent IMM use^[19]. Overall AVA were again infrequent, 4.1% at "any time", and 0.4% on ≥ 2 samples. The authors of each study commented that "concomitant immunosuppressive therapy was associated with decreased immunogenicity (data not shown)".

More recently an analysis of the phase 2 and 3 trials for both CD and UC has been preformed, addressing the issue of CT^[20]. Among a total of 2830 patients, covering 4811 patient years there was no observed increased risk of adverse events. During active VDZ therapy, CT patients had a 3% risk of AVA, compared to 4% for VDZ monotherapy. As has previously been noted for TNF- α inhibitors, higher levels of anti-drug antibody were seen following completion of VDZ therapy among those patients without IMM as compared to those

Table 1 Author's summary of the evidence for combination therapy

	Crohn's disease		Ulcerative colitis	
	Clinical benefit	Pharmacokinetic/immunogenic benefit	Clinical benefit	Pharmacokinetic/immunogenic benefit
IFX + AZA/6MP (treatment naïve)	+	+	+	+
IFX + AZA/6MP (step-up from immunomodulator monotherapy)	-	NA	NA	NA
IFX + MTX	+/-	+	NA	NA
ADA + IMM	+/-	+/-	NA	NA
VDZ + IMM	NA	+	NA	NA
Ustekinumab + IMM	NA	NA	NA	NA

IFX: Infliximab; AZA: Azathioprine; 6-MP: 6-mercaptopurine; MTX: Methotrexate; ADA: Adalimumab; VDZ: Vedolizumab; IMM: immunomodulatory; +: beneficial; +/-: Possible benefit; NA: No adequate data available.

with ongoing IMM use, 18% vs 3%. Theoretically, this may have implications for issues such as prevention of AVA during VDZ drug holiday, and potential infusion reactions and/or drug effectiveness on resuming therapy. It does not however offer answers to the key question of risks and benefits of CT with VDZ and IMM.

Even more recently Ustekinumab, targeting the p40 subunit of IL-12/23 has obtained regulatory approval for induction and maintenance therapy for CD. In the recently published phase 3 induction and maintenance trials, approximately a third of patients received concurrent IMM with Ustekinumab or placebo^[21]. The investigators have yet to publish data analyzing the effect of CT, though they did report an overall low level of antidrug antibodies at 44 wk of 2.3%. Again, while there is no prospective clinical trial data yet available on CT, a recent retrospective study from the GETAID group analyzed their experience with 122 treated patients^[22]. All 122 patients were prior treatment failures with TNF- α inhibitors, with only 18 using IMM at the time of ustekinumab therapy. Of all factors analyzed, only IMM use was found to be a predictor of 3 mo clinical benefit, OR = 5.43; 95%CI: 1.14-25.77; $P = 0.03$ (See summary of evidence for induction CT, Table 1).

IS CT EFFECTIVE AT ALL STAGES OF IBD THERAPY?

Step up therapy: Adding biologic to failing IMM

As we have seen, most of the available evidence suggesting a benefit to CT involves the use of IFX and IMM begun simultaneously, especially in those naïve to biologic as well as to IMM. In reality, IMM is still widely used as part of a step up algorithm of care, with biologics employed as additional therapy in cases of IMM failure as in the early clinical trials. Given the frequent positioning of IMM as mono-therapy prior to biologic, a specific look is required into the role of continuing IMM as part of a combination step-up therapy.

A recent analysis by Osterman *et al*^[23] retrospectively analyzed a cohort of CD patients beginning biologic therapy with either IFX or ADA, 1459 and 871 patients

respectively. In total 381 CT patients using IFX and IMM were matched to 912 monotherapy IFX patients, as were 196 CT using ADA and IMM matched to 505 ADA monotherapy patients. In the IFX group, 86% of the CT patients were part of a step-up protocol, adding biologic to existing IMM, as were 89% in the ADA group. These high percentages effectively made the analysis of the effect of CT into an analysis of CT as part of a step-up treatment approach. Thiopurines accounted for 90% of IMM use. Given the retrospective design, the authors were unable to analyze for common clinical trial outcomes such as improvement in CDAI or endoscopic response and remission. Looking at alternate outcomes, they were unable to show any benefit to CT in terms of surgery (HR = 1.20, OR: 0.73-1.96), hospitalization (HR = 0.82, OR: 0.57-1.19), rates of combined biologic discontinuation and surgery (HR = 1.09, OR 0.88-1.34) or serious infections overall (HR = 0.93, OR 0.88-1.34). Rates of opportunistic infections were significantly increased (HR = 2.64, OR: 1.21-5.73), mostly due to increased rates of herpes zoster (HR = 3.16, OR: 1.25-7.97). These findings were consistent across the subgroups for both IFX and ADA. The overall conclusion: there is no apparent benefit to continuing IMM, in cases of IMM failure, once biologic therapy is begun. Similarly, a recent meta-analysis by Jones *et al*^[24] reviewed the results of 11 randomized trials of anti-TNF- α therapies including IFX, ADA and certolizumab, among 1601 patients of which 40% were on CT. All patients on CT received biologic as part of a step-up approach after failing to achieve remission with IMM. Again, there was no benefit to CT for the outcomes of 6-mo remission (OR = 1.02; CI: 0.80-1.31), 6-mo response (OR = 1.08; CI: 0.79-1.48). Neither however was there any increase risks of adverse events with CT (OR = 0.71; 95%CI: 0.41-1.25).

Step up therapy: Adding IMM to failing biologic

The issue of stepping up to CT by the addition of IMM to failing biologic is less well studied. A small retrospective cohort analysis by Ben-Horin *et al*^[25] examined the outcomes of 5 patients (3 with CD, 2 with UC) with a secondary loss of response to IFX associated with

high ATI levels and undetectable trough. Two patients were treated with MTX and 3 received either AZA/6MP. In all cases patients experienced a decrease in ATI, an increase in trough, and a recapturing of clinical response. Despite the questionable efficacy of CT when the anti-TNF is ADA, the same group has recently shown a similar result when adding IMM as salvage therapy to failing ADA in 23 patients (21 with CD, 2 with UC) with confirmed antibodies to ADA. Salvage therapy with IMM (14 with thiopurines, 9 with MTX) was associated with elimination of antibodies to ADA, increased ADA levels, and recapturing of response (median time to sero-reversal 5 mo) in 11 patients (48%)^[26].

Optimal duration of successful CT

The final issue to address with regard to effectiveness of CT is the question of duration: For those patients in remission on CT, for how long should they continue to take the IMM? The retrospective data on de-escalation is mixed^[27]. There is very limited prospective controlled data to guide therapy. Van Assche *et al.*^[28] from Belgium reported on a group of 80 CD patients with disease controlled on CT for a minimum of 6 mo, at IFX doses of 5 mg/kg, at intervals of every 8 wk or greater. Patients were randomized to maintenance with IFX and placebo vs continued CT, and followed for 104 wk. The primary outcome was the need to decrease the IFX dosing interval or discontinuation of IFX. Secondary outcomes included IFX trough levels and safety. While those patients discontinuing IMM showed significantly lower IFX trough levels at 54 wk, 1.65 µg/mL vs 2.87 µg/mL ($P < 0.0001$), and a trend towards higher CRP levels, there was no difference at 104 wk with regards to the need for rescue IFX, discontinuation of IFX. The authors concluded that there was no benefit to IMM beyond 6 mo in patients achieving remission with combination IFX and IMM. Another more recent prospective study however suggested a possible benefit to continued CT. Eighty-one patients on CT for at least 1 year were randomized to continuation of CT at the same dose (Cohort A), reduction of azathioprine dose by 50% (Cohort B), or complete cessation of azathioprine (Cohort C)^[29]. While differences in clinical outcomes at one year were not statistically significant ($P = 0.1$), there was a trend towards higher relapse rates in Cohort C (30.7% vs 17.8% and 11.5% in Cohorts A and B). Only in Cohort C were infliximab trough levels significantly decreased at one year as compared to study initiation (4.2 µg/mL vs 2.1 µg/mL, $P = 0.02$). This data also suggests that a reduced dose of maintenance immunomodulator may provide similar benefits as full dose maintenance CT.

IS CT SAFE?

CT and lymphoma

Though most of the additional risk associated with CT relates to an increased risk of infections, particularly

opportunistic infections with Candida and Herpes Zoster^[30] risk of lymphoma casts a long shadow over any discussion of CT. Since CT has typically meant thiopurines with biologic, it is first important to acknowledge that the vast majority of evidence points to a 4 to 5 fold increased risk of lymphoma associated with thiopurine use. This figure has been observed both in a meta-analysis of referral center IBD patients, as well as in the recent CESAME population study from France, which noted that this risk was primarily associated with active thiopurine use^[31,32]. The case for an increased risk of lymphoma with biologic monotherapy is far weaker, particularly for those with IBD^[33]. Most evidence supporting this increased risk is drawn from the larger rheumatoid arthritis population, for which the disease itself is known to carry an increased risk^[34].

In the absence of large population data on lymphoma risk with CT, investigators have employed mathematical modeling incorporating the observed increased risk with thiopurines to predict the risk/benefit of lymphoma with CT. Scott *et al.*^[35] in a recent Markov model analyzed the risk/benefit of IFX monotherapy vs CT at a variety of patient ages, utilizing quality of adjusted life years (QALY) as their primary outcome measure. The analysis accounted for the benefits of CT including increased response and remission rates, decreased surgery and less CD related death, balanced against the risk of death related to lymphoma and infections. They concluded that CT increased QALY for all patients, with that benefit decreasing as the patients aged. A patient 55 years or younger could expect to benefit from CT for at least 7 years. Even for those over 75 years, with the highest background risk of lymphoma, they estimated that it would take almost 5 years for QALY to suffer by continued use of CT. Another recent analysis by Siegel *et al.*^[36] utilized a Monte Carlo Simulation to predict the effects of one year of IFX monotherapy vs CT. in a theoretical population of 100000 thirty-five-year-old modeled on the SONIC trial. Here again the authors predicted that CT would result in an increased numbers of lymphomas for CT vs IFX monotherapy, 60 vs 40 cases respectively. However, since most infections observed in CD are related to the underlying disease activity rather than opportunistic infections, they also predicted that the more effective treatment of CD with CT would result in far fewer serious infections with CT vs IFX monotherapy, 3892 vs 4884, ultimately resulting in fewer deaths (399 vs 446). The authors concluded that the benefits of CT would continue to outweigh the risks unless serious infections occurred in over 20% of CT patients—a rate 5 fold greater than predicted, or if lymphoma occurred in over 3.9% of CT patients—a rate 65 fold higher than predicted.

No review, however, of CT can be complete without addressing the rare, but frightening complication of hepatosplenic T-cell lymphoma (HSTL), an aggressive and almost uniformly fatal disease that has been described

among IBD patients using CT. A recent systematic review of the literature by Kotlyar *et al.*^[37] documented 36 IBD patients who developed HSTCL. Of these, 20 received CT with a thiopurine and a TNF- α inhibitor, and 16 had thiopurine monotherapy. There were no cases reported of HSTCL with TNF- α inhibitor monotherapy. Only 2 (6.5%) were female, and the median age was 22.5 years. Notably only one patient, in the CT group, had a history of less than 2 years of thiopurine use. Overall, the authors concluded that the risk of HSTCL was highest for young men on CT, estimated at 1:3534.

Utilization of CT

Just as the literature addressing CT provides a variety of outcomes depending upon the population analyzed and the question being asked, so too does the real world data on the utilization of CT. In a recent large prospective survey study of seven high volume tertiary referral IBD practices, 1659 patients with CD, 946 with UC, and 60 indeterminate colitis, a wide variation of usage of CT was noted, particularly among those with CD^[38]. While initially only including those with an IBD diagnosis of less than 4 years, the authors ultimately included patients with all disease durations in their cohort. For those with CD, the lowest site utilization rate of CT was 8%, vs 32% at the site with the highest frequency, adjusted OR (95%CI) 3.15 (1.79-5.56). The authors report that the results observed were similar when excluding the site with the lowest frequency from each parameter of analysis.

Among the entire CD cohort, slightly more than half of anti-TNF use was as part of CT, with 47% overall on anti-TNF and 21% on CT. For those with UC, the range of usage of CT was 6% to 13%, OR 1.14 (0.48-2.78). Among the entire UC cohort, less than a third of anti-TNF use was part of CT, with 23% overall on anti-TNF and 9% on CT. It should be noted that the authors did not provide a breakdown of the type of biologic therapy used, so we have no way of knowing if the proportion of CT usage was higher among IFX patients, where the evidence to support CT is significantly stronger. Additionally, the results do not specify rates of CT usage for induction vs maintenance, where we have also seen differing degrees of supporting data.

A recent population wide study from France^[39] prospectively followed all IBD patients affiliated to the French national health insurance, tracking treatment and outcomes over the years 2009-2014. During that time there were 69725 new incident patients with IBD. CT was defined as the concomitant initiation of anti-TNF's and thiopurines in a period of 30 d. Among these newly diagnosed CD patients, the 5-year cumulative probability of CT and anti-TNF monotherapy was 18.3% and 33.8% respectively. For UC, the 5-year cumulative probability of CT and anti-TNF monotherapy was 7.4% and 12.9% respectively, *i.e.*, CT accounted for just slightly more than half of anti-TNF use. The authors report that CT was more frequent with IFX after one

year than with ADA for both CD and UC patients (4.2% vs 3.1% and 1.7% vs 0.6%) respectively. Given that this data arises from a large/general population, it is not surprising to see lower overall rates of biologic use and CT use than in the population from the IBD referral centers. It is noteworthy however that the proportion of CT use among those using anti-TNF is fairly similar.

In a retrospective review of community trends of biologic use from the US, we analyzed referrals to our institution's infusion center which provided IFX infusion services to both the full time teaching faculty, as well as to private practice gastroenterologists^[40]. Overall 247 new IFX referrals (154 CD, 93 UC) started on treatment from 2002 to 2014. Only 23.3% of patients received CT at the time of their first infusion (24% CD, 20.4% UC). These results were similar when analyzing the subgroup of 127 patients receiving IFX as part of a standard 0, 2, 6 wk induction regimen. Again, only 26% of CD and 28% of UC patients were on CT during their first induction IFX infusion. Notably, there was no trend observed of increasing use of CT over the years, despite the accumulating evidence of its benefit.

WHAT DO THE EXPERTS SAY?

Guideline recommendations

Finally, taking into account the available evidence, major GI professional societies have provided their consensus guidelines regarding CT use in the management of IBD. As with any guideline, it is important to note not only the type of recommendation provided, but also the grading of the recommendation based on the quality of supporting evidence and the year in which the guideline appeared (Table 2).

In 2009 the Practice Parameters Committee of the American College of Gastroenterology (ACG) recommended IFX monotherapy or IFX combined with AZA as more effective than AZA in the treatment of patients with moderate to severe CD failing first-line therapy with mesalamine and/or corticosteroid who were naïve to IMM and biologic^[41]. Additional ACG guidelines the following year were unable to support the same recommendation for UC^[42]. The 2011 guidelines from the World Congress of Gastroenterology with the European Crohn's and Colitis Organization concluded that CT of IFX and AZA was superior to induction of remission and mucosal healing over a 1 year time period. The authors further stated that it was uncertain if this was the best strategy beyond one year of treatment, and that it was unknown if this was true for other biologic/IMM combinations^[43]. In 2013 the American Gastroenterological Association (AGA) published its guidelines on the use of thiopurines, MTX and anti-TNF- α drugs for the treatment of CD. The authors suggested using anti-TNF- α in combination with thiopurines over anti-TNF- α monotherapy to induce remission in cases of moderately severe CD (Weak Recommendation, moderate quality evidence), again showing the strong impact of SONIC on clinical thought.

Table 2 Summary: Major society guidelines addressing combination therapy

	CD	UC
American College of Gastroenterology (2009 CD, 2010 UC)	IFX or IFX and AZA superior to AZA	Unknown efficacy of CT
European Crohn's and Colitis Organization and World Congress of Gastroenterology (2011)	IFX and AZA superior to monotherapy (in treatment naïve)	Unknown efficacy of CT
American Gastroenterological Association (CD guidelines (2013)	Anti-TNF- α and AZA superior to monotherapy	
American Gastroenterological Association Clinical Care Pathways (2014 CD, 2015 UC)	Consider IMM with anti-TNF- α or 2 nd /3 rd line biologic	Consider IMM with all anti-TNF- α or VDZ use
Hong Kong IBD Society (2013)	Anti-TNF- α and AZA superior to monotherapy	CT not addressed
Indian Society of Gastroenterology (UC consensus)		CT not addressed
Asian Pacific Association of Gastroenterology (UC consensus)		CT not addressed
Japanese Society of Gastroenterology (CD guidelines)	CT Not addressed	

IFX: Infliximab; AZA: Azathioprine; IMM: Immunomodulator (includes AZA, 6-mercaptopurine, Methotrexate); VDZ: Vedolizumab; CT: Combination therapy; UC: Ulcerative colitis; CD: Crohn's disease.

The authors go on to acknowledge the uncertain benefits of CT in cases of prior IMM failure, CT with other anti-TNF- α drugs, as well as CT using MTX^[44].

More recently in 2015, a panel of IBD experts in association with the AGA published pathways of care to aid clinical decision making. In the UC care pathway, at all steps where treatment with anti-TNF or VDZ is indicated, the authors recommend consideration of the addition of either a thiopurine specifically, or IMM generally. The authors support the use of MTX as an alternate IMM to thiopurine^[45]. A similar AGA pathway for CD in 2014, the "Crohn's Disease Evaluation and Treatment: Clinical Decision Tool", also supports CT as an option for all patients receiving anti-TNF therapy. The pathway emphasizes that the addition of an IMM offers improved efficacy and should be considered in moderate to high risk patients receiving their 2nd or 3rd biologic^[46]. Neither pathway addresses how long CT should be utilized.

Consensus statements from Asian medical societies do not emphasize CT as much as their western counterparts. The Japanese, Indian and Asia-Pacific societies for gastroenterology do not address the potential therapeutic benefits of CT in their respective IBD guidelines nor do they cite the SONIC trial^[47-49]. In contrast, in a guideline issued by the Hong Kong IBD society a class A recommendation states that CT is the most effective way to induce remission in moderate to severe CD^[50]. The guideline goes on to recommend an individualized weighing of risks and benefits of CT for each patient. It is likely that further patient experience and review may lead to increased attention into the role of CT in non-European/North American expert reviews and guidelines. As for now, those studies showing the greatest benefit to CT, specifically SONIC and UC SUCCESS, almost exclusively studied European/North American populations. Patient characteristics with regard to race are not addressed in UC SUCCESS, but the population in SONIC is specifically identified as over 90% "white race". This raises the possibility that our strongest data on CT may not be generalizable to those in other regions.

CONCLUSION

While newer IBD therapies continue to be developed and tested in clinical trials, for the vast majority of patients and their physicians the emphasis remains on the best possible use of currently approved therapies to control disease activity. With the available choices expanding, the definition of CT may eventually broaden to include combinations of multiple biologics, but for now CT is defined by IMM use along with biologic.

The available evidence does suggest a benefit to CT, but this evidence is clearer for the use of IMM with IFX specifically, and especially in those without prior IMM or IFX use. This benefit appears to apply to both patients with CD and UC. The level of evidence for the benefit of IMM with other biologics is not a clear, nor is it certain that this combination if applied sequentially as step up therapy offers the same improved response as starting the two together. The main mechanism of benefit of IMM in the setting of biologic appears to be through the suppression of antibody formation to the biologic treatment. With less inherent immunogenicity to newer biologics, it is perhaps not surprising that the benefit of adding IMM is harder to define with other combinations. To better answer the question would require dedicated prospective studies of each CT as was the case with IFX, which are unlikely to be performed. With regards to the safety of CT, there is valid concern regarding the increased risk of opportunistic infections, though perhaps outweighed by the benefits of better disease control. As for the risks of malignancy with CT, the numbers again suggest that any increased risk is far outweighed by the potential benefits, at least over a "short term" of several years. Even though patients and physicians may understand that this risk is minor in comparison to potential benefits, the observed rates of CT use suggest that fear of this complication is still a strong motivating force away from CT. Overall, GI professional societies have advocated the use of CT when the anti-TNF is IFX, but not explicitly for other combinations. As we have seen, there is evidence to support other forms of CT, but both the physician and

the patient need to be aware of the strength of this evidence, be certain that the risks are understood, and the goals of therapy are achieved if other forms of CT are used.

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P- Reviewer: Freeman HJ, Seow-Choen F **S- Editor:** Song XX
L- Editor: A **E- Editor:** Lu YJ



Inflammatory bowel disease: Efficient remission maintenance is crucial for cost containment

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Conflict-of-interest statement: The authors declare no potential conflicts of interest and no financial support.

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Manuscript source: Invited manuscript

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Received: July 27, 2016
Peer-review started: July 29, 2016
First decision: October 20, 2016
Revised: October 28, 2016
Accepted: January 11, 2017
Article in press: January 13, 2017
Published online: May 6, 2017

Abstract

The inflammatory bowel diseases (IBD) are chronic

incurable inflammatory disorders of the gut. Some 10% run a downhill course, requiring emergency medical support and often surgery; another small subset are monogenic, and, threatening pediatric patients, are the challenge of these days. The majority of the IBDs, however, are polygenic low-penetrance diseases, running a lifetime waxing-and-waning course. The prevalent trend is towards a slow worsening and steady cost increase. Each and all drugs of the available arsenal exhibit strengths and weaknesses: Mesalamines are chiefly effectively for mild-moderate colitis, and do not work in Crohn's; steroids do not control some 40% of the ulcerative colitis cases, and are not indicated for Crohn's; thiopurines are effective in the maintenance of the IBDs but do not prevent relapses on withdrawal; biologics are still being used empirically (not monitored) causing further increase of their cost over that of hospitalization. Against all these caveats, two simple rules still hold true: Strict adherence maintenance and avoidance of colitogenic drugs. This matter is expanded in this minireview.

Key words: Inflammatory bowel disease; Therapy; Cost containment; Budget; Treatment adherence; Inflammatory bowel disease managed care

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Core tip: Cost-effective maintenance of remission of inflammatory bowel diseases (IBD) is a traditionally unsolved challenge for care-takers and budget supervisors. The newly released (biologic) formulations, though purported to act as disease terminators, have failed to pay back their initial cost. We have faced the issue by reappraising initial simple tenets and found the following: (1) usually, uncomplicated IBD rests in remission by using cheap traditional drugs, provided the indication is correct, and, chiefly, that adherence is tightly maintained. Non compliant IBD patients cost manifold the compliant ones, and are the main cause of budget distortion; and (2) third-party drugs (nonsteroidal anti-inflammatory drugs, *e.g.*, should be avoided. A frozen steady-state is the regime to

effectively maintain IBD.

Actis GC, Pellicano R. Inflammatory bowel disease: Efficient remission maintenance is crucial for cost containment. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 114-119 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/114.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.114>

EPIDEMIOLOGY

The Italian health service does not cover medical expenses in full, but requires patients to partially contribute to extents that vary according to income and social positions. Patients suffering from chronic incurable disease including inflammatory bowel diseases (IBD) may apply for full coverage. Hence, the number of applications may yield an estimate of the prevalence of IBD in Italy. Such estimates, dating back to 2009^[1], are showing an IBD prevalence in Italy of 177-254 cases/10⁵. Regional incidence data of pooled Crohn's disease (CD) and ulcerative colitis (UC) yield figures between 2.7 and 13 cases per 10⁵ per year. A recently published Survey of Italian Gastroenterology Societies^[2] indicates that: (1) Despite a recent increase between 1970 and 1990, the incidence of IBD in Italy is still exceeded by the Northern Europe figures; (2) Pediatric incidence figures of both IBD phenotypes has gone up from 0.89 to 1.39 between 1996 and 2003; (3) With UC being slightly more frequent in males, general data confirm the existence of two incidence peaks, at 25/35 years and around the sixth life decade; and (4) An increased family risk, various extra-intestinal manifestations, and the association with immune-mediated disease (multiple sclerosis, psoriasis, and celiac disease just as examples) all mark the clinical IBD presentations.

MORBIDITY AND MORTALITY

Large population studies demonstrate that active IBD does significantly reduce quality of life, with young fertile women being mostly affected^[3,4]. In Italy, IBD-dependent disability is quantified in classes from the lowest 15% to the maximum of 70% (fourth class) if surgery has been needed. By contrast, IBD does not seem to significantly reduce life expectancy; notably, however, mortality is estimated to be increased in the first year of diagnosis as well as in patients younger than 30 years^[5].

ADMISSIONS

IBD patients do need hospitalization more frequently than the general population, with most of admissions ending in surgery. About 4.6%-7.5% of UC cases and 36% of CD patients become operated at 5 years. The figure is 17% for pediatric cases^[4].

THERAPEUTIC ARSENAL

There are two main challenges in the management of IBD, and these divide the list of the available drugs into two distinct chapters: induction of a response, and maintenance of the remission.

Mesalamines and its derivatives

Pioneered by Nanna Svartz studies on salazopyrin, mesalamines and its derivatives have been a mainstay for IBD treatment for the last 60 years. The modern version of salazopyrin, 5-aminosalicylic acid (5-ASA), has been tested in a large population study employing a range of doses between 1 and 4 daily g. Such dosages were shown to induce remission in 30% of the cases (12% for placebo); the figures rose to 80% if limiting the end-point to the clinical response^[6]. Looking at remission maintenance, a series of Cochrane studies have shown that each and all of the FDA-approved formulations can yield a 30% advantage over placebo^[7]. Mesalamines have proven not so readily effective for the treatment of CD. Initial data suggesting that daily 4 g could strongly reduce the Crohn's Disease Activity Index (CDAI) score vs placebo, achieving remission in 43% of the treated patients (placebo 18%) were not duplicated^[8].

Antibiotics

Some antibiotic molecules of the imidazole class have shown effectiveness in CD. A study already completed in 2005 showed that post-operative administration of ornidazole could reduce relapse rates from 37% to 7%^[9]. By contrast, UC has proven unresponsive to antibiotics^[10]. Ciprofloxacin and metronidazole are advantageous for CD; this issue is exhaustively illustrated in a freshly updated review^[11].

Corticosteroids

Population studies have shown that 34% and 44% of UC and CD patients, respectively, need a variable number of steroid courses to achieve remission^[12]; by contrast, steroids are contraindicated for remission maintenance.

Thiopurines

Experience achieved over the last 30 years has consistently indicated that thiopurines are effective in the maintenance of remission of both IBD phenotypes. A classic controlled study published in 1980, including steroid-dependent and/or fistulizing CD patients, showed that 31% experienced fistula closure, and 75% were weaned from steroids if treated with 6-mercaptopurine (6-MP); these figures were respectively 6% and 36% in the placebo-treated subgroup^[13]. By contrast, evidence favoring the use of thiopurines to treat UC has lingered a little behind: A recent study from us has shown that of 127 Italian patients who had had their azathioprine withdrawn, one-third, 50%, and two-thirds did relapse

at 12 mo, at 2 years, and at 5 years respectively^[14]. A significant added value of thiopurines has been documented in a recent Dutch study. This nationwide survey has shown that chronic thiopurine treatment significantly protects patients from developing colitic cancer^[15]. This breakthrough finding represents an authoritative correction of previous limited work that had claimed negative results^[16].

RESCUE TREATMENTS FOR REFRACTORINESS TO CONVENTIONAL DRUGS

Preliminary work published in 1990 showed that cyclosporine, a fungal derived peptide able to inhibit T-lymphocyte responses, could achieve remission in a significant proportion of patients facing colectomy for refractory acute UC^[17]. Later in 1994 such initial data were then confirmed in a controlled fashion^[18]. The number of refractory colitic patients that had received cyclosporine was estimated to reach the number of 700 in 2005^[19]. Interestingly, an English survey showed that only 7%-8% of all hospitalized IBD patients do receive cyclosporine; however, if asked whether they would opt to be treated, their positive responses often outweigh their own doctors' intentions^[20]. The literature consistently indicates that cyclosporine effectively avoids immediate colectomy in 60% to 80% of steroid refractory UC patients; subsequent ability to maintain remission may fall around 60%, and is potentiated by the concomitant administration of a thiopurine^[21]. In the suggestion of a leading center^[22] cyclosporine must be considered a mainstay treatment for refractory colitis. Along this line, we have recently reviewed the pharmacologic profiles of cyclosporine, mesalamine, and thiopurines on the basis of the experience of treatment of 100 consecutive patients between 1991 and 2007. We succeeded in confirming the data discussed above, and stressed the need for further efforts in the direction to improve the pharmacologic profile of these drugs^[23]. As of today, official position statements^[24] hold that cyclosporine is as effective as infliximab to control severe refractory colitis, whereas it is not indicated for Crohn disease.

Recent Cochrane reviews have shown that tumor necrosis factor (TNF)-inhibitors (chiefly infliximab and adalimumab) can effectively treat steroid-dependence and fistula formation in CD^[25]; similar but weaker evidence (owing to patient heterogeneity) have been published for UC^[26]. Such favorable evidence seems not to be reflected in real-world practice, whereby it is estimated that not more than 15% of candidate IBD patients do receive an anti-TNF molecule^[27]. A recent in-depth analysis conducted in Europe^[28] has found that the healthcare costs for IBD are mainly influenced by medication, chiefly anti-TNF molecules, despite the potential of these measures to restrict resort to hospitalization; notably, similar research carried out in Canada has come to the same conclusions^[29]. The

implications of such findings can probably be re-shaped by the evidence that in losers of response, replacement of a blind dose escalation with therapeutic drug monitoring (test-based strategy) can lead to major cost saving^[30].

THE IBDS: NATURAL HISTORY

Before the release of drugs such as mesalamines and steroids, and the availability of adequate resuscitation and surgical techniques, UC turned out to be a rather ominous disease: 33% risk of death in the first year; 12% mortality rate at relapse; the cumulative death risk 20 years following diagnosis was 40%; 40 years after diagnosis the colon carcinoma risk was 40%^[31]. The scenario of 1983^[32], namely 30 years after Truelove and Witts demonstration of the effectiveness of steroids had begun to change, contradictory areas persisted. The survival rate of those diagnosed with mild/moderate disease matched that of controls; yet, severe disease presentation still entailed mortality rates of 31% as distributed in the first 4 years. Nowadays, severe UC is expected to present with a frequency of 10-15% at any time of disease course: According to updated evidence the expected mortality is null, but sporadic fatal cases cannot be excluded^[33].

Some 50% to 80% of the patients run a waxing-and-waning course, whereas a chronic active course may be observed in 15%-30%^[34]. According to a reference publication: Young age, previous relapses, and presence of residual histologic disease (plasmacytosis) are all predictors of relapse^[35]. The frequencies of resort to surgery are reported to range between 9.6% after 5 years and 31% after 18 years^[36].

The natural history of CD is driven by disease localization and its strength to evolve. In population studies, a non-stenosing pattern, a stenosing pattern, and a penetrating course may be described with frequencies of 70%, 17%, and 13% respectively. In the follow-up, a switch to a stenosing pattern and to a penetrating one was recorded in 27% and 28% respectively. Some 50% of the patients did exhibit an ileal localization, an ileo-colic one by contrast affected the other half^[37].

The data of two population studies including some 600 patients were rewarding: 10%-30% of the cases may expect a relapse in the first year of diagnosis; 15%-25% linger in a condition of low disease activity, whereas remission might remain the outcome in 50%-65%. Resort to surgery is a likely outcome in CD: 30% probability in the first year; the patient majority undergoes an operation after 20 years of disease. Those with ileo-cecal disease are the most likely to undergo operation: Specifically, the risk of an emicolectomy is 35% after 10 years^[38,39].

THE BUDGET OF UC

According to a study of 1992, the annual cost per

patient was dollars 1488^[40]. The 24% of this sum included three items of 8% each: The diagnostic algorithm, the out-patient services, the drug cost; direct and indirect costs of hospitalization made the remaining 47%. Two further data are to be emphasized: In a sample observation year, 39% of the bills charged to providers had been meant to cover the needs of only 2% of the insured clients (the subset with the worst disease forms), whereas from another point of evaluation, the majority of the insured subjects were responsible for less than 7% of the costs.

This data are a spy of the heterogeneity of the sources of expense in an IBD population: As a general rule, firmly controlled disease costs dramatically less than the chronically uncontrolled presentations that often face surgery.

This trend of surgery to make the most part of the budget is further strengthened by several factors. The three-steps reconstructive proctocolectomy with pouch anal anastomosis has significantly benefited patients by ensuring digestive tract continuity, but, making the patient hospital-dependent for 6 mo, have raised the costs sky-high. One other factor is the natural tendency of the disease to worsen, to increase the need for drugs and care, and to become laden with complications, including neoplasia.

The need to aggressively maintain the disease in remission to minimize costs stems clear from the above discussion^[41]. To achieve this goal one may need a costly drug armamentarium (including biologic drugs in the last years) but most American providers do retain that this cost can be paid back by the advantages of managing a disease in remission. Direct costs (hospitalization) and indirect costs (drugs, sick leaves, family disruption) are to be chiefly accounted for in an unstable disease, and can be abolished by its stabilization^[42].

TWO MAIN FACTORS THREATENING REMISSION MAINTENANCE IN IBD

Lack of adherence

Among the main missions of private care systems relies the identification and control of conditions of major cost. The American health care system has long pursued this goal, eventually collecting a large wealth of data. The essential message is that disease management is mostly expensive in unstable phases^[43]. Lack of compliance has been identified as one of the capital factors in the loss of IBD remission. This matter may be discussed by differentiating four main topics: (1) The facts; (2) The causes and modalities of non-compliance; (3) The costs; and (4) Possible counter measures.

Facts: One hundred UC patients had mesalamine prescribed and were then followed prospectively for two years, with checkups at 6, 12, and 24 mo; the re-appearance of at least 4 bloody urgent stools a day was defined as relapse. Non-adherent patients showed

a 5-fold higher relapse rate; at 24 mo, 39% of non-adherent subjects were in remission, as opposed to 89% of adherent ones^[44]. IBD patients seem to be maximally keen at non-compliance, as suggested by the following data. The adherence percentages during clinical trials may attain 80%; this contrasts with data in population studies, whereby the majority of subjects in remission opt for taking the risk of relapse for non-compliance than to accept the burden of a daily drug administration^[45].

Causes and modalities: Pooled results from different studies indicated that favoring factors for non-adherence were a condition of male-single, and a left-sided colitis; a colonoscopy in the preceding 2 years and being married were opposing factors, instead^[46]. When requested to declare their reasons for non-adherence, the answers were: Forgetfulness (50%); too many daily administrations (30%); doubts on the indication (20%).

Costs: Non-adherence entails extra-costs: increased morbidity; rescue drugs are more expensive; risk for complications including cancer; sick leaves; stress and family disruption. In pure terms of numbers, one should bear in mind that any single failure of a mesalamine prescription costs dollars 11500 per person^[41].

Countermeasures: According to the experience of American health providers, patient counseling and release of single-dose drugs are the only worthy measures to reduce non-adherence.

Improper use of third-party drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics have long been suspected as factors of IBD reactivation or *de-novo* IBD causation. Recently, our attention got specifically concentrated on the role of macrolide antibiotics. Capable to favor gut colonization by *Candida*, these antibiotics might increase intestinal permeability, a favorable ground for IBD triggering^[47]. In our out-patient clinic, it has become routine to warn referring doctors and patients against the unjustified use of macrolide molecules or NSAIDs. Dental surgery and orthopedic traumatology remain the main indication source for these drugs, and merit careful surveillance by academic gastroenterology centers.

CONCLUSION

While the prevalence of IBD is roughly stable in the Western World, the figures are on the rise of its incidence in two other contexts: Pediatric IBD and migrants.

As an incurable chronic disorder capable to disable the GI tract, IBD can easily impact a country's budget. In moments of financial restriction, care providers may duly concentrate their attention on the list of "traditional therapies", seeking optimization (increasing therapeutic

effects while diminishing costs). Current evidence recommends now that this optimization path be based on the evidence that the easiest at maintenance and less costly are the quiescent phases of IBD. Thus, such phases are to be vigorously achieved and tenaciously maintained, adhering to the following rules: (1) Pursue remission by early giving steroids and/or mesalamines at full doses. Proceed to a prompt and rapid steroid tapering once clinical remission is achieved. Continue mesalamines in most of the cases; (2) Respecting safety rules, use thiopurines as the best option in maintaining remission, smartly minding the strong synergism that might develop with mesalamines, both in terms of therapeutic or toxic effects^[48]; (3) As said above, patients' compliance must strictly be monitored and corrected, as faulty compliance has been shown to be a strongly negative factor in remission maintenance and cost control; (4) Instruct family physicians and patients to carefully consider prescriptions of antibiotics and NSAIDs: Though some antibiotics may be therapeutic for IBD's, some other commonly prescribed formulations (macrolides) may activate or generate de-novo IBD, as NSAIDs can do^[49]; and (5) Bear in mind that average IBD can be controlled by the timely use of correctly dosed traditional molecules: Sometime the need for costly therapies is provoked by the late or inadequate use of common treatments^[50].

To give the reader an idea of how important it might be to fully exploit conventional therapies before resorting to biologic strategies, we like to implement the end of this paragraph by showing the cost for one day of treatment with the molecules mentioned in this text (expressed in euro) as reported by us in 2010^[51]: Mesalamine: 3.06; first-generation steroids: 1.02; thiopurines 0.87; infliximab/adalimumab: 894/1675.

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P- Reviewer: Hokama A, Ierardi E, Mulder CJJ **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Lu YJ



Case Control Study

Thiol/disulphide homeostasis in celiac disease

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Institutional review board statement: The study was designed around the 2013 Brazil version of the Declaration of Helsinki. It was approved by the Turkey Yuksek Ihtisas Training and Research Hospital Ethical Board Research Commission.

Informed consent statement: Written consent was taken from all participants who were included in the study.

Conflict-of-interest statement: The authors declared that there is no conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at dr.ihsanates@hotmail.com. No additional data are available.

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Manuscript source: Invited manuscript

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Received: November 30, 2016

Peer-review started: December 2, 2016

First decision: January 5, 2017

Revised: January 25, 2017

Accepted: March 12, 2017

Article in press: March 14, 2017

Published online: May 6, 2016

Abstract

AIM

To determine dynamic thiol/disulphide homeostasis in celiac disease and to examine the associate with celiac autoantibodies and gluten-free diet.

METHODS

Seventy three patients with celiac disease and 73 healthy volunteers were enrolled in the study. In both groups, thiol/disulphide homeostasis was examined with a new colorimetric method recently developed by Erel and Neselioglu.

RESULTS

In patients with celiac disease, native thiol ($P = 0.027$) and total thiol ($P = 0.031$) levels were lower, while disulphide ($P < 0.001$) level, disulphide/native thiol ($P < 0.001$) and disulphide/total thiol ($P < 0.001$) ratios were higher compared to the control group. In patients who do not comply with a gluten-free diet, disulphide/native thiol ratio was found higher compared to the patients who comply with the diet ($P < 0.001$). In patients with

any autoantibody-positive, disulphide/native thiol ratio was observed higher compared to the patients with autoantibody-negative ($P < 0.05$). It is found that there is a negative correlation between celiac autoantibodies, and native thiol, total thiol levels and native thiol/total thiol ratio, while a positive correlation is observed between disulphide, disulphide/native thiol and disulphide/total thiol levels.

CONCLUSION

This study is first in the literature which found that the patients with celiac disease the dynamic thiol/disulphide balance shifts through disulphide form compared to the control group.

Key words: Anti-gliadin antibodies; Anti-tissue transglutaminase antibody; Gluten-free diet; Oxidative stress; Thiol oxidation

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Core tip: To the best of our knowledge, for the first time in this study, total and native thiol levels in celiac patients were found lower compared to the control group while disulphide level, disulphide/total thiol and disulphide/native thiol ratios were found to be higher. Also, this study is first in which a negative correlation between celiac autoantibodies and native thiol, and total thiol levels and native thiol/total thiol ratio is observed while there is a positive correlation between disulphide level and disulphide/native thiol and disulphide/total thiol ratios.

Kaplan M, Ates I, Yuksel M, Ozderin Ozin Y, Alisik M, Erel O, Kayacetin E. Thiol/disulphide homeostasis in celiac disease. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 120-126 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/120.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.120>

INTRODUCTION

Celiac disease (CD), observed in genetically predisposed individuals, is a chronic/autoimmune disease of the small intestine, characterized by symptoms such as mucosal damage induced by gliadin, malabsorption, anemia, diarrhea and growth retardation^[1,2]. While environmental, genetic and immunological factors have a role in etio-pathogenesis of the disease, oxidative stress has also been proved to play a critical role in development of disease^[3,4].

With the development of diagnostic methods, gliadin and related toxic effects of prolamines on small intestine are understood better. Gluten peptides in enterocytes, particularly p31-43 α -gliadin peptides, induce certain signal transduction pathways by accumulating in lysosomes and increase the levels of oxidant radicals^[5]. Based on increased free radicals, a deterioration occurs in the oxidation redox equilibrium^[6]. At the first stage of

oxidative damage in cellular level based upon free radicals, disulphide (-S-S) linkages are formed by thiol groups (-SH) of amino acids such as sulfur containing cysteine and methionine being oxidized as well as the thiol/disulphide balance collapses in favor of disulphide^[7-12]. The resulting disulphide bonds are reduced to thiol groups and thiol reserves increase again. Through these reactions at the cellular level, dynamic thiol/disulphide homeostatic status is maintained^[13]. This dynamic equilibrium is considered to be effective in many cellular processes such as cell death and proliferation, and especially antioxidant balance^[14,15]. Due to these effects, there are certain studies showing that dynamic equilibrium collapses in cardiovascular diseases and cancer, the oxidative stress of which is particularly evident^[16-18].

Dynamic thiol/disulphide homeostasis began to be measured in an easy and repeatable way in 2014 by a new method developed by Erel *et al.*^[19] with high accuracy and sensitivity. In the literature review, we have not found any study examining dynamic thiol/disulphide homeostatic status in celiac patients using this new method.

In this study, we aimed to measure native thiol, total thiol, disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol levels in celiac patients with a new and fully automated method of analysis and determine dynamic thiol/disulphide homeostasis.

MATERIALS AND METHODS

Study population

This study was conducted in Turkey Yuksek Ihtisas Training and Research Hospital Gastroenterology Clinic and Ankara Numune Training and Research Hospital Internal Medicine Clinic between January and June 2015.

The study included a total of 146 participants including 73 celiac patients and 73 healthy volunteers. Celiac group is composed of first 73 celiac patients, over the age of 18, who admitted to the polyclinic for routine control. Patients that were diagnosed with CD *via* endoscopic biopsy and subject to regular follow-up in our clinic were included in the patient group in order of their applications. The healthy control group consisted of healthy volunteers, who have applied to our hospital for a check-up, without a chronic disease and drug use and those with similar demographic characteristics to the patient group.

Patients with known diabetes mellitus, kidney failure, malignancy, liver disease, thyroid disease, rheumatic disease, cardiovascular and cerebrovascular disease; smoking, alcohol consumption, vitamin supplements and unfollowed patients were excluded from the study.

In our clinic, the diagnosis of celiac disease in routine is made endoscopically with 2nd part duodenal biopsy and anti-gliadin antibody IgA-G or anti-tissue transglutaminase IgA-D positivity. Crypt hyperplasia, villus atrophy and submucosal lymphocytic infiltration is considered significant in the biopsy.

We created two subgroups (GCD: Patients non-

compliant with gluten free diet, GFD: Patients compliant with gluten free diet) to understand the effect of diet in oxidative stress in CD. Poor compliance to diet is defined as taking any kind of gluten containing materials. Patients' compliance to gluten diet is obtained from patient files and applied questionnaires. Patients that are compliant to gluten free diet from the beginning and for at least 5 years are included in GFD group.

Body mass index (BMI) was calculated by dividing body dry weight to the square of tall stature in meters ($\text{BMI} = \text{kg}/\text{m}^2$).

The study was conducted in accordance with the Declaration of Helsinki 2013 Brasil version and was approved by the Local Ethics Research Committee. All subjects provided written informed consent prior to participation in the study.

Biochemical parameters

For thiol/disulphide hemostasis tests, venous blood samples were drawn from patient and control groups after overnight fasting. Blood samples were swiftly centrifuged at 4000 rpm for 10 min, then plasma and serum samples were separated and stored at -80°C . Then all parameters were studied in the same session and in the same serum sample.

Laboratory parameters other than thiol/disulphide hemostasis parameters of the participants were their routine parameters at the time they were included in the study and those were recorded from patient files.

Thiol/disulphide homeostasis

Thiol/disulphide levels were measured by a newly developed, fully-automated and colorimetric method by Erel and Neselioglu^[19]. When disulphide levels were divided to native thiol and total thiol levels: Disulphide/native thiol and disulphide/total thiol ratios were obtained. When native thiol level was divided to total thiol level, native thiol/total thiol ratio was obtained as a result.

Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, United States) program was employed for statistical assessments. Kolmogorov-Smirnov test was utilized to determine the distribution of data. Continuous variables with normal distribution were expressed as mean \pm SD, and continuous variables without normal distribution were expressed as median (min-max). Categorical variables were presented in numbers and percentage. Continuous variables were compared to independent sample *t*-test or Mann-Whitney *U* test where necessary. The relationship between the numeric parameters was analyzed by Pearson and Spearman correlation analysis. In the examination of the relation between thiol/disulphide homeostasis parameters and celiac antibodies, the effects of demographic and clinical factors were adjusted by partial correlation. A $P < 0.05$ was considered significant for statistical

analyses.

RESULTS

The demographic characteristics and laboratory findings of all groups are summarized in Table 1. The study population consisted of a total of 146 patients, including 73 celiac patients (female/male: 58/15; age: 44.1 ± 13 years, BMI: $24.5 \pm 4.7 \text{ kg}/\text{m}^2$) and 73 controls (female/male: 55/18; age: 43.7 ± 13.6 years, BMI: $24.9 \pm 4.7 \text{ kg}/\text{m}^2$). There were no significant difference between two groups in terms of sex, age and BMI levels ($P > 0.05$). The median disease duration of followed celiac patients was determined as 6 years (min: 1 years, max: 25 years).

The mean total protein levels in celiac patients were determined similar to the control group ($P > 0.05$). In celiac patients, mean albumin ($4.4 \pm 0.3 \text{ g/L}$ vs $4.1 \pm 0.3 \text{ g/L}$, respectively; $P = 0.002$), median alanine aminotransferase (23 IU/L vs 20 IU/L , $P = 0.035$), aspartate aminotransferase (20 IU/L , etc., 17 IU/L , respectively; $P = 0.002$) and c-reactive protein (3.5 mg/L vs 1.2 mg/L , respectively, $P = 0.008$) levels were higher, compared to the control group.

Mean native thiol ($322.7 \pm 39.7 \text{ mmol/L}$ vs $339.6 \pm 51.3 \text{ mmol/L}$, respectively, $P = 0.027$) and total thiol levels ($343.7 \pm 41.9 \text{ mmol/L}$ vs $360.4 \pm 50.3 \text{ mmol/L}$, $P = 0.031$) were determined lower in celiac patients, compared to the control group, while native thiol/total thiol ratio did not differ significantly between the groups ($P > 0.05$). Mean disulphide level ($13.0 \pm 3.7 \text{ mmol/L}$ vs $10.2 \pm 3.9 \text{ mmol/L}$, respectively; $P < 0.001$), disulphide/native thiol ($3.8\% \pm 1.2\%$ vs $2.8\% \pm 1.1\%$, respectively, $P < 0.001$) and disulphide/total thiol ratio ($4.1\% \pm 1.4\%$ vs $2.9\% \pm 1.1\%$, respectively, $P < 0.001$) were determined higher in celiac patients compared to the control group.

According to dietary compliance and antibody positivity in the celiac group, the distribution of native thiol, total disulphide and disulphide/native thiol ratios were shown in detail in Table 2. According to this; in patients with dietary compliance, mean native thiol was higher ($327.9 \pm 35.6 \text{ mmol/L}$ vs $310.6 \pm 46.8 \text{ mmol/L}$, $P = 0.013$), mean disulphide ($12.0 \pm 3.3 \text{ mmol/L}$ vs $13.8 \pm 3.2 \text{ mmol/L}$, respectively; $P = 0.034$) level and disulphide/native thiol ratio ($3.5\% \pm 1.7\%$ vs $5.2\% \pm 1.4\%$, respectively, $P < 0.001$) were much lower compared to patients without dietary compliance. As for antibody positive patients, native thiol level was determined low, disulphide level and disulphide/native thiol ratio were determined higher.

The correlation analysis of native thiol, total thiol, disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol with demographic and clinical findings is shown in Table 3 in detail. Celiac autoantibodies displayed a negative correlation with native thiol, total thiol and native thiol/total thiol levels and a positive correlation with disulphide, disulphide/native thiol and disulphide/total thiol ratio. The relation

Table 1 Demographic characteristics and laboratory findings of study population

Variables	Celiac (n = 73)	Control (n = 73)	P value
Gender (male), n (%)	15 (20.5)	18 (24.7)	0.553
Age (yr)	44.1 ± 13	43.7 ± 13.6	0.866
BMI (kg/m ²)	24.5 ± 4.7	24.9 ± 4.7	0.867
Smoking, n (%)			
Non-smokers	49 (67.1)	50 (68.5)	
Smokers	18 (24.7)	17 (23.3)	0.981
Quit smoking	6 (8.2)	6 (8.2)	
Alcohol, n (%)	2 (2.7)	-	-
Duration of disease (yr)	6 (1-25)	-	-
Total protein (g/L)	7.4 ± 0.6	7.4 ± 0.5	0.964
Albumin (g/L)	4.4 ± 0.3	4.1 ± 0.3	0.002 ^a
ALT (IU/L)	23 (8)	20 (7)	0.035 ^a
AST (IU/L)	20 (12)	17 (9)	0.002 ^a
CRP (mg/L)	3.5 (8.4)	1.2 (2)	0.008 ^a
Native thiol (μmol/L)	322.7 ± 39.7	339.6 ± 51.3	0.027 ^a
Total thiol (μmol/L)	343.7 ± 41.9	360.4 ± 50.3	0.031 ^a
Disulphide (μmol/L)	13.0 ± 3.7	10.2 ± 3.9	< 0.001 ^a
Disulphide/native thiol (%)	3.8 ± 1.2	2.8 ± 1.1	< 0.001 ^a
Disulphide/total thiol (%)	4.1 ± 1.4	2.9 ± 1.1	< 0.001 ^a
Native thiol/total thiol (%)	93.8 ± 2.6	94.3 ± 5.7	0.553

^aP < 0.05. BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein.

Table 2 Dietary compliance of native thiol, disulphide and disulphide/native thiol and its distribution regarding antibody positivity

Variables	Native thiol (μmol/L)	P value	Disulphide (μmol/L)	P value	Disulphide/native thiol (μmol/L)	P value
Diet						
GCD (n = 22)	310.6 ± 46.8	0.013 ^a	13.8 ± 3.2	0.034 ^a	5.2 ± 1.4	< 0.001 ^a
GFD (n = 51)	327.9 ± 35.6		12.0 ± 3.3		3.5 ± 1.7	
AGA-IgA						
(-) (n = 33)	310.5 ± 39.5	0.015 ^a	14.1 ± 3.7	0.020 ^a	4.7 ± 1.9	0.005 ^a
(+) (n = 40)	333.8 ± 40.1		12.0 ± 3.8		3.6 ± 1.4	
AGA-IgG						
(-) (n = 47)	308.5 ± 36.8	0.027 ^a	13.9 ± 3.1	0.001 ^a	4.6 ± 1.7	< 0.001 ^a
(+) (n = 26)	330.5 ± 45.2		11.1 ± 3.9		3.0 ± 1.1	
Anti-t TGA						
(-) (n = 29)	315.5 ± 38.2	0.001 ^a	13.9 ± 3.9	0.019 ^a	4.5 ± 1.9	0.007 ^a
(+) (n = 44)	346.2 ± 40.5		11.7 ± 3.8		3.4 ± 1.5	
Anti-t TGG						
(-) (n = 61)	318.1 ± 37.6	0.002 ^a	13.5 ± 3.9	0.009 ^a		0.035 ^a
(+) (n = 12)	345.3 ± 51.5		10.3 ± 3.0			

^aP < 0.05. GCD: Gluten-containing diet; GFD: Gluten-free diet; AGA-IgA: Anti gliadin antibodies IgA; AGA-IgG: Anti gliadin antibodies IgG; Anti-t TGA: Anti-tissue Transglutaminase IgA antibodies; Anti-t TGG: Anti-tissue Transglutaminase IgA antibodies.

between thiol/disulphide homeostasis parameters and celiac autoantibodies were observed to continue even when the effects of demographic and clinical findings were removed.

C-reactive protein level displayed a negative correlation with native thiol, total thiol and native thiol/total thiol levels, and a positive correlation between disulphide, disulphide/native thiol, disulphide/total thiol levels.

DISCUSSION

To our knowledge, for the first time in this study, total and native thiol levels in celiac patients were

determined lower compared to the control group while disulphide level, disulphide/total thiol and disulphide/native thiol ratios were found to be higher. Also this is the first study to determine a negative correlation of celiac autoantibodies with native thiol and total thiol levels with native thiol/total thiol ratio, and a positive correlation of disulphide level with disulphide/native thiol and disulphide/total thiol ratios.

Celiac disease is a disease characterized by the inflammatory response created by intestinal mucosa based upon gliadin peptides taken with gluten containing food and consequently mucosal inflammation, crypt hyperplasia and villus atrophy^[20]. The most important factor in etiopathogenesis of the disease is considered

Table 3 Findings related to thiol/disulphide hemostasis parameters in celiac patient group

Variables	Native thiol		Total thiol		Disulphide		Disulphide/total thiol		Disulphide/native thiol		Native thiol/total thiol	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Age	0.261	0.026 ^a	0.262	0.025 ^a	-0.041	0.729	-0.132	0.264	-0.122	0.302	0.021	0.861
BMI	0.19	0.107	0.187	0.114	-0.033	0.783	-0.096	0.421	-0.113	0.34	0.045	0.702
Total protein	-0.032	0.786	0.005	0.97	0.059	0.618	0.032	0.787	0.086	0.472	-0.156	0.187
Albumin	0.009	0.937	0.025	0.835	-0.037	0.754	-0.065	0.582	-0.040	0.735	-0.071	0.548
AST	0.051	0.666	0.046	0.702	-0.03	0.801	-0.057	0.631	-0.031	0.796	0.033	0.781
ALT	-0.091	0.444	-0.116	0.329	-0.063	0.598	-0.012	0.919	0.002	0.985	0.094	0.427
CRP	-0.327	0.018 ^a	-0.304	0.038 ^a	0.369	0.015 ^a	0.287	0.043 ^a	0.332	0.029 ^a	-0.244	0.038 ^a
AGA-IgA	-0.325	0.009 ^a	-0.266	0.035 ^a	0.384	0.024 ^a	0.324	0.010 ^a	0.325	0.009 ^a	-0.266	0.035 ^a
AGA-IgG	-0.332	0.008 ^a	-0.271	0.022 ^a	0.298	0.010 ^a	0.297	0.011 ^a	0.253	0.031 ^a	-0.279	0.017 ^a
Anti-t TGA	-0.342	0.007 ^a	-0.28	0.017 ^a	0.305	0.009 ^a	0.311	0.004 ^a	0.280	0.035 ^a	-0.294	0.028 ^a
Anti-t TGG	-0.35	0.00 ^a	-0.316	0.004 ^a	0.315	0.007 ^a	0.34	0.001 ^a	0.302	0.014 ^a	-0.304	0.019 ^a
AGA-IgA ¹	-0.313	0.006 ^a	-0.301	0.026 ^a	0.334	0.004 ^a	0.353	< 0.001 ^a	0.315	0.011 ^a	-0.319	0.013 ^a
AGA-IgG ¹	-0.335	0.004 ^a	-0.324	0.005 ^a	0.309	0.018 ^a	0.366	0.023 ^a	0.349	0.033 ^a	-0.288	0.045 ^a
Anti-t TGA ¹	-0.261	0.043 ^a	-0.243	0.035 ^a	0.376	0.036 ^a	0.322	0.011 ^a	0.335	0.009 ^a	-0.273	0.038 ^a
Anti-t TGG ¹	-0.333	0.032 ^a	-0.282	0.037 ^a	0.294	0.031 ^a	0.305	0.026 ^a	0.336	0.036 ^a	-0.314	0.013 ^a

^a*P* < 0.05. ¹Demographic characteristics and laboratory parameters are adjusted. BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; AGA-IgA: Anti gliadin antibodies IgA; AGA-IgG: Anti gliadin antibodies IgG; Anti-t TGA: Anti-tissue Transglutaminase IgA antibodies; Anti-t TGG: Anti-tissue Transglutaminase IgA antibodies.

to be environmental factors such as gliadin and the autoimmune response against them. Although the role of oxidative stress in the etiopathogenesis of the disease is unknown, in studies conducted with different cell models, intracellular oxidative imbalance occurs as a result of gliadin exposure and oxidant radicals are formed as a result of lipid peroxidation^[21]. These oxidant radicals have been shown to form -S-S bonds by oxidizing -SH groups found in the side chain of sulfur containing amino acids and consequently increase oxidized metabolites in the cell^[22]. In this case thiol/disulphide equilibrium, which is balanced under physiological conditions, is weakened and disrupted in favor of disulphide form. As a result of all these reactions, cell morphology, membrane permeability and vital cellular activities such as apoptosis and cell proliferation are disrupted^[1,5].

There are certain studies in the literature investigating thiol and disulphide amounts in low molecular thiol compounds that constitute a small portion of total body thiol pool such as cysteine, glutathione (GSH) and oxidized glutathione thiol^[23,24]. Until 2014, any colorimetric method that measures total thiol and disulphide amount in the body had not yet been developed. But Erel *et al*^[19] developed a fully-automated method in 2014, by which total thiol, native thiol and disulphide amounts can be measured easily and repetitively with high sensitivity and specificity.

We have not found any study in the literature examining dynamic thiol/disulphide balance in celiac disease. However, there are studies conducted with low molecular weight thiol compounds. Stojiljković *et al*^[25] have shown that in intestinal tissues of celiac patients in the pediatric age group, GSH level that constitutes a big part of intracellular thiol content decreases and lipid hydroperoxide level which is an oxidant substance that plays a role in cell membrane damage increases. These results have indicated that GDH redox cycle is disrupted in celiac patients. In a

study conducted with asymptomatic celiac patients by Odetti *et al*^[6] oxidant radicals derived from protein (carboxyl groups) and lipids (thiobarbituric acid-reactive substances) were determined high.

In our study, total and native thiol levels in celiac patients were determined lower compared to the control group; disulphide level, disulphide/total thiol and disulphide/native thiol ratios were found to be higher and eventually dynamic equilibrium was observed to shift to disulphide form. This case may be due to high levels of oxidant radicals in celiac disease. Our hypothesis is supported by the two studies mentioned above, in which the level of oxidant radicals increase in celiac patients. The increase in the level of oxidant radicals in celiac disease may be due to two cases. Firstly, the disease being a chronic inflammatory disease and secondly, being an autoimmune disease. Previously many studies have indicated that oxidant radicals increase in inflammatory/autoimmune diseases and accordingly oxidative stress level increases^[26-28].

For instance, Nanda *et al*^[29] have determined that in autoantibody positive hypothyroidis patients, levels of oxidant radicals are higher compared to those with autoantibody negative and observed a positive correlation between autoantibodies and oxidant radicals. Determining a positive correlation of C-reactive protein and celiac autoantibodies with disulphide/native thiol level and determining the disulphide form significantly high in autoantibody positive celiac patients strongly supports our thesis.

Another reason for determining low thiol reserve in celiac patients compared to the control group may be due to lack of thiol-containing food intake based upon deteriorated intestinal mucosa. However determining disulphide form and albumin level higher in celiac group compared to the control group indicates that this abnormal

thiol/disulphide equilibrium in celiac patients is not due to lack of oral intake but rather to oxidative stress.

In our study, disulphide/native thiol ratio was determined higher in patients who do not comply with gluten diet compared to those who comply with the diet. We think that this case could be associated with inflammation. Because previous studies have indicated that inflammation is higher in patients who do not comply with gluten diet than those who comply with diet^[30,31]. Another reason may be due to the significant increase in oxidative stress based upon gliadin toxicity in patients who do not comply with gluten diet^[21].

The main limitation of our study is its cross-sectional design and that repetitive measurements have not been done in the patient group. The other limitation is that the information whether participants in the control group have taken thiol containing nutrients or not, is only limited to anamnesis.

For the first time in this study, thiol/disulphide balance was shown to shift towards disulphide form in celiac patients, compared to the control group. Also this is the first study to examine the effects of celiac autoantibodies and gluten-free diet on dynamic thiol/disulphide equilibrium. According to all these results, disrupted thiol/disulphide equilibrium in celiac patients was thought to be associated with autoimmunity and inflammation. In order these results to be clarified, further studies are required to examine the association between thiol/disulphide homeostasis parameters and proinflammatory cytokines that play an active role in celiac disease.

COMMENTS

Background

Celiac disease (CD), observed in genetically predisposed individuals, is a chronic/autoimmune disease of the small intestine, characterized by symptoms such as mucosal damage induced by gliadin, malabsorption, anemia, diarrhea and growth retardation.

Research frontiers

Dynamic thiol/disulphide homeostasis began to be measured in an easy and repeatable way in 2014 by a new method developed by Erel and his colleagues with high accuracy and sensitivity.

Innovations and breakthroughs

The authors to measure native thiol, total thiol, disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol levels in celiac patients with a new and fully automated method of analysis and determine dynamic thiol/disulphide homeostasis.

Applications

Disrupted thiol/disulphide equilibrium in celiac patients was thought to be associated with autoimmunity and inflammation. In order these results to be clarified, further studies are required to examine the association between thiol/disulphide homeostasis parameters and proinflammatory cytokines that play an active role in CD.

Peer-review

In the present paper, entitled "Thiol/disulphide homeostasis in celiac disease", Kaplan *et al* measured thiol/disulphide homeostasis, an indirect evaluation for oxidative stress, in patients with CD.

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P- Reviewer: Ierardi E, Tarocchi M **S- Editor:** Qi Y **L- Editor:** A
E- Editor: Lu YJ



Observational Study

Correlation of rapid point-of-care vs send-out fecal calprotectin monitoring in pediatric inflammatory bowel disease

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Author contributions: Rodriguez A and Yokomizo L contributed equally to this work; Park KT conceptualized the study; Rodriguez A, Yokomizo L, Christofferson M, Barnes D, Khavari N and Park KT participated in sample analysis and assisted in the logistics of the study; Rodriguez A, Yokomizo L and Park KT participated in the statistical analysis, wrote the manuscript and approved the final manuscript draft; Christofferson M, Barnes D and Khavari N edited and approved the final manuscript draft.

Institutional review board statement: This study had IRB approval from Stanford University.

Informed consent statement: Informed consent and assent forms were obtained prior to patient enrollment.

Conflict-of-interest statement: KT Park has served as consultant for Inova Diagnostics and received research support from BUHL MANN Laboratories.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: May 25, 2016

Peer-review started: May 27, 2016

First decision: July 22, 2016

Revised: December 21, 2016

Accepted: January 16, 2017

Article in press: January 18, 2017

Published online: May 6, 2017

Abstract**AIM**

To assess the correlation between the send-out enzyme-linked immuno sorbent assay (ELISA) and the point-of-care (POC) calprotectin test in pediatric inflammatory bowel disease (IBD) patients.

METHODS

We prospectively collected stool samples in pediatric IBD patients for concomitant send-out ELISA analysis and POC calprotectin testing using the Quantum Blue® (QB) Extended immunoassay. Continuous results between 17 to 1000 µg/g were considered for comparison. Agreement between the two tests was measured by a Bland-Altman plot and statistical significance was determined using Pitman's test.

RESULTS

Forty-nine stool samples were collected from 31 pediatric IBD patients. The overall means for the rapid and ELISA tests were 580.5 and 522.87 µg/g respectively. Among the 49 samples, 18 (37.5%) had POC calprotectin levels

of ≤ 250 $\mu\text{g/g}$ and 31 (62.5%) had levels > 250 $\mu\text{g/g}$. Calprotectin levels ≤ 250 $\mu\text{g/g}$ show good correlation between the two assays. Less correlation was observed at quantitatively higher calprotectin levels.

CONCLUSION

In pediatric IBD patients, there is better correlation of between ELISA and POC calprotectin measurements at clinically meaningful, low-range levels. Future adoption of POC calprotectin testing in the United States may have utility for guiding clinical decision making in real time.

Key words: Calprotectin; Stool biomarker; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Point-of-care test

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Core tip: Quantitative fecal calprotectin (FC) measurements, particularly in children affected by inflammatory bowel disease (IBD), is an important element of disease monitoring in a patient population vulnerable to repeated endoscopic confirmation of mucosal healing. In the United States, rapid FC assays are not yet Food and Drug Administration approved, and send-out FC assays require processing delay, preventing point-of-care usefulness. The significance of our findings in this study reiterate the clinical utility of the point-of-care FC testing in children with IBD, who are at-risk for subclinical mucosal-level inflammation. Our study confirms good correlation between the send-out and rapid point-of-care FC tests at the clinically-meaningful target range (≤ 250 $\mu\text{g/g}$) associated with endoscopic remission.

Rodriguez A, Yokomizo L, Christofferson M, Barnes D, Khavari N, Park KT. Correlation of rapid point-of-care vs send-out fecal calprotectin monitoring in pediatric inflammatory bowel disease. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 127-130 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/127.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.127>

INTRODUCTION

Reliable mucosal-level monitoring of inflammatory bowel disease (IBD) is important for appropriate disease management response. Although endoscopy remains the current gold standard for mucosal-level evaluation, the invasive nature, anesthesia requirement, and potential for procedure-related complications including bowel perforations are valid considerations for pediatric IBD patients to be disease-monitored using non-invasive stool biomarkers^[1].

As the strength of evidence for longitudinally monitoring IBD using serial calprotectin measurements is emerging, most clinical laboratories in the United States do not analyze fecal calprotectin in-house and require quantification *via* a send-out method. As a result, cal-

protectin measurement by the traditional enzyme-linked immunosorbent assay (ELISA) can be time intensive, potentially leading to delays in clinical decision-making - especially in children with IBD who may have discordance of biochemical markers (*e.g.*, CRP) with subjective assessments of disease activity (*e.g.*, abdominal pain).

Rapid fecal calprotectin testing, using immuno-chromatographic assays, could overcome this time delay and can result in point-of-care (POC) calprotectin measurements within minutes. One POC test - Quantum Blue® Extended immunoassay (Bühlmann Laboratories, Switzerland) - is approved for clinical use in Europe, Canada, and countries in Asia and South America. While there are a few studies showing good correlation of this particular assay with an ELISA test in mainly an adult, IBD and non-IBD cohort^[2,3], there is only one European study to our knowledge assessing the strength of correlation for POC testing with the standard ELISA in children with IBD. In the United States, POC calprotectin testing is not yet Food and Drug Administration (FDA) approved at this time for clinical use^[4]. We aimed to assess the correlation between the send-out ELISA and the POC calprotectin test in pediatric IBD patients.

MATERIALS AND METHODS

This was a Stanford University IRB approved prospective study conducted from October 2014 to May 2015. In previously diagnosed pediatric IBD patients who were being assessed for routine fecal calprotectin levels, their tested stool sample was also analyzed for calprotectin using the Quantum Blue® POC test. Informed consent by the parent or legal guardian was required for participation. During standard of care inpatient and outpatient encounters, fecal samples were collected from patients by our hospital laboratory for processing and sent to one centralized laboratory for ELISA analysis (Genova Diagnostics, NC, United States). No samples were collected from patients undergoing colonic cleanout. ELISA results were reported back within 10-14 d as $\mu\text{g/g}$ within a continuous range of < 17 to 2500 $\mu\text{g/g}$. Results > 1000 were recorded as 1000 to match the range of the POC calprotectin test.

For POC calprotectin testing, stool samples (1 g) were extracted using the CALEX® cap device by unscrewing the cap and inserting it into the stool sample. The collection stick was removed with 1 g of adhering stool and inserted into the collection container that contained the antibody reagent. The device was then vigorously homogenized using a vortex mixer, and 60 μL of the mixed sample was placed in the QB test cartridge and loaded into the reader. After 12 min, the test cartridge was read and displayed the amount of FC present in the sample. The results were reported as $\mu\text{g/g}$ with a continuous range of < 30 to 1000 $\mu\text{g/g}$. From stool extraction to results, the test required approximately 15 min to complete.

Previous studies and clinical experience have indicated that calprotectin ≤ 250 $\mu\text{g/g}$ correlates with lower disease activity at the mucosal-level on endoscopic evaluation^[5-7].

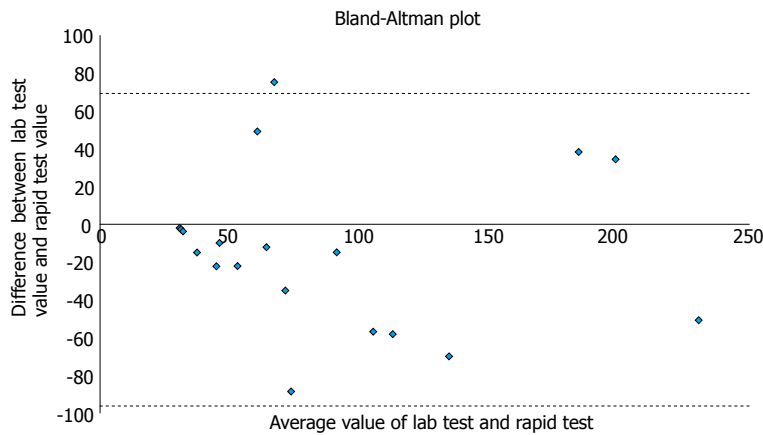


Figure 1 Bland-Altman plot for calprotectin values ≤ 250 $\mu\text{g/g}$. Pitman's test showed $r = 0.072$, with the value close to zero indicating good concordance between the two tests ($P = 0.779$).

Table 1 Patient characteristics n (%)

	Total (%)	FC ≤ 250 $\mu\text{g/g}$	FC > 250 $\mu\text{g/g}$
Samples	49	21 (43)	28 (57)
Age (yr)	12.8	13.3	12.4
Diagnosis			
CD	21 (43)	9 (43)	12 (43)
UC	22 (45)	10 (48)	12 (43)
IBD-U	6 (12)	2 (9)	4 (14)
Gender			
Male	24 (49)	8 (38)	16 (57)
Female	25 (51)	13 (62)	12 (43)
CRP (mg/dL)	2.29	1.12	3.31
ESR (mm/h)	25.54	13.09	34.23

CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; IBD-U: IBD-unclassified; FC: Fecal calprotectin; CRP: C-reactive protein.

Therefore, we were particularly interested in the strength of correlation between the ELISA and POC calprotectin test within this lower range of values. Agreement between the two tests was measured by a Bland-Altman plot and statistical significance was determined using Pitman's test in STATA 12.1 (StataCorp, College Station, TX, United States).

RESULTS

From routine inpatient or outpatient care, 49 stool samples were collected from 31 pediatric IBD patients (Table 1). The overall means for the rapid and ELISA tests were 580.5 $\mu\text{g/g}$ and 522.87 $\mu\text{g/g}$ respectively. Among the 49 samples, 18 (37.5%) had POC calprotectin levels of ≤ 250 $\mu\text{g/g}$ and 31 (62.5%) had levels > 250 $\mu\text{g/g}$.

Among samples resulting in ≤ 250 $\mu\text{g/g}$, mean calprotectin levels were 74.1 $\mu\text{g/g}$ from the ELISA and 86.2 $\mu\text{g/g}$ from the POC calprotectin, a mean difference of 12.0 $\mu\text{g/g}$. Among samples resulting in > 250 $\mu\text{g/g}$, mean calprotectin levels were 783.5 $\mu\text{g/g}$ from the ELISA and 867.6 $\mu\text{g/g}$ from the POC calprotectin test, a mean difference between of 84.1 $\mu\text{g/g}$.

In order to test whether these differences were significant, we used a Bland-Altman plot, graphing the difference between the two test values against their mean

value (Figure 1). Pitman's test was used to determine if there was a correlation between the two values.

For values ≤ 250 $\mu\text{g/g}$, Pitman's test showed $r = 0.072$, with the value close to zero indicating good concordance between the two tests; further, $P = 0.779$, confirming that we cannot reject the null hypothesis of equal variances. For values > 250 $\mu\text{g/g}$ (not graphed), the $r = 0.109$, suggesting that higher absolute values have less correlation between ELISA and POC tests, although the test of significance supported the null hypothesis $P = 0.564$.

DISCUSSION

Our prospective cohort study showcases the reliability of a POC calprotectin test that is currently being used in routine clinical care in Europe and Canada but not yet approved in the United States. While we acknowledge the limited sample size, the data from our study show good correlation between send-out ELISA and POC calprotectin tests. We show that agreement between the two tests appears to be stronger for lower values - a finding that is corroborated by Kolho *et al*^[8] in a pediatric IBD cohort. Of note, our investigation used a classical statistical method in the Bland-Altman plot which descriptively and quantitatively showcases the strength of correlation between the two tests.

Our results also agree with previous studies that showed increased inter-test variability at higher calprotectin levels - with greater divergence from expected values above 250 $\mu\text{g/g}$ ^[9,10]. In order to optimize the utility of our study despite our limited sample size, we focused our analysis around values ≤ 250 $\mu\text{g/g}$ since literature in IBD cohorts supports endoscopic disease quiescence at or below 300 $\mu\text{g/g}$ cut-off level. Targeting low-range levels appear to be the clinical goal in calprotectin monitoring.

We also found that values of the POC test were overall higher than the values obtained from ELISA, although the Pitman's tests indicate that this difference was not statistically significant. Several previous studies from Europe and Asia demonstrate excellent correlation of a rapid assay similar to the one used in this study to ELISA^[8,11], but they do not showcase the differential strength of correlation at low vs high calprotectin levels.

In summary, we present the first correlation study of rapid POC calprotectin testing in a pediatric IBD cohort in the United States. Unlike the conventional send-out ELISA which typically takes 10-14 d to result, the future clinical use of POC calprotectin could improve the utility in the decision-making process if levels were available at or near the time of actual care.

COMMENTS

Background

Rapid fecal calprotectin (FC) assays are useful for point-of-care decision making in inflammatory bowel disease (IBD), particularly in children. Within-patient correlation data between send-out and rapid point-of-care FC tests are incomplete in pediatric IBD.

Research frontiers

Repeated measurements of low FC in patients with IBD are associated with endoscopic remission, although more data are necessary to confirm optimal cut-off levels for different patients with various IBD subtypes. A target range of ≤ 250 $\mu\text{g/g}$ is often used in clinical practice.

Innovations and breakthroughs

This study confirms good correlation between the send-out and rapid point-of-care FC tests at the clinically-meaningful target range (≤ 250 $\mu\text{g/g}$) associated with endoscopic remission.

Applications

Ensuring low levels of FC using the rapid point-of-care FC assay in children affected by IBD appear to be reliable and useful in clinical practice.

Peer-review

This is a well done prospective study about the comparison of two types of fecal calprotectin diagnostic methods as possible markers for assessment the pediatric IBD disease severity.

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P-Reviewer: Homan M, Posovszky C, Wedrychowicz A
S-Editor: Gong ZM **L-Editor:** A **E-Editor:** Lu YJ



Observational Study

Clinical and economic impact of infliximab one-hour infusion protocol in patients with inflammatory bowel diseases: A multicenter study

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Institutional review board statement: The study was reviewed and approved by the Ethical Committee of the Participating Centres.

Informed consent statement: All study participants, or their legal tutor, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflicts of interests. None of the authors have any financial or other relations that could lead to a conflict of interest.

Data sharing statement: No additional data are available.

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Manuscript source: Invited manuscript

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Received: September 5, 2016

Peer-review started: September 5, 2016

First decision: October 20, 2016

Revised: December 30, 2016

Accepted: January 16, 2017

Article in press: January 18, 2017

Published online: May 6, 2017

Abstract**AIM**

To assess the impact of short infliximab (IFX) infusion on hospital resource utilization and costs.

METHODS

All inflammatory bowel diseases (IBD) patients who received IFX 1 h infusion from March 2007 to September 2014 in eight centers from Southern Italy were included in the analysis. Demographic, clinical and infusion related data were collected. The potential benefits related to the short infusion protocol were assessed both in terms of time saving and increased infusion unit capacity. In addition, indirect patient-related cost savings were evaluated.

RESULTS

One hundred and twenty-five patients were recruited (64 with ulcerative colitis and 61 with Crohn's disease). Median duration of disease was of 53 mo and mean age of pts at diagnosis was of 34 years (SD: ± 13). Adverse infusion reactions were reported in less than 4% both before and after short infusion. The total number of infusions across the selected centers was of 2501 (30.5% short infusions). In the analyzed cohort, 1143 h were saved (762 in the infusion and 381 in observation phases) through the rapid IFX infusion protocol. This time saving (-15% compared to the standard protocol in infusion phase) represents, from the hospital perspective, an opportunity to optimize infusion unit capacity by allocating the saved time in alternative cost-effective treatments. This is the case of opportunity cost that represents the value of forgone benefit which could be obtained from a resource in its next-best alternative use. Hence, an extra hour of infusion in the case of standard 2-h IFX represents a loss in opportunity to provide other cost effective services. The analysis showed that the short infusion increased the infusion units capacity up to 50% on days when the IFX infusions were scheduled (infusion phase). Furthermore, the analysis showed that the short IFX infusion protocol leads to time savings also in the post-infusion phase (observation) leading to a time saving of 10% on average among the analyzed centers. Finally, the short infusion protocol has been demonstrated to lead to indirect cost savings of €138/patient (average -€17.300 on the whole cohort).

CONCLUSION

A short IFX infusion protocol can be considered time and cost saving in comparison to the standard infusion protocol both from the hospital's perspective, as it contributes to increase infusion units capacity, and the patients' perspective, as it reduces indirect costs and the impact of treatment on everyday life and work productivity.

Key words: Infliximab; One-hour infusion; Cost savings; Economic impact; Multicenter study

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Core tip: Infliximab (IFX) is a monoclonal antibody anti-tumour necrosis factor used in the treatment of moderate-to-severe inflammatory bowel diseases refractory to conventional therapy. It is usually administered *i.v.* at a dose of 5 mg/kg as a 2-h infusion. Shortening the infusion

protocol to 1 h is equally safe and positively affects quality of life. This paper analyzes the impact of short IFX infusion on hospital resource utilization and costs, both in terms of time saving and increased infusion unit capacity. In addition, we provide evidence of indirect patient-related cost savings.

Viola A, Costantino G, Privitera AC, Bossa F, Lauria A, Grossi L, Principi MB, Della Valle N, Cappello M. Clinical and economic impact of infliximab one-hour infusion protocol in patients with inflammatory bowel diseases: A multicenter study. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 131-136 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/131.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.131>

INTRODUCTION

Infliximab (IFX) is a chimeric monoclonal antibody anti-tumour necrosis factor (anti-TNF) effective in inducing and maintaining remission of moderate to severe luminal and fistulizing Crohn's disease (CD)^[1,2] and of moderate to severe refractory ulcerative colitis (UC)^[3]. It is also used to treat rheumatoid arthritis and moderate to severe psoriasis^[4,5]. IFX is usually administered intravenously at a dose regimen of 5 mg/kg as a 2-h infusion followed by a monitoring time of 2 h thereafter^[6-8]. This standard practice has been adopted in order to minimize infusion reactions, which are known to occur during infusion and later in the immediate post infusion period^[9]. However, the standard practice has a significant impact in the setting of limited healthcare resource in terms of dedicated areas (infusion units), facilities and, mostly, time. Short infusion (1-h) protocols have been found safe in patients with rheumatoid arthritis^[10]. Recently, a shorter infusion time of one hour has been used also in inflammatory bowel diseases (IBD) patients, in maintenance therapy and who tolerated a 2-h infusion without adverse events, in referral centers^[11,12]. Tolerability of one hour infusion has also been reported for 10 mg/kg IFX^[13]. One hour infusions are less time-consuming and might be considered in clinical practice to improve patients' quality of life and compliance to IFX therapy^[14]. Moreover, infusion therapy is also costly for patient in terms of expenses related to travel to the hospital and of hours spent in the infusion clinic (work loss). At present evidence on cost savings of short infusion is scanty. We have previously confirmed in a pilot study^[15] that shortening the infusion protocol to 1 h is equally effective and safe than standard protocol. The aim of the present study was to assess the impact of short IFX infusion on hospital resource utilization and costs in a multicenter study from eight referral centers in Italy.

MATERIALS AND METHODS

All patients who received 1 h infusion of IFX from

Table 1 Traditional *vs* short infusion protocols time duration

	Traditional infusion (min)	Short infusion (min)
Observation phase	90	60
Infusion phase	120	60
Total minutes	210	120
Total hours	3.5	2

March 2007 to September 2014 in eight centers from Southern Italy were included in the analysis. Written informed consent was obtained prospectively from each patient. For each patient, demographic, clinical and infusion related data were collected retrospectively on a shared dedicated database (Excel). All patients received the dose of 5 mg/kg. Optimization of therapy was achieved by shortening the interval between infusions.

On the basis of available data, the potential benefits related to the short infusion protocol were considered both in terms of potential time saving and increased infusion unit capacity. As there was no difference in terms of drug costs, nursing and specialist service costs in both protocols, it was not possible to assess the short infusion protocol impact in direct costs terms. Instead, it was possible to estimate the related productivity loss/gain of the two different protocols. Indirect costs were expressed in terms of working hours lost due to the infusion. Indirect costs were calculated on the basis of productivity lost according to the human capital approach. The value was collected through available literature^[16]. In particular, the indirect costs were calculated by multiplying infusion hours by work/hour/loss in order to assess the difference between the two different protocols. Details on infusion time for both protocols are reported in Table 1. Furthermore, we assessed the impact related to the short infusion protocol on the units capacity in term of number of treated patients; a questionnaire was sent to the participating centers to collect data on the number of patients submitted to IFX infusion/day by adopting the short infusion schedule which was compared with the same data when a standard infusion time was used. This comparison was possible just in one center (University Hospital Palermo); because of different work organization, this value was not available in other centers. Continuous variables were expressed as mean \pm standard deviation, and categorical variables as absolute frequency and percentage. The comparison between continuous variables was made by the Student *t*-test and categorical variables were analysed by using the chi-square test. Statistical significance was reached when *P* was < 0.05. Data were analyzed using the statistics software SPSS version 15.0.

RESULTS

A total of 125 patients with IBD were included in the study, 64 with UC and 61 with CD. Seventy-one (61.6%) were male and 48 (38.4%) were female. Mean age of patients

Table 2 Demographics and characteristics of patients

Gender	
Male	77 (61.6%)
Female	48 (38.4%)
Mean age at diagnosis	33.6 (range: 10-80)
Smoke	
No	76 (70.8%)
Yes	26 (20.8%)
Former	23 (18.4%)
Family history	
No	106 (84.8%)
Yes	19 (15.2%)
Appendicectomy	
No	116 (92.8%)
Yes	9 (7.2%)
Characteristics of disease	
Ulcerative colitis	64 (51.2%)
Crohn's disease	61 (48.8%)
Duration of disease at 1 st infusion (median)	52 mo (IQR: 16-110.5)
Duration of follow-up (median)	34 mo (IQR: 19-55.5)

at diagnosis was 34 years (SD: \pm 13). Characteristics of the patients are given in Table 2. Median duration of disease was of 53 mo (IQR: 16-110.5) and median duration of follow-up was 34 mo. The mean number of total infusion/patient was 20 (range: 4-60) and the mean number of short infusions was 6.1 (range: 1-19). Patients were shifted to one-hour infusion after a median interval of 21 mo. Median follow-up of patients in short infusion was 12 mo. Indications for IFX were steroid-dependence in 61.6%, steroid-resistance in 8%, failure of thiopurines (9.6%), fistulizing disease (5.6%), rescue therapy in severe UC (2.4%). A total of 33 patients (26.4%) were taking steroids. Concomitant use of immunomodulators (azathioprine or methotrexate) was reported in 28 patients (22.4%). Seventy-five patients received mesalamine.

Fifty-seven (45.6%) patients received no premedication. A total of 68 patients (54.4%) was submitted to premedication: 51 (40.8%) with steroids, 1 with antihistaminic (0.8%) and 16 patients with both (12.8%). Details are reported in Table 3.

Adverse infusion reactions were observed in about 4% of patients both before (4 patients) and after short infusion (5 patients). Among the 9 patients who experienced an infusion reaction we recorded 7 being acute, 1 acute-severe, 1 delayed. Adverse infusion reactions occurred at a median of 3 (IQR 3-23) mo after the first infusion. In patients with mild or moderate infusion reaction the infusion was interrupted, medical therapy was administered and after resolution of symptoms, infusion was restarted slowly. The use of premedication was not significantly associated with different rates of infusion reactions. Opportunistic infections occurred in 5 patients (4%) both before and after short infusion. Opportunistic infections occurred at a median of 32 (IQR: 18-39) mo after the first infusion. No death occurred. Details are given in Table 3.

The total number of infusions across the selected centers was of 2501 (30.5% short infusions). We therefore calculated the potential related benefits both in

Table 3 Indication for biologic, concomitant therapies and premedication

Patients treated with IFX (total 125)	
Indication for IFX	
Steroid-dependent	77 (61.6%)
Steroid-resistant	16 (12.8%)
Rescue therapy severe UC	3 (2.4%)
EIM	0
Failure of thiopurine	12 (9.6%)
Fistulizing disease	7 (5.6%)
Prevention of postoperative recurrence	1 (0.8%)
Indication for IFX (dual indication)	
Steroid-dependent + EIM	3 (2.4%)
Steroid-dependent + failure of thiopurine	3 (2.4%)
Steroid-dependent + fistulizing disease	1 (0.8%)
Fistulizing disease + EIM	2 (1.6%)
Total infusions (mean)	20 (range: 4-60)
Short infusion (mean)	6.1 (range: 1-19)
Concomitant therapies	
None	12 (9.6%)
Steroids	25 (20%)
Thiopurine	10 (8%)
Methotrexate	2 (1.6%)
5ASA	56 (44.8%)
Concomitant therapies (polipharmacy)	
Steroids + thiopurine	1 (0.8%)
Steroids + 5ASA	4 (3.2%)
Steroids + thiopurine + 5ASA	3 (2.4%)
Thiopurine/methotrexate + 5ASA	12 (9.6%)
Total use of steroids	33 (26.4%)
Total COMBO therapy (Thiopurine or Mtx)	28 (22.4%)
Total use of mesalamine	75 (60%)
Premedication	
None	57 (45.6%)
Steroids	51 (40.8%)
Antihistaminic	1 (0.8%)
Steroids + antihistaminic	16 (12.8%)
Time of premedication	
None	57 (45.6%)
From first infusion	65 (52%)
From second Infusion	3 (2.4%)
Only short infusion	0

IFX: Infliximab; EIM: Excitability-inducing material; UC: Ulcerative colitis; 5ASA: 5-aminosalicylates.

terms of time saving and increased infusion unit capacity. In the analyzed cohort, 1143 h were saved (762 in the infusion and 381 in the observation phase) through the rapid IFX infusion protocol. This time saving (-15% compared to traditional protocol in infusion phase) represents, from the hospital perspective, an opportunity to optimize infusion unit capacity by allocating the saved time in alternative cost-effective treatments. This is the case of opportunity cost that represents the value of forgone benefit which could be obtained from a resource in its next-best alternative use. Hence, an extra hour of infusion in the case of standard 2-h IFX represents a loss in opportunity to provide other cost effective services. The analysis showed that the short time infusion increased the infusion units capacity up to 50% on days when the IFX infusions were scheduled (infusion phase). In the center which provided the data, by using the one-hour infusion protocol, the number of patients treated

per day increased from 3 to 6 (a 50% increase), leaving enough time to schedule additional therapies such as *i.v.* iron infusions. Furthermore, our analysis showed that the short IFX infusion protocol leads to time savings also in the post-infusion phase (observation) by leading to a time saving of 10% on average among the analyzed centers. Finally, the short infusion protocol has been demonstrated to lead to indirect cost savings of €138/patient (average -€17.300 on the whole cohort). In Table 4 we report the details on the split between short and traditional infusion.

DISCUSSION

IFX therapy is effective in the management of IBD both in the induction and in maintenance of remission, in preventing the rate of postoperative recurrence in CD and in reducing the need of hospital admission and surgery. Recently, IFX therapy has been shown to promote mucosal healing, an outcome strongly related to long-term remission^[17]. This treatment is widely used, since about 15%-20% of patients with IBD are currently on anti-TNFs and usually for long periods of time since most patients will be kept on maintenance therapy^[18] for 12-24 mo or even longer. IFX is administered at a dose of 5 mg/kg as a 2-h infusion followed by a monitoring time of additional 2 h. Efficacy and safety of shorter IFX infusion times have been recently demonstrated both in the setting of rheumatological disorders and IBD in observational studies. A good tolerability profile of one-hour infusion (3 or 5 mg/kg) was reported first in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis patients^[10,19] and recently for IBD patients who tolerated a 2-h infusion without adverse reactions (acute or delayed)^[20]. A meta-analysis has confirmed that rapid IFX infusions of ≤ 1-h duration are safe and not associated with increased risk of infusion reaction when compared to standard infusions in patients with IBD, rheumatoid arthritis, spondylarthropathy and psoriatic disease^[20].

Short IFX infusion could also influence patients' quality of life. Principi *et al.*^[14] reported an improvement in social and job quality of life in patients treated with 1-h infusion of IFX. However, though some Authors^[21] have suggested the possibility of reducing costs for the healthcare provider of patient daycare attendance combined with medical staffing requirements, a pharmacoeconomic evaluation of the accelerated infusion protocol has never been approached. To our knowledge, data in the literature on economic impact of one-hour infusion in IBD patients comparing standard infusion are scanty. Only one study, carried on in the United States, has been published so far, enrolling patients on accelerated infusions (both 90 min and 60 min long) at various IFX dosage^[22]. This study focused on hospital cost savings, by estimating the cost required to deliver infusions over 120-min vs using the accelerated infusion times: 118 h of infusion time and \$53632 were saved by using the accelerated protocols ($P < 0.001$).

Kuin *et al.*^[23] evaluated both safety and costs of home-

Table 4 Infusion time and indirect cost savings: Traditional *vs* short infusion protocol

	w/out SI (min)	w SI (min)	Delta (min)	Saving (min)	Delta %	Hours	Saving indirect costs (€)
Infusion time	300120	254400	-45.72	-45720	-15%	-762	-11.525
Post infusion time	225090	202230	-22.86	-22860	-10%	-381	-5.763
Total time	525210	456630	-68.58	-68580	-13%	-1143	-17.288
Costs saving/patient						-9	-138

based IFX infusion as an alternative to hospital-based infusions for the management of CD patients. Home-based IFX infusions were associated with a cost saving of €55 per infusion. Another study, conducted in a small pediatric population in United States, obtained similar results^[24]. Home-based therapy, though fascinating, is not applicable to all health care systems. In Italy, there are also regional differences.

Our findings suggest that in terms of indirect costs a short IFX infusion protocol in the hospital can be considered time and cost saving in comparison to the traditional infusion protocol. Our analysis could not assess differences in direct costs since costs of devices and hospital staff were similar whatever protocol is used.

The strengths of our study are: Firstly, the assessment of indirect costs of the two different infusion protocols which has never been approached and that is the most relevant from the patients' perspective; secondly, the evaluation of the improvement of organizational efficiency in terms of health care utilization resources. The use of short infusions seems to increase the unit capacity up to 50%, though this evaluation was possible only in one of the participating centers.

Our study has however some limitations. Firstly, the impact on hospital resource utilization was assessed in only one center. It could be argued that this result may not be representative of all the involved centres as it depends also on hospitals' specific organizational features. Secondly, the retrospective methodology of our study could influence the accuracy of the results. However, detailed notes of infusion characteristics were made at the time of each infusion in all participating centers so that underreporting was not expected. Finally, an activity based costing approach would be recommended in order to assess the "real" direct cost impact from the hospital perspective.

In conclusion, this study can be considered an important step in the economic evaluation of the short infusion protocol within the Italian context, although it would be recommended to perform a full economic evaluation considering both costs and related outcomes in order to provide comprehensive evidence based data useful for decision makers at local level.

A short IFX infusion protocol can be considered time and cost saving in comparison to the standard 2-h infusion protocol as it contributes to increase infusion units capacity up to 50%. From the patients' perspective, reduces indirect costs and the impact of treatment on everyday life and work productivity. On the basis of our study, we

believe that the one hour IFX infusion protocol in patients in stable maintenance therapy should be implemented in clinical practice.

COMMENTS

Background

Infliximab (IFX) is a chimeric monoclonal antibody anti-tumour necrosis factor effective in inducing and maintaining remission of moderate to severe luminal and fistulizing Crohn's disease and of moderate to severe refractory ulcerative colitis. It is also used to treat rheumatoid arthritis and moderate to severe psoriasis. IFX is usually administered intravenously at a dose regimen of 5 mg/kg as a 2-h infusion followed by a monitoring time of 2 h. This standard practice has been adopted in order to minimize infusion reactions. Previous reports have shown that shortening the infusion to one hour is equally safe. The key-question addressed by this manuscript is whether this accelerated infusion protocol is cost-saving both on the hospital's and on the patient's perspective.

Research frontiers

Data in the literature on economic impact of one-hour infusion in inflammatory bowel diseases patients are scanty. Only one study, carried on in the United States, focused on hospital cost savings, by estimating the cost required to deliver infusions over 120-min *vs* using the accelerated infusion times.

Innovations and breakthroughs

The methodology adopted in this research explores the potential benefits related to the short infusion protocol both in terms of potential time saving and increased infusion unit capacity. Indirect costs were expressed in terms of working hours lost due to the infusion. This approach has been recently applied in pharmaco-economic research.

Applications

The future application of the research could be the use of the accelerated infusion protocol not only with the infliximab originator molecule, but also with biosimilars. This could significantly reduce direct and indirect costs, increase infusion units' capacities and allow access of increased number of patients to effective therapy even in low income countries.

Terminology

Standard infusion practice requires dedicated areas (infusion units), facilities and time. Saving time is an opportunity to optimize infusion unit capacity by allocating the saved time in alternative cost-effective treatments or by increasing the number of treated patients. Indirect costs reflect patients' expenses related to travel to the hospital and of hours spent in the infusion clinic (work loss).

Peer-review

Manuscript is well written and easy to follow.

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P- Reviewer: Okello M, Puri K, Vradelis S **S- Editor:** Song XX
L- Editor: A **E- Editor:** Lu YJ



Observational Study

Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting

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Supported by Fundación Burgos por la Investigación de la Salud and Gerencia Regional de Salud de Castilla y León, No. BUO/06/15.

Institutional review board statement: The study was reviewed and approved by the Comité Ético de Investigación Clínica de Burgos y Soria (Spain).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

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Received: November 4, 2016
Peer-review started: November 5, 2016
First decision: December 13, 2016
Revised: January 14, 2017
Accepted: February 8, 2017
Article in press: February 9, 2017
Published online: May 6, 2017

Abstract

AIM

To investigate the real-world effectiveness and safety of various regimens of interferon-free treatments in patients infected with hepatitis C virus (HCV).

METHODS

We performed an observational study to analyze different antiviral treatments administered to 462 HCV-infected patients, of which 56.7% had liver cirrhosis. HCV RNA after 4 wk of treatment and at 12 wk after treatment sustained virological response (SVR) as well as serious adverse events (SAEs) was analyzed first for the whole cohort and then separately in patients who met or did not meet the inclusion criteria of a clinical trial (CT-met and CT-unmet, respectively).

RESULTS

The most frequently prescribed treatment was simeprevir/sofosbuvir (36.4%), followed by sofosbuvir/ledipasvir (24.9%) and ombitasvir/paritaprevir/ritonavir (r)/dasabuvir (19.9%). Ribavirin (RBV) was administered in 198 patients (42.9%). SVRs occurred in 437/462 patients (94.6%). The SVRs ranged between 93.3% and 100% for genotypes 1-4. SVRs were achieved in 96.2% patients in the CT-met group *vs* 91.9% patients in the CT-unmet group ($P = 0.049$). Undetectable HCV RNA at week 4 occurred in 72.9% of the patients. In the univariate analysis, the factors associated with SVRs were lower liver stiffness, absence of cirrhosis, higher platelet count, higher albumin levels, no RBV dose reduction, undetectable HCV RNA at week 4 and CT-met group. In the multivariate analysis, only albumin was an independent predictor of treatment failure ($P = 0.04$). Eleven patients (2.4%) developed SAEs; 5.2% and 0.7% of the patients in the CT-unmet and CT-met groups, respectively ($P = 0.003$).

CONCLUSION

A high proportion of patients with HCV infection achieved SVRs. For patients who did not meet the CT criteria, treatment regimens must be optimized.

Key words: Hepatitis C virus infection; Genotype 1-4; Real world treatment; Direct-acting antiviral agents

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Core tip: Our study analyzes the hepatitis C virus (HCV) most common genotypes treatment and all the possible combinations with direct-acting antiviral agents which are nowadays available in our country. We have found sustained virological response rates up to 90%, even in genotypes 1 and 3. The current study analyzes HCV RNA after 4 wk of treatment and 12 and 24 wk after the end of the treatment, as well as the adverse events. We analyze, separately, the patients who meet or do not meet the inclusion criteria of a clinical trial, finding that in this last group the response is lower.

Ramos H, Linares P, Badia E, Martín I, Gómez J, Almohalla C, Jorquera F, Calvo S, García I, Conde P, Álvarez B, Karpman G, Lorenzo S, Gozalo V, Vázquez M, Joao D, de Benito M, Ruiz L, Jiménez F, Sáez-Royuela F; Asociación Castellano y Leonesa de Hepatología (ACyLHE). Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 137-146. Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/137.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.137>

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide, and its long-term impacts range from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma^[1,2].

The objective of chronic HCV infection treatment is to achieve a sustained virological response (SVR). A SVR is stable over time, reduces morbidity and mortality, and is equivalent in most cases to curing the HCV infection^[3-5].

In 2011, the association of pegylated-interferons (Peg-IFNs) and ribavirin (RBV) with the first direct-acting antiviral agents (DAAs), telaprevir and boceprevir, increased the rate of SVRs in HCV genotype 1 from 30%-40% to 65%-75%^[6,7]. However, all these treatments had limited efficacy and low tolerability^[8-11].

Subsequently, next-generation DAAs which are produced with or without RBV, have been associated with improved efficacy (resulting in SVR rates greater than 90% in clinical trials), safety, tolerability, and shorter durations than first-generation protease inhibitor regimens^[2,12,13].

However, information derived from HCV anti-viral clinical trials have limited applicability in clinical practice. Understanding the effectiveness of anti-viral regimens in real-world settings is essential to providing practical information and adopting better HCV treatment decisions^[14,15].

The objective of this prospective study was to describe the clinical characteristics of real-world patients and evaluate the effectiveness and safety of different treatment regimens with different HCV genotypes according to real-world scenarios. We also aimed to investigate whether

patients who met or did not meet the usual inclusion criteria of clinical trials (CTs) have the same efficacy and safety profile when they are treated in real-world practice.

MATERIALS AND METHODS

Study design

This prospective, observational, intent-to-treat study analyzed different antiviral treatments for HCV-infected patients in routine clinical practice. The study was conducted in 9 (5 university and 4 non-university) hospitals in north-central Spain (Castilla y León).

Ethics statement

All study participants, or their legal guardian, provided informed written consent prior to study enrollment. The study protocol was performed according to the ethical guidelines of the 1975 Declaration of Helsinki and was approved in advance by the Research Ethics Committee of the Hospital Universitario de Burgos (Burgos, Spain).

Patient selection

The cohort consisted of all consecutively evaluated HCV patients of any genotype treated with INF-free treatments from December 1, 2014 to August 31, 2015. The patients were visited at baseline, at weeks 4, 12 and 24 (if necessary) during treatment, and at weeks 12 and 24 after completing treatment.

Inclusion criteria

Inclusion criteria were as follows: (1) underwent a complete clinical history and physical examination; (2) HCV documented by the presence of detectable serum RNA-HCV; (3) liver stiffness measurement was performed using transient elastography (FibroScan, Echosens, Paris France) in the six months before starting treatment and/or cirrhosis diagnosed either by liver biopsy and/or clinical plus ultrasound criteria; (4) absence of anti-HIV 1 and 2 antibodies; (5) absence of other causes of liver disease (autoimmune disorders, primary biliary cholangitis, Wilson's disease, α 1-antitrypsin deficiency, and hemochromatosis); and (6) desire for and compliance with treatment.

Exclusion criteria

Exclusion criteria were as follows: (1) recipients of liver transplantation; (2) women who were pregnant or unable to adopt contraceptive measures; (3) hypersensitivity to therapy drugs; (4) previous treatment with another interferon-free combination; (5) coinfections (HBV, HDV, HIV); and (6) failure to establish the grade of fibrosis according to the criteria outlined. The presence of hepatocellular carcinoma was not considered an exclusion criterion.

Treatment

The decision to treat and the choice of treatment, including the treatment duration and the use or not of

concomitant RBV, was entirely at the discretion of the treating physician in accordance, of the majority of the cases, with the product label, the European Association for the Study of the Liver clinical practice guidelines and the National Hepatitis C Plan developed by the Spanish Ministry of Health, giving priority to the treatment of patients with significant liver fibrosis (F2-F4)^[2]. The availability of each DAA varied throughout the inclusion period of the patients (Supplementary material Table 1). The use of blood transfusion or erythropoietin in case of anemia was too entirely at the discretion of the treating physician.

Study variables

All data collection and analyses were performed anonymously. A range of continuous and categorical variables was tested (Supplementary material Table 2). The HCV RNA levels were determined using the COBAS AmpliPrep®/COBAS TaqMan® (Roche Molecular Systems, Pleasanton, CA, United States; lower limit of detection: 15 IU/mL). In previously treated patients, the last prescribed treatment and the type of prior response were registered. Cirrhosis (F4) was defined by a transient elastography score > 12.5 kPa, liver biopsy or data indicating clinical, analytical and ultrasound evidence of liver cirrhosis.

Virological response

The virological response, which is defined as undetectable HCV RNA, was assessed at week 4 of the treatment (undetectable HCV RNA at week 4), at week 12 after the EOT (SVR) and at week 24 after the EOT (SVR24). Virologic failure was defined as detectable HCV RNA at any time during treatment (with the exception of week 4 of treatment) or post-treatment follow-up.

Clinical trial inclusion criteria

Patients were arbitrarily divided into two groups based on the fulfillment or not of the more usual phase III CT inclusion criteria: Age 18-70 years, HCV RNA > 10000 IU/mL, hemoglobin \geq 11 g/dL in women and \geq 12 g/dL in men, platelet count \geq 50 \times 10³/ μ L, ALT \leq 200 UI/mL, total bilirubin \leq 1.5 mg/dL, albumin \geq 3.5 mg/dL, INR \leq 1.5, Child-Pugh score A and MELD score < 12. Patients fulfilling all these criteria were classified as CT-met patients; however, if one or more criteria were unmet, they were considered CT-unmet patients.

Adverse events

Adverse events (AEs) were reported from the time of the initial drug administration to week 12 after the planned EOT. Serious adverse events (SAEs) were defined as any event that was life-threatening; an event that led to a hospital admission, prolonged an existing hospital stay or resulted in death; or an event that was considered serious based on the judgment of the treating physician. Incident hepatic decompensation was defined as the presence of variceal hemorrhage, ascites, and/or porto-

systemic (hepatic) encephalopathy. Anemia was defined as a hemoglobin levels < 10 g/dL.

End points

The primary efficacy end point was the SVR rate in all patients who received at least one dose of treatment. Secondary end points included the rate of undetectable HCV RNA at week 4, the rate of SVR in CT-met patients and CT-unmet patients and the rate of adverse events and treatment discontinuation because of adverse events.

Statistical analysis

The data analysis was performed with SPSS 19 statistical software (IBM Corp., Armonk, New York, United States) after collecting and organizing the data with Excel 2010 (Microsoft Corp., Redmond, Washington, United States). A descriptive analysis of the sample was conducted by determining the means (SD), medians (IQR), and frequencies (percentages) according to variable characteristics and distributions. Differences between variables were evaluated using the χ^2 or Fisher's tests for qualitative variables. For quantitative variables, Student's *t*-test (if normality conditions were met) or its corresponding nonparametric tests, including the Mann-Whitney *U*-test or the Kruskal-Wallis test (if data were not normally distributed), were used. Finally, a binary logistic regression was performed using the RVS as the dependent variable. The significance level was $\alpha = 0.05$, and 95% CIs were calculated.

RESULTS

During the study period, 468 patients received an interferon-free treatment. Of these patients, 6 could not be reached or did not complete follow-up. Thus, 462 patients were included in the analysis.

Baseline characteristics

Of the 462 patients included in the study, 311 (67.3%) were male, and the median age was 54 years (range 15-87 years). Cirrhosis (F4) was present at baseline in 56.7% of the cohort. The majority of patients with cirrhosis (86.7%) were Child-Pugh A class (Table 1 and Supplementary material Table 1).

The most frequent treatment prescribed was SMV and SOF (36.4%), which was followed by SOF and LDV (24.9%) and OBV, PTV/r, and DSV (19.9%). A RBV occurred in 198 patients (42.9%; Table 1).

Clinical effectiveness

Overall, 437 of the 462 patients (94.6%) achieved a SVR (Figure 1A, Tables 2 and 3). The proportion of patients with HCV genotypes 1, 2, 3 and 4 who achieved a SVR was 94.5% (1a, 97.3%; 1b, 93.4), 100%, 93.3% and 95.5%, respectively. The SVR was above 91% in all genotypes and with all treatment combinations (Table 2 and Supplementary material Tables 3 and 4).

HCV RNA at week 4 data were available for 457/462 patients (98.9%), of which 333/457 (72.9%) showed

an undetectable viral load at week 4 of treatment. Patients who presented an undetectable HCV RNA at week 4 achieved a SVR (96%) more frequently than patients who did not present it (90%, $P = 0.004$; Figure 1B and Supplementary Material Table 3).

Twenty-five patients (5.4%) failed to achieve a SVR. Two patients (0.4%) who had achieved a SVR experienced a relapse with RNA-HCV detectable at week 24 after EOT. Therefore, of the 437 patients with a SVR, 435 (99.6%) maintained SVR24 (positive predictive value of SVR for SVR24 of 99.5% and negative predictive value of 100%).

In the univariate analysis, the following factors were associated with a SVR: Liver stiffness (continuous, < 20 kPa vs ≥ 20 kPa and < 25 kPa vs ≥ 25 kPa), cirrhosis vs non-cirrhosis (Figure 1B), platelet count ($\geq 100000/\text{mm}^3$ vs < 100000/ mm^3), albumin (continuous), RBV dose reduction or not, undetectable HCV RNA at week 4 vs non-undetectable HCV RNA at week 4 and CT-met vs CT-unmet (Supplementary material Table 3 and 4). In the multivariate analysis, only baseline albumin (continuous) was an independent predictor of treatment failure ($P = 0.04$; Supplementary material Table 3 and 4).

Safety and tolerability

Four patients (0.9%) with genotype 1 discontinued treatment early, with three (0.6%) discontinuing because of a SAE and one discontinuing at the patient's request. Altogether, 321 patients (69.5%) experienced one or more AEs, and most of them (96.6%) were mild. The AEs that appeared with a frequency over 3% are described in Table 3. The most commonly reported AE was fatigue (22.5%), which was followed by headache (11.7%) and anemia (11.3%). Anemia was present in 47/198 (23.7%) of patients who received RBV, compared with 5/264 (1.9%) of patients who did not receive it ($P = 0.000$). In 21 patients (8.5%), the dose of RBV had to be modified. Two patients (0.4%) required a blood transfusion, and none required erythropoietin.

Eleven patients (2.4%) developed SAEs. Ten of these patients had liver cirrhosis (three Child-Pugh score A, 6 Child-Pugh score B and one Child-Pugh score C at baseline). Nine of the eleven patients who developed SAEs were also treated with RBV. SAEs were related to hepatic decompensation in seven patients with six of these patients experiencing ascites (one with hepatocellular carcinoma and another one with hepatic encephalopathy) and one patient developing only hepatic encephalopathy. Two patients developed severe anemia; both of these patients were cirrhotic and treated with RBV, and one patient developed suicidal ideation and the other developed hyperbilirubinemia. There were no deaths during treatment or follow up.

Subanalysis of patients with met or unmet clinical trials criteria

The predefined requirements to participate in a theoretical CT were not fulfilled by 173 patients. Regarding the

Table 1 Baseline characteristics of patients receiving direct-acting antiviral agents: Overall patients, patients subgroup clinical trial-met and clinical trial-unmet

Characteristics	Total <i>n</i> = 462	CT-met <i>n</i> = 289	CT-unmet <i>n</i> = 173	<i>P</i> value
Sex, male	311 (67.3)	196 (67.8)	115 (66.5)	0.765 ¹
Age, yr	54 (15-87)	53 (30-69)	59 (15-87)	
BMI, kg/m ² , <i>n</i> = 368	26.4 (17.6-47)	26.2 (17.6-47)	26 (18.6-40.6)	0.132
IL28B genotype CC/CT/TT, <i>n</i> = 367	80/231/56	39/153/34	41/78/22	0.021
HCV genotype 1/2/3/4	78.4/2.4/9.7/9.5	76.1/2.1/10.4/11.4	82.1/2.9/8.7/6.4	0.549 ²
HCV genotype 1a/1b/1	31.2/66.6/2.2	40.1/58.6/2.7	16.2/78.9/1.4	0.000 ³
Baseline HCV RNA, log ₁₀ IU/mL	6.1 (3.0-7.8)	6.5 (4.2-7.6)	6.4 (3.0-7.8)	¹
HCV antiviral treatment history				0.233
Naïve	186 (40.0)	112 (38.8)	74 (42.8)	
Non-responders	211 (45.7)	131 (45.6)	80 (46.2)	
Relapsers	64 (13.9)	46 (15.9)	18 (10.4)	
Fibrosis stage, <i>n</i> (%)				0
F0-1	26 (5.6)	21 (7.3)	5 (2.9)	
F2	100 (21.6)	83 (28.7)	17 (9.8)	
F3	77 (16.7)	59 (20.4)	15 (8.7)	
F4	259 (56.1)	126 (43.6)	136 (78.6)	
Transient elastography, kPa, <i>n</i> = 435	13.5 (2.8-65)	10.9 (2.8-75)	18.2 (3.5-75)	0
Cirrhosis				
No	200 (43.3)	163 (56.4)	37 (21.4)	0
Yes	262 (56.7)	126 (43.6)	136 (78.6)	
Child-Pugh Score, <i>n</i> = 209				¹
A	180 (86.1)	116 (100)	64 (68.8)	
B	22 (10.5)	0 (0.0)	22 (23.7)	
C	7 (3.3)	0 (0.0)	7 (7.5)	
MELD score, <i>n</i> = 229	8.1 (6-29)	6.9 (6-11)	9.4 (6-29)	¹
Hemoglobin level, g/dL,	15.3 (11-19.1)	14.3 (8-19.5)	15 (8-19.5)	¹
Platelets, /mm ³ , <i>n</i> = 446	158666 (23000-457000)	177301 (50000-457000)	124363 (23000-436000)	¹
ALT, IU/L, <i>n</i> = 461	81 (64)	71.8 (43.9)	97.6 (79.8)	¹
Bilirubin > 1 mg/dL, <i>n</i> = 243	94 (38.7)	19 (15.3)	75 (63.0)	¹
Albumin < 3.5 g/dL, <i>n</i> = 239	25 (10.3)	0 (0.0)	25 (21.2)	¹
INR	1.1 (0.7-2.9)	1.0 (0.7-1.3)	1.1 (0.9-2.9)	¹
Treatment prescribed				0.024 ⁴
SMV and SOF	168 (36.4)	90 (31.1)	78 (45.1)	
SMV and DCV	7 (1.5)	1 (0.3)	6 (3.5)	
SOF and DCV	56 (12.1)	40 (13.8)	17 (9.8)	
SOF	11 (2.4)	9 (3.1)	2 (1.2)	
OMV and PTV/r	13 (2.8)	10 (3.5)	3 (1.7)	
OMV, PTV/r, and DSV	92 (19.9)	60 (20.8)	31 (17.9)	
SOF and LDV	115 (24.9)	79 (27.3)	36 (20.8)	
+ RBV	198 (42.9)	131 (45.3)	67 (38.7)	165
Treatment duration				0.973 ⁵
8 wk	12 (2.6)	9 (3.1)	3 (1.7)	
12 wk	407 (88.1)	253 (87.5)	154 (89.0)	
24 wk	43 (9.3)	27 (9.3)	16 (9.2)	
Treatment at University Hospital	395 (85.5)	259 (89.6)	136 (78.6)	0.001

¹The *P* value was not calculated because the variable was part of inclusion criteria in the C-met group; ²Genotype 3 *vs* the rest; ³1a *vs* 1b; ⁴To calculate the *P* value the SMV and DCV, SOF and OMV and PTV/r groups were excluded because of a low *n*; ⁵8 plus 12 wk *vs* 24 wk. Continuous variables reported as median (range). Categorical variables reported as *n* and/or %. DDAs: Direct-acting antiviral agents; CT: Clinical trial; BMI: Body mass index; PEG: Pegylated interferon; PIs: Protease inhibitors; ALT: Alanine aminotransferase; SMV: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; OMV: Ombitasvir; PTV/r: Paritaprevir/ritonavir; DSV: Dasabuvir; RBV: Ribavirin.

basal characteristics and apart from the CT inclusion criteria, which were obviously different, the patients in the CT-unmet group presented the IL28B CC genotype more frequently, which is a genotype 1 subtype, and more advanced fibrosis, and they were more frequently treated in a non-university hospital (Table 1). These CT-unmet patients had a globally lower SVR than the CT-met patients (91.9% *vs* 96.2%, *P* = 0.049; Figure 1C, Supplementary material Table 3). However, the undetectable HCV RNA at week 4 was similar in both

groups [75.0% in the CT-unmet group and 71.6% in the CT-met group (*P* = 0.426)] (Figure 1C). The frequency of AEs was significantly higher in the CT-unmet group (52.2% *vs* 32.9%, *P* = 0.000). However, there were no differences regarding the development of anemia and the need for RBV dose reductions between the two groups. Importantly, SAEs (including hepatic decompensation) appeared more commonly in the CT-unmet group (5.2% *vs* 0.69%, *P* = 0.003 and 3.47% *vs* 0.35%, *P* = 0.013, respectively).

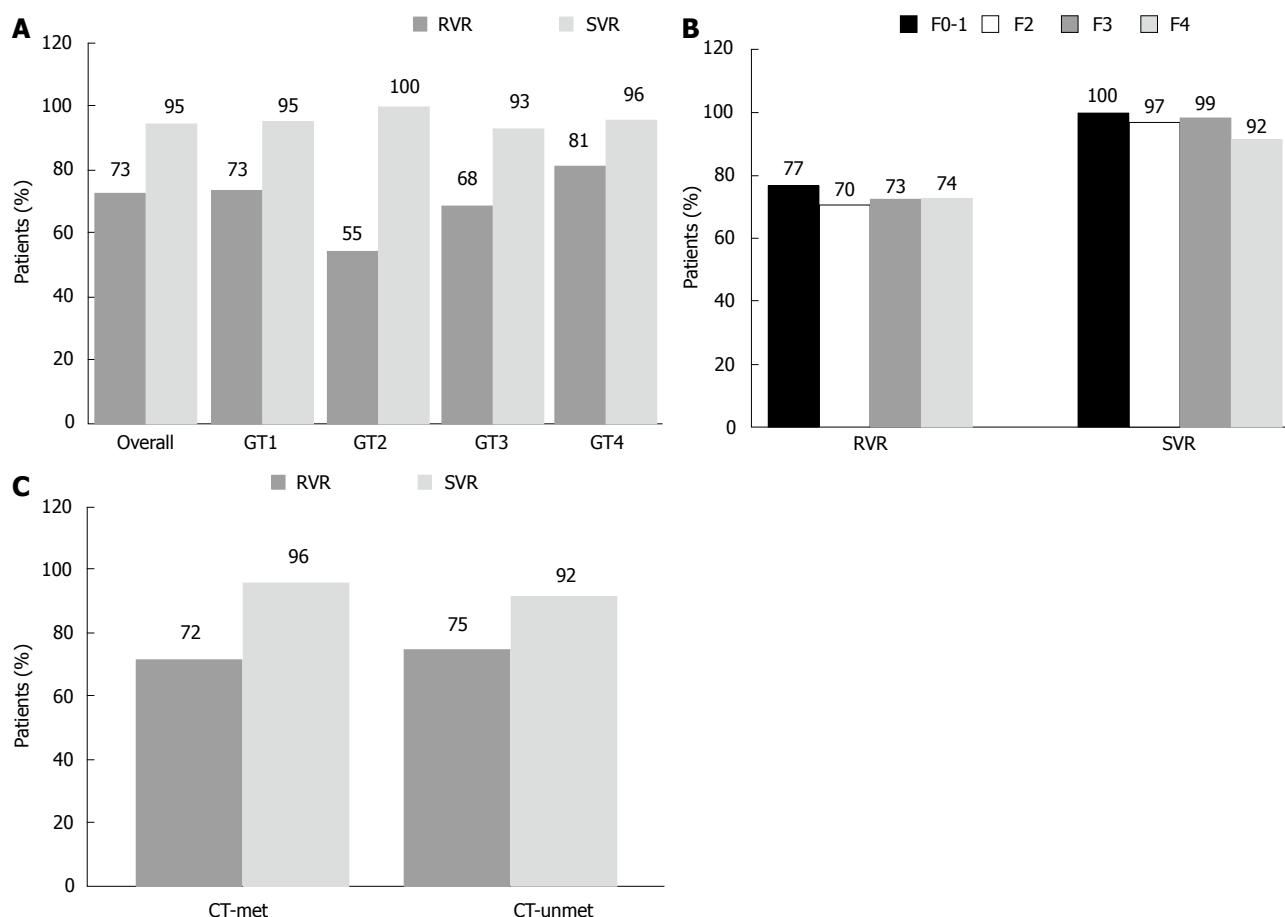


Figure 1 Rates of virological response. Patients with undetectable viral loads during and post treatment. A: At treatment week 4 and post-treatment week 12 (sustained virological response) by genotype; B: At treatment week 4 and post-treatment week 12 (sustained virological response) by fibrosis stage; C: At treatment week 4 and post-treatment week 12 (sustained virological response) by CT-met and CT-unmet. Data for 5 patients were lost: genotype 1, data from three patients were lost; genotype 3 and 4, a patient data in each genotype were lost. Data for 4 patients were lost. Data for 1 patient were lost. GT: Genotype; RVR: Undetectable HCV RNA at week 4; SVR: Sustained virological response; CT: Clinical trial.

Three of four patients who stopped treatment and 9 of 11 patients with SAEs were included in the CT-unmet group. In 6 of the 7 patients with a liver cirrhosis decompensation, a SAE was included in the CT-unmet group.

DISCUSSION

Our real-world study is representative of monoinfected, non-transplanted patients and the treatment regimens available in Spain in 2015. Because the decision to treat and the choice of treatment were entirely at the discretion of the treating physician and randomization was not possible, this study could not directly compare the effectiveness and safety of the treatment regimens.

In the general cohort, the global efficacy was high (94.6% SVR) and the results were similar to those achieved in the CTs, although almost 60% of the patients had received previous HCV antiviral treatment and more than half had liver cirrhosis.

We found that 0.4% of the subjects who achieved a SVR at week 12 subsequently relapsed at week 24 (did not achieve SVR24), and this percentage was a similar

to or even lower than those found in other studies^[16,17]. Therefore, this finding confirmed previous results in a real-world setting and showed good concordance between SVRs at week 12 and week 24 based on different new AAD-based regimens, including those with shorter durations and/or with drugs with lower barriers to resistance. However, in our opinion, to definitively determine a “cure” in every patient in clinical practice, a SVR must be confirmed at week 24.

Until now, few real-world setting studies have included results that consider the most frequent genotypes (1 to 4). The most significant study is the US retrospective analysis of data from 17487 patients with genotypes 1 to 4 from the Veterans Affairs (VA) National Healthcare System^[18], in which a global SVR of 90.7% was found, which was lower than that in our study. This difference may be linked to early discontinuation of treatment in 4.4% of patients with available SVR data^[18].

In our study, albumin was the only independent predictor of a SVR. Other studies^[14,18] have also shown that albumin and other variables associated with cirrhosis or worse liver function were related to a lower SVR, thus confirming these findings in a real-world setting and with

Table 2 Sustained virological response by genotype and treatment regimen

Treatment regimen	Patients in each	SVR
Genotype 1		
SMV and SOF	149 (41.2)	139 (93.3)
SMV and DCV	7 (1.9)	7 (100)
SOF and DCV	15 (4.1)	15 (100)
OMV, PTV/r, and DSV	91 (25.1)	86 (94.5)
SOF and LDV	100 (27.6)	95 (95.0)
Total	362 (100)	342 (94.5)
Genotype 2		
SOF and DCV	5 (45.5)	5 (100)
SOF	5 (45.5)	5 (100)
SOF and LDV	1 (9.1)	1 (100)
Total	11 (100)	11 (100)
Genotype 3		
SOF and DCV	37 (82.2)	34 (91.9)
SOF	5 (11.1)	5 (100)
SOF and LDV	3 (6.7)	3 (100)
Total	45 (100)	42 (93.3)
Genotype 4		
SMV and SOF	19 (43.2)	18 (94.7)
SOF	1 (2.3)	1 (100)
OMV and PTV/r	13 (29.5)	12 (92.3)
SOF and LDV	11 (25.0)	11 (100)
Total	44 (100)	42 (95.5)

SVR: Sustained virological response; SMV: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; OMV: Ombitasvir; PTV/r: Paritraprevir/ritonavir; DSV: Dasabuvir.

a wide number of patients and supporting the results of CTs in which patients with a more advanced liver disease have a worse response to treatment.

Most real-world studies reported results in genotype 1 HCV patients^[14,19,20]. The SVR rate in our study, which included 362 genotype 1 patients, was 94.5% of the overall genotype 1 patients, which was somewhat higher than previously reported rates (SVRs over 91%), although limited differences were observed among the different DAA combinations, treatment durations and use of RBV. SMV and SOF with or without RBV was the most used treatment in our genotype 1 patients, which was likely because it was the best combination available at the beginning of the study. This treatment was used in 149 of the total genotype 1 patients. Most of these patients had liver cirrhosis and were included in the CT-unmet group because the most severe patients were prioritized. However, these patients achieved a SVR of 93.3%. In other studies with thousands of patients with genotype 1 HCV treated with this regimen, the SVR rates were lower at between 75% and 84%^[14,15,21]. The main cause of the differences between our cohort and the others was likely the lower rate of subtype 1a (31.2%) and Q80K variants in our genotype 1 patients. Although these variants were not analyzed in the current study, they appeared in only 2.7% of Spanish genotype 1 patients^[22].

Other treatment combinations also showed high rates of SVR in our study; *i.e.*, 95.0% with SOF/LDV and 94.5% with OBV/PTV/r/DSV. These rates were similar to the 92.9% or 92% SVR rates derived from

Table 3 Safety profile *n* (%)

Patients	<i>n</i> = 462
Severe AEs	
Any AE ¹	11 (2.4)
AEs	321 (69.5)
Fatigue	104 (22.5)
Headache	55 (11.7)
Anemia	52 (11.3)
Insomnia	23 (5.0)
Infection	20 (4.3)
Arthralgia, myalgia	19 (4.1)
Dyspepsia	15 (3.2)
Rash	14 (3.0)
Deaths	0 (0.0)

¹Adverse events (AEs) occurring during treatment or follow-up in $\geq 3\%$ patients.

the first regimen presented in two US VA National Healthcare System studies^[18,19] and the 94.9% or 95.1% SVR rates achieved with the second regimen in other studies in clinical practice^[18,20].

In our cohort, only eleven genotype 2 patients were treated, and all of them achieved a SVR regardless of the treatment regimen used. High rates of SVR with the combination SOF + RBV were more similar to those described in Asian CTs^[23] than the SVR of 79.0% or 86.2% achieved in clinical practice in the two VA studies^[14,18] or the SVR of 88.2% from the recent analysis of 321 genotype 2 HCV infected HCV-TARGET participants^[24]. However, the low number of genotype 2 patients in our study indicate that several of the currently recommended combinations in clinical guidelines, such as SOF and DCV^[25] should be favored because they presented 100% SVR rates in all patients.

Patients with HCV genotype 3 are at a higher risk of liver disease progression and hepatocellular carcinoma development^[26,27]. However, compared with other HCV genotypes, DAA combinations have lower efficacy against genotype 3 in patients with liver cirrhosis in CTs.

In the current study, the global SVR in patients with genotype 3 HCV infection was 93.3%. In our cohort, 82.2% of patients with this genotype were treated with SOF and DCV, with a global SRV rate of 90.3%-91.9% in patients with liver cirrhosis and 100% without. In others studies in real-world settings, a global SVR of 60%-70% was achieved in genotype 3 infection with SOF plus RBV^[18,28]. All these studies had remarkably low rates, which was likely related to the use of combinations that are currently not recommended because of their low efficacy^[25].

Patients with HCV genotype 4 infection are poorly represented in pivotal CTs of second-generation DAAs^[25] and in most real-world studies. In the VA study, a SVR of 87.6% with SOF and LDV and 96.4% with OBV and PTV/r was achieved in patients with this genotype^[18]. In the current study, 44 patients who were HCV genotype 4-infected were treated and the SVR rate was 95% (100% with SOF and LDV, 92.3% with OBV and PTV/r

and 94.7% with SMV and SOF).

The week 4 response data were available for almost all patients in the current study. We found that 72.9% of patients had an undetectable HCV RNA at week 4, similar to another analysis^[19,29]. In this last real-world setting study, significant SVR rate reductions of 7.1% to 10.5% according to the addition of RBV or not, respectively, were observed in patients who did not have an undetectable HCV RNA at week 4 compared with those with undetectable HCV RNA at week 4, which was similar to the 6% observed in the current study^[19]. The clinical implications of this finding on treatment decisions, such as potentially adding RBV or extending the treatment duration based on 4 wk of on-treatment HCV RNA, warrants further study.

Despite the real-world nature of our cohort, which included a higher proportion of elderly patients and many patients with liver cirrhosis, the safety and tolerability of all regimens were good. Discontinuation rates were low (< 1%), which is similar to that of CTs, and there were no deaths during treatment or follow up. In Backus *et al.*^[20] higher early discontinuation rates of 5.3% to 15.2% according to the treatment combination were found. In contrast, of the 802 patients in the genotype 1 group from the HCV-TARGET cohort treated with SMV and SOF, the rate of discontinuation for adverse events was only 2%^[15].

In patients from the genotype 1 and genotype 3 groups from the HCV-TARGET cohort, the most commonly reported AEs were fatigue and headache, which is consistent with the results presented here^[15,28]. However, anemia associated with RBV was less frequent in our study.

Overall, the reported rates of SAEs (2.4%) were similar to those reported in the pivotal CTs and lower than the 5.3% or the 7.3% described in other studies in "real-world"^[15,28]. Again, in the three studies, the most frequent SAEs were the same decompensating events. However, in the current study, only seven of 262 cirrhotic patients experienced decompensation.

Because the real-world population is heterogeneous, it is important to investigate the treatment outcomes in patients excluded from CTs. Thus, we divided patients into two groups: Patients who met the requirements to take part in a CT and patients who did not meet these requirements. We found that the CT-unmet patients had lower rates of SVR and higher rates of SAEs, liver decompensation and treatment interruptions than the CT-met patients. Thus, in this group of patients, it might be advisable to conduct a more rigorous follow-up investigation to closely monitor tolerability and optimize treatment regimens.

This study has the usual limitations related to its observational, real-world design and electronic data collection. Resistance testing was not performed; thus, we were unable to assess the impact of this factor. The lack of randomization limited the ability to directly compare treatment groups, which is further compounded by the small number of patients in certain subgroups.

In conclusion, our study confirmed the efficacy and safety data reported in CTs in a cohort of patients with genotypes 1-4 and a wide range of basal characteristics, including a high proportion of patients with advanced fibrosis and treatment experience. Our results confirmed and occasionally improved upon the efficacy and safety results reported in other recently published real-world setting studies with a large number of patients^[8,19], and these results are in sharp contrast to the lower SVR rates reported in certain early real-world studies on interferon-free therapy with second generation DAAs^[14,15]. Moreover, our results indicate that treatment regimens should be optimized in patients that do not fulfill classical CT inclusion criteria because of their lower rates of SVR and higher rates of SAEs.

COMMENTS

Background

New direct-acting antiviral agents (DAAs) have shown higher efficacy (with sustained virological response, SVR, over 90%), safety, tolerability and shorter durations than previous antiviral agents used in the treatment of hepatitis C. However, information derived from hepatitis C virus (HCV) anti-viral clinical trials has limited applicability in clinical practice. Understanding the effectiveness of anti-viral regimes in real-world settings is essential to provide practical information in order to adopt better HCV treatment decisions.

Research frontiers

The research hotspot is to check whether the results of HCV anti-viral clinical trials can be extrapolated to the real world HCV population.

Innovations and breakthroughs

This study analyzes the efficacy and safety of all possible combinations of DAAs available in the authors' country in multiple HCV genotypes, in contrast to other studies where just one DAA treatment regimens and usually one genotype is analyzed. In this real world cohort, which includes a high proportion of elderly patients and patients with cirrhosis, the efficacy, safety and tolerability of all DAA regimens are good, and similar to the clinical trials results. However, patients who do not meet the requirements to participate in a theoretical clinical trial, have lower SVR rates and a higher proportion of adverse and serious adverse events, including liver disease decompensation, and more treatment interruptions.

Applications

The authors found that 0.4% of patients who achieved SVR at week 12 subsequently relapsed at week 24 so, in the authors' opinion, to definitively determine the infection cure in clinical practice, SVR should be confirmed at week 24. Moreover, as patients who do not meet clinical trial requirements have lower SVR and more adverse events, it might be advisable to conduct a more rigorous follow-up and to optimize treatment regimens in this population.

Terminology

DAAs: Direct-acting antiviral agents are molecules that target specific nonstructural proteins of the virus and result in disruption of HCV replication. There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target. The four classes are nonstructural proteins 3/4A (NS3/4A), protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors (NPIs), NS5B non-nucleoside polymerase inhibitors (NNPIs), and NS5A inhibitors. SVR: sustained virological response, is defined as undetectable HCV RNA at week 12 after the end of HCV treatment. It is equivalent to the virological cure of the infection, and the goal of HCV treatment, although it does not mean the disease resolution in patients with advanced fibrosis.

Peer-review

This real-world prospective multi-center study was conducted at 9 centers in

Spain on a fair number of patients, the study is well designed and the paper is well written.

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P- Reviewer: Kim SR, Kohla MAS, Zeng Z **S- Editor:** Qi Y
L- Editor: A **E- Editor:** Lu YJ



Randomized Controlled Trial

Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial

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Institutional review board statement: The study was reviewed and approved institute ethics committee at All India Institute of Medical Sciences, New Delhi.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Clinical trial registration statement: This trial was done from 2003 till 2005. Since there was no trial registry in India at that time, this trial did not have a registration number.

Conflict-of-interest statement: No conflict of interest for all authors.

Data sharing statement: No additional data are available.

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Received: October 17, 2016

Peer-review started: October 19, 2016

First decision: December 27, 2016

Revised: January 5, 2017

Accepted: March 12, 2017

Article in press: March 14, 2017

Published online: May 6, 2017

Abstract

AIM

To evaluate the role of oral curcumin in inducing clinical remission in patients with mild to moderate ulcerative colitis (UC).

METHODS

A prospective randomized double-blind placebo-controlled trial comparing the remission inducing effect of oral curcumin and mesalamine 2.4 g with placebo and mesalamine 2.4 g in patients of ulcerative colitis with mild to moderate severity was conducted from January 2003 to March 2005. The included patients received 1 capsule thrice a day of placebo or curcumin (150 mg) for 8 wk. Patients were evaluated clinically and endoscopically at 0,

4 and 8 wk. The primary outcome was clinical remission at 8 wk and secondary outcomes were clinical response, mucosal healing and treatment failure at 8 wk. The primary analysis was intention to treat worst case scenario (ITT-WCS).

RESULTS

Of 300 patients with UC, 62 patients (curcumin: 29, placebo: 33) fulfilled the inclusion criteria and were randomized at baseline. Of these, 21 patients did not complete the trial, 41 patients (curcumin: 16, placebo: 25) finally completed 8 wk. There was no significant difference in rates of clinical remission (31.3% *vs* 27.3%, $P = 0.75$), clinical response (20.7% *vs* 36.4%, $P = 0.18$), mucosal healing (34.5% *vs* 30.3%, $P = 0.72$), and treatment failure (25% *vs* 18.5%, $P = 0.59$) between curcumin and placebo at 8 wk.

CONCLUSION

Low dose oral curcumin at a dose of 450 mg/d was ineffective in inducing remission in mild to moderate cases of UC.

Key words: Curcumin; Mesalamine; Ulcerative colitis; Ulcerative colitis disease activity index; Mucosal healing

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Core tip: Not all patients with mild to moderate ulcerative colitis (UC) respond to available treatment options. Curcumin, an active ingredient of turmeric has anti-inflammatory properties and has been shown to play a protective role in chemically induced mouse models of inflammatory bowel disease and to reduce relapse rates in human UC. However, optimum dose ranging studies for curcumin in ulcerative colitis have not been performed. The present study shows that low dose curcumin (450 mg/d) is ineffective in inducing remission in mild to moderate ulcerative colitis. Therefore, higher doses with effective modes of delivery are required for optimal efficacy of curcumin.

Kedia S, Bhatia V, Thareja S, Garg S, Mouli VP, Bopanna S, Tiwari V, Makharia G, Ahuja V. Low dose oral curcumin is not effective in induction of remission in mild to moderate ulcerative colitis: Results from a randomized double blind placebo controlled trial. *World J Gastrointest Pharmacol Ther* 2017; 8(2): 147-154 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v8/i2/147.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v8.i2.147>

INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing and remitting inflammatory condition of the intestinal tract without a known etiology^[1,2]. The interaction between environmental factors, genetic susceptibility, and immune dysregulation is implicated in the pathogenesis of UC,

although their precise contributions remain incompletely understood^[3-6].

Oral 5-aminosalicylates (5-ASA) compounds are the first line therapy used for inducing clinical remission in mild to moderate UC. Treatment options for patients not responding to oral 5-ASA include oral corticosteroids, immunomodulators such as 6-mercaptopurine and azathioprine, topical agents like 5-ASA and steroid enemas and biologicals. However, steroids are associated with significant side effects, immunomodulators are slow to act, topical agents would only be effective in left-sided colitis and biologicals are costly and not every patient can afford them, especially in resource constraint countries like India. Surgery is an option but every patient does not want it, and one likes to defer surgery in mild to moderate cases. Therefore, there is a need for an agent which is safe, efficacious and cheap and can be added with 5-ASA to increase the remission rates, especially in developing countries like India, where the incidence of IBD is on the rise^[7].

Pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , IL-12, and interferon (IFN)- γ are upregulated in patients with UC^[8]. Nuclear factor (NF) κ B is the main up-regulator of expression of these cytokines and is strongly activated in UC and Crohn's disease suggesting the important role in pathogenesis. Curcumin is the major constituent of turmeric powder extracted from the rhizomes of the plant *Curcuma longa* Linn. Turmeric is used as a spice to give the specific flavor and yellow color to curry. Curcumin has been identified as the most active constituent of turmeric and has been described as an anti-inflammatory, antioxidant, pro-apoptotic, and anti-proliferative compound^[8,9]. As a traditional medicine, turmeric has also been widely used for centuries to treat inflammatory disorders in India^[9]. The pleiotropic effects of curcumin owe to inhibition of transcriptional factor nuclear NF- κ B. Curcumin blocks a signal upstream of NF- κ B-inducing kinase and I κ B kinase in intestinal epithelial cells^[10]. The effects of curcumin on the immune response (both innate and adaptive) have been a subject of much attention in the past decade^[11-15]. Curcumin has been shown to play a protective role in chemically induced mouse models of IBD^[16-19] and to reduce the relapse rate in human UC^[20-22].

Hence this study was carried out to determine the efficacy and safety of oral curcumin therapy in inducing remission in mild to moderate cases of UC.

MATERIALS AND METHODS

Study design

This study was a single center prospective randomized double-blind placebo-controlled trial comparing the remission inducing effect of oral curcumin and mesalamine (2.4 g/d in three divided doses) with placebo and mesalamine (2.4 g/d in three divided doses) in patients with UC with mild to moderate severity. The study was

carried out from January 2003 to March 2005. The study was approved by the institutional ethics committee.

Participants

All patients were recruited from the Inflammatory Bowel Disease clinic at All India Institute of Medical Sciences, New Delhi, India. Adult patients (≥ 18 years) who had mild-to-moderately active UC [Ulcerative Colitis Disease Activity Index (UCDAI) score^[23], 3-9]; with a minimum sigmoidoscopic score of 2 with at least one previously documented attack of active disease were included in this study. Patients were excluded if they had evidence of severe disease (UCDAI, > 10), concurrent enteric infection, use of oral steroids within the past 4 wk, use of antibiotics within the past 2 wk, change in dose of oral mesalamine within the past 4 wk, and initiation of azathioprine less than 6 mo before initiation of the study. Patients requiring hospitalization and imminent need for surgery, lactating and pregnant women, and those who received any investigational medicines within 3 mo were excluded. Patients with significant hepatic, renal, endocrine, respiratory, neurologic, or cardiovascular diseases also were excluded. Demographic information was recorded on a structured pro-forma.

Randomization

Sequence generation: The random numbers were generated by computerized random number (The RAND corp. Inc). The randomization list and numbered packing of the intervention were prepared by a person not involved in the study. Randomization was performed using permuted blocks of 6.

Randomization-allocation concealment: Allocation concealment was ensured by the use of sequentially numbered boxes coded using alphabet containing identical curcumin or placebo capsules, according to the allocation sequence.

Randomization implementation: All the study personals were blinded to the treatment assignment (placebo or curcumin) for the duration of the study. Placebo and curcumin capsules were similar in appearance and in their method of administration. The codes were reserved with a no-interest party and were revealed only after the recruitment and data collection had been completed.

Blinding

The individual sealed box method was used to maintain blinding of the investigators and study participants.

Study intervention

Included patients were randomized to receive 1 capsule thrice a day of either placebo or curcumin for a duration of 8 wk. Each curcumin capsule contained 150 mg of purified curcumin. The placebo was supplied as

an indistinguishable capsule containing starch with a yellow edible dye-caramel yellow. The curcumin and placebo capsules were supplied by Himalaya Drug Company (Bangalore, India). The patients in both the groups received mesalamine at a dose of 2.4 g/d. Other supportive treatment and standard care were provided to both the groups.

Follow-up

Patients were evaluated at the study center at weeks 0, 4, 8 (or as required) after recruitment. Clinical Assessment was done on the basis of UCDAI score. A sigmoidoscopic evaluation with endoscopic scoring was also done according to Baron score^[24] at each visit. Biochemical parameters like hemoglobin, erythrocyte sedimentation rate, leukocyte count, urea, creatinine, bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and albumin were performed at each follow-up visit.

Compliance was measured by obtaining a detailed study history during a personal interview as well as compliance was judged at the 4 and 8 wk follow-up visits by a blister count of the remaining capsules. Non-compliance was defined as failure to take $\geq 80\%$ of the medication.

Outcomes

The primary outcome measure was clinical remission (UCDAI ≤ 2) at 8 wk. Secondary outcomes were clinical response (defined as a reduction from baseline in the UCDAI of ≥ 3 , sigmoidoscopic remission (Baron endoscopic score of 0/1), and treatment failure defined by an increase in UCDAI scores by ≥ 3 points or treatment intolerance by the patient.

Activity of UC

The activity of UC was assessed using the UCDAI^[23]. The UCDAI was calculated by the investigator by adding the individual scores of the 4 parameters: Bowel frequency, rectal bleeding, endoscopic score, and physician's rating of severity. (Rectal bleeding and stool frequency score was assessed by asking the patient about his/her symptoms over the past 3 d. The score for these parameters was calculated individually by taking the average of the scores for the last available 3 d before the study visit. The composite score ranges from 0 (inactive disease) to 12 (severe disease activity). The Baron score^[24], represents an endoscopic classification, ranges from 0 to 3, with 0 denoting normal mucosa, (1) granularity of mucosa with loss of vascular pattern; (2) bleeding to touch; and (3) spontaneous bleeding. Sigmoidoscopic remission was defined by a Baron score of 0 or 1 (normal looking mucosa or mucosal edema alone as indicated by loss of normal vascular pattern).

Sample size estimation and statistical analysis

This study was conducted in 2003 and the efficacy of curcumin in induction of remission in UC had not been

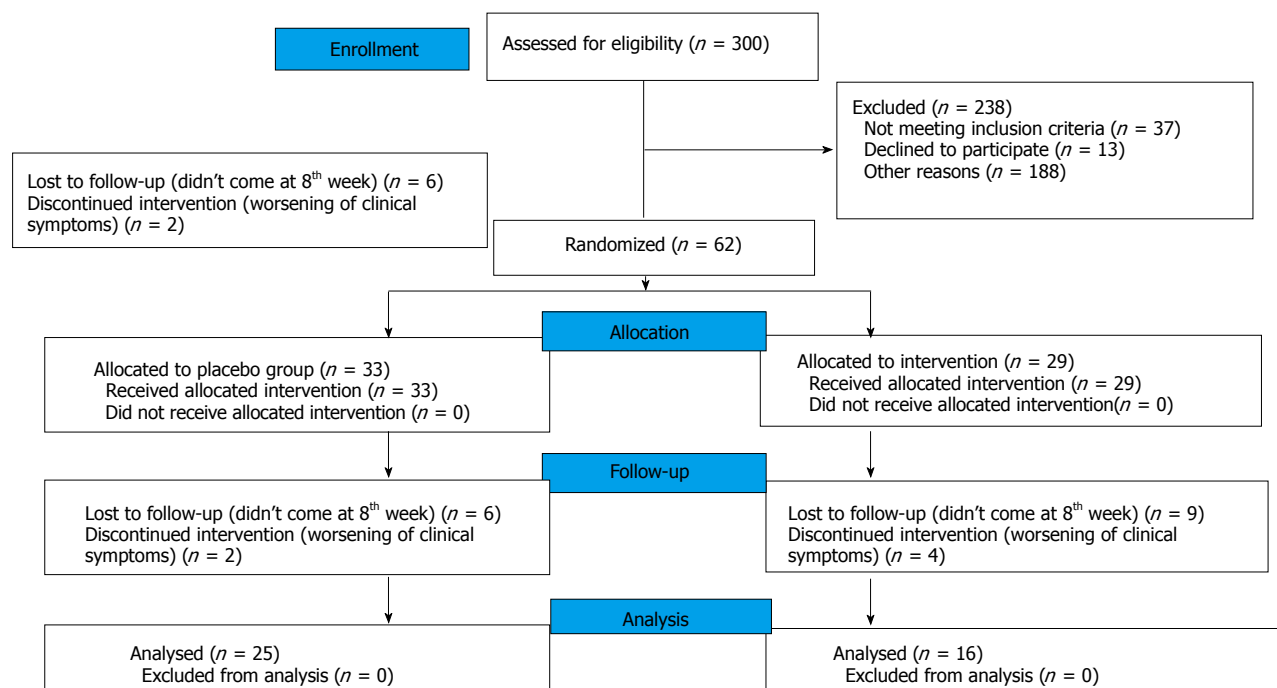


Figure 1 Flowchart demonstrating patient recruitment in curcumin and placebo group.

studied previously in any human trial. Hence, this was an exploratory pilot trial where consecutive patients of UC fulfilling the inclusion criteria were enrolled over a period of January 2003 to March 2005. The primary analysis was intention to treat worst-case scenario.

The data was entered in a Microsoft excel spreadsheet (MS Office version 2003). Descriptive statistics including measures of central tendency and dispersion were calculated for all variables. Continuous variables were compared using *t*-test for independent samples and categorical variables were compared using χ^2 test. Measures of risk were computed along with 95%CI. Changes in symptom scores and clinical sign scores from baseline to the final follow-up visit were calculated and compared between the placebo and curcumin groups. A *P*-value of < 0.05 was considered statistically significant. All calculations were done with SPSS software (v. 16).

RESULTS

A total of 300 patients presenting at the Inflammatory Bowel Disease clinic of the Department of Gastroenterology, at All India Institute of Medical Sciences (AIIMS), New Delhi, from January 2003 to March 2005 were assessed for eligibility. Of them, 62 patients fulfilled the inclusion criteria and agreed to participate (Figure 1). Thirty three patients were randomized to the placebo group and 29 to curcumin group. A total of 21 patients did not complete the trial (8 patients in the placebo group, and 13 patients in curcumin group). Thus, a total of 41 participants, 25 in the placebo group and 16 in curcumin group, completed the trial and were analyzed. The participant flow through the trial is given in Figure 1.

Demographic and clinical characteristics

Baseline characteristics were comparable between the 2 groups (Table 1). The mean baseline UCDAI score was also comparable between the two groups (5.2 ± 2 vs 5.5 ± 1.9 , $P = 0.63$) (Table 2). All subsequent analyses are presented according to ITT-WCS.

Primary and Secondary outcome measures

Induction of clinical remission (Table 3): Clinical remission was achieved in 31.03% of patients (9 out of 29) in curcumin group and 27.27% (9 out of 33) in the placebo group at 8 wk, the difference being statistically insignificant (OR = 1.20, 95%CI: 0.40-3.60; $P = 0.745$).

Improvement in UCDAI (Table 3): The UCDAI was similar between the two randomized groups at baseline (Table 2). There was no difference in the UCDAI among the randomized patients at 4 and 8 wk. Six out of 29 (20.69%) patients in curcumin group reported an improvement in DAI score by 3 or more as compared to 12 out of 33 (36.36%) in the placebo group but the difference was not statistically significant (OR = 0.46, 95%CI: 0.14-1.43; $P = 0.175$).

Mucosal healing (Table 3): Mucosal healing was achieved in 34.48% of patients (10 out of 29) in curcumin group and 30.30% (10 out of 33) in the placebo group at 8 wk, the difference being statistically insignificant (OR = 1.21, 95%CI: 0.42-3.52; $P = 0.725$).

Treatment failure: Amongst the patients who completed the study, 1 out of 16 in curcumin group and 3 out of 25 in the placebo group were found to be the cases of treatment failure defined as increase in UCDAI

Table 1 Baseline clinical and biochemical parameters of the randomized patients *n* (%)

	Curcumin group (<i>n</i> = 29)	Placebo group (<i>n</i> = 33)
Age (yr)	36 ± 12	34 ± 7
Sex (females)	13 (44.83)	8 (24.24)
Weight (kg)	55.1 ± 10.0	55.7 ± 11.7
BMI (kg/m ²)	20.8 ± 3.1	20.5 ± 3.3
Disease duration (yr)	3.83 ± 4.00	3.64 ± 2.59
Disease extent		
E3 (pancolitis)	7 (25.9)	6 (20.7)
E2 (left sided colitis)	17 (58.6)	21 (63.6)
E1 (proctitis)	3 (11.1)	2 (6.90)
Current smoking	5 (17.24)	4 (14.81)
Current alcohol use	3 (10.34)	4 (14.81)
Hemoglobin (g/dL)	12.12 ± 2.76	13.35 ± 1.72
Total leukocyte count (per cubic millimeter)	8586 ± 2306	8221 ± 2104
Platelet count (× 1000/mm ³)	256.25 ± 131.98	257.53 ± 113.01
ESR (mm/1 st h)	3 ± 2	4 ± 3
Urea (mg/dL)	22.0 ± 5.2	21.5 ± 5.2
Creatinine (mg/dL)	0.84 ± 0.26	1.19 ± 1.69
Potassium (meq/L)	4.41 ± 0.33	4.26 ± 0.78
Bilirubin (mg/dL)	0.7 ± 0.2	0.6 ± 0.1
Aspartate aminotransferase (U/L)	28 ± 6	30 ± 8
Alanine aminotransferase (U/L)	26 ± 9	28 ± 19
Total protein (g/L)	8.0 ± 0.2	7.9 ± 0.8
Albumin (g/L)	4.4 ± 0.5	4.5 ± 0.3
Current treatment		
5-ASA	29 (100)	33 (100)
Steroids	0	0
Azathioprine	2 (6.9)	2 (6.2)
Rectal steroids	0	0
Mesalamine enema	0	0

Data are given as mean ± SD. 5-ASA: 5-aminosalicylates; BMI: Body mass index; ESR: Erythrocyte sedimentation rate.

score by 3 or more. The difference between the two groups was not statistically significant (OR = 0.489, 95%CI: 0.046-5.155; *P* = 0.545).

Moreover, 4 out of 13 dropouts in curcumin group and 2 out of 8 dropouts in placebo group cited worsening of clinical symptoms as reasons for dropout were also categorized as treatment failure as per protocol. Hence, the total treatment failure rate in curcumin and placebo groups were 25% (5 out of 20) and 18.52% (5 out of 27) respectively. The difference between the treatment failure rates in the two groups was not statistically significant (OR = 1.47, 95%CI: 0.361-5.952; *P* = 0.591).

Comparison of laboratory parameters between the two randomized groups

No significant improvement in hemoglobin or albumin was reported within either group at 8th week. On comparing the two groups, no significant difference was found between any laboratory parameter at either 4 or 8 wk (Table 4).

Compliance

In the placebo group, 8 out of 33 patients did not complete the study. Two of them cited worsening of

clinical symptoms, categorized as treatment failure, to be the cause of dropout. Others were lost to follow-up. In curcumin group, 13 out of 29 patients did not complete the study. Four of them cited worsening clinical symptoms, categorized as treatment failure, to be the cause of dropout. Patient drop out due to worsening of symptoms is the main reason for reporting the ITT-WCS analysis. In patients continuing in the trial, the compliance was more than 80% in all patients in both the treatment arms.

Safety and adverse drug reactions

No adverse clinical or biochemical effects were observed in either group. One patient complained of self-limited arthralgia in the placebo group.

DISCUSSION

This was the first randomized controlled trial of oral curcumin in the induction of remission in UC. This study showed that oral curcumin at a dose of 450 mg a day was ineffective in inducing remission or attaining clinical response. Curcumin has been shown to play a protective role in chemically induced mouse models of IBD^[16-19]. Mechanisms by which curcumin exerts its pharmacological effects are thought to involve antioxidation^[4], inhibition of kinases, interference with the activity of transcription factors such as NF-κB and AP-1^[5]. Cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) are inhibited by curcumin through NF-κB dependent or independent pathway^[6,7]. NF-κB has been shown to activate, *via* transcription, the genes encoding pro-inflammatory cytokines (TNF-α, IL-1β and IL-12), cell adhesion molecules (vascular cell adhesion molecule (VCAM)-1 and intercellular cell adhesion molecule (ICAM)-1, inducible nitric oxide synthase (iNOS) and COX-2^[25-27].

We recently published a randomized controlled trial using curcumin enemas in patients with mild to moderate distal colitis^[28]. Per protocol analysis revealed significantly better outcomes in curcumin enema group, in terms of clinical response (92.9% vs 50%, *P* = 0.01), clinical remission (71.4% vs 31.3%, *P* = 0.03), and improvement on endoscopy (85.7% vs 50%, *P* = 0.04). However, in the present study, oral administration of curcumin did not induce remission after 8 wk of therapy. In a recent randomized controlled trial from Israel which enrolled 50 patients with mild to moderate UC, oral curcumin was found to be effective in inducing remission^[29]. The dose of curcumin used was 3 g/d. In the intention-to-treat analysis, 14 patients (53.8%) receiving curcumin achieved clinical remission at week 4, compared with none of the patients receiving placebo (*P* = 0.01). Clinical response (reduction of ≥ 3 points in SCCAI) was achieved by 17 patients (65.3%) in the curcumin group vs 3 patients (12.5%) in the placebo group (*P* < 0.001).

We did not find a significant effect of using curcumin on the response, remission, or mucosal healing at 4 and 8 wk as compared with placebo. The following factors

Table 2 Comparison of the Ulcerative Colitis Disease Activity Index between the two randomized groups at baseline, 4, and 8 wk

	Curcumin group		Placebo group		Mean difference (95%CI)	Significance
	<i>n</i>	UCDAI	<i>n</i>	UCDAI		
Week 0	29	5.2 ± 2.0	33	5.5 ± 1.9	-0.244 (-1.256 to 0.77)	0.632
Week 4	16	3.6 ± 2.4	23	4.4 ± 3.2	-0.823 (-2.678 to 1.020)	0.37
Week 8	16	3.4 ± 3.1	25	3.8 ± 2.8	-0.362 (-2.343 to 1.168)	0.711

UCDAI is expressed as mean ± SD. UCDAI: Ulcerative Colitis Disease Activity Index.

Table 3 Comparison of clinical remission, improvement in Ulcerative Colitis Disease Activity Index and Baron's score, and mucosal healing at 8th week between two randomized groups

	Curcumin group	Placebo group	OR (95%CI)	<i>P</i> value
Clinical remission				
PP ¹	9/16 (56.25%)	9/25 (36%)	2.28 (0.634-8.264)	0.202
ITT ²	9/29 (31.03%)	9/33 (27.27%)	1.20 (0.40-3.60)	0.745
UCDAI improvement by ≥ 3				
PP	6/16 (37.5%)	12/25 (48%)	0.65 (0.18-2.34)	0.509
ITT	6/29 (20.69%)	12/33 (36.36%)	0.46 (0.14-1.43)	0.175
Mucosal healing ¹				
PP	10/16 (62.5%)	10/25 (40%)	2.50 (0.69-9.09)	0.16
ITT	10/29 (34.5%)	10/33 (30.3%)	1.21 (0.4 - 3.5)	0.72

¹Healing defined by either endoscopically normal mucosa or only mucosal granularity. Any ulceration or friability was taken as non-healed mucosa. PP: Per-protocol; ITT: Intention to treat; UCDAI: Ulcerative Colitis Disease Activity Index.

Table 4 Comparison of the biochemical parameters between the two randomized groups at 4 and 8 wk

	Week 4			Week 8		
	Curcumin group	Placebo group	<i>P</i> value	Curcumin group	Placebo group	<i>P</i> value
Hemoglobin (g/dL)	12.0 ± 2.3	13.3 ± 2.2	0.235	12.1 ± 2.7	13.2 ± 2.6	0.404
Total leukocyte count (per mm ³)	7900 ± 2449	8085 ± 2494	0.87	8957 ± 1705	7086 ± 1969	0.082
ESR (mm/1 st h)	21.5 ± 13.4	22.2 ± 15.2	0.91	23.0 ± 17.1	25.9 ± 9.4	0.707
Urea (mg/dL)	23.1 ± 8.5	22.8 ± 7.0	0.922	24.7 ± 6.0	24.3 ± 6.7	0.89
Alanine aminotransferase (U/L)	26.5 ± 8.4	35.5 ± 20.6	0.178	29.5 ± 15.4	25.3 ± 5.4	0.516
Total protein (g/L)	7.9 ± 0.4	8.1 ± 0.8	0.666	8.3 ± 0.3	8.3 ± 0.9	0.963
Albumin (g/L)	4.7 ± 0.2	4.6 ± 0.3	0.869	4.8 ± 0.2	4.6 ± 0.2	0.169

were likely responsible for observed non-response. The first reason could be the use of an inadequate dose of curcumin. A daily total of 450 mg curcumin per day in three divided doses was used in this study. In another study where curcumin was used for inducing remission, a 3 g/d dose was used^[29], which is much higher than the dose used in our study. In a second study, curcumin in combination with 5-ASA was shown to be effective in maintaining remission in UC patients as compared to placebo^[20,22]. Again the dose of curcumin used in that study was 2 g/d, much higher than the present study. However, at the same time, none of these studies had incorporated a dose finding study design. Hence, the present study clearly adds to the knowledge that low dose oral curcumin is not effective in inducing remission in UC. The second reason could be poor bioavailability. A phase I clinical trial conducted on 25 patients with various precancerous conditions indicated that curcumin is poorly absorbed and may have limited systemic

bioavailability. Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavailability. Other studies have also demonstrated the safety of curcumin, including a phase-1 trial in which doses of up to 8000 mg of curcumin per day were administered without toxicity^[30]. We have not used any such complex formulations, which could have produced a difference. We have shown the efficacy of topical curcumin enemas in combination with oral 5-ASA in inducing remission in a similar group of patients. The dose of curcumin used in this study was just 140 mg which was lower than the dose used in this study, indicating that curcumin indeed would be effective but with proper dosage and route of administration. There have been multiple studies on this aspect that have investigated various formulations of curcumin, some of which increase systemic bioavailability

of curcumin and some have lead to increased colonic delivery^[31,32]. In a mice study, Curcumin-Zn(II) complex was prepared by stirring curcumin with anhydrous zinc chloride at a molar ratio of 1:1. Kinetic stability studies showed a good stability of the metallo-complex with zinc and *in vivo* study revealed a significant reduction in severity and extent of colonic damage with this preparation^[31]. Another study assessed the role of pH-triggered Eudragit-coated chitosan microspheres of curcumin in managing UC. *In vivo* organ bio-distribution study showed a negligible amount of curcumin in the stomach and small intestine and there was a significant reduction in extent and severity of colonic damage with these microspheres^[32]. A trial investigating these newer formulations of curcumin could better define the role of curcumin in UC. Another limitation of this study is the small sample size as it was an exploratory pilot study. In absence of any data on the use of curcumin in UC, when this study was conducted, no sample size calculations could be done. However, the study by Lang et al which had a small sample size of 50 UC patients showed the efficacy of curcumin in inducing remission as compared to placebo^[29]. Future studies are needed to prove (or disprove) the hypothesis that oral curcumin is effective in induction of remission in mild to moderate UC^[33]. The dose can range from 1 to 4 g considering that doses up to 8 g are safe^[30]. The sample sizes for these studies would have to be approximately 100 or 170 in each arm to detect an absolute difference of 20% and 15% respectively, assuming the baseline remission rate of 27% (from the placebo group).

In conclusion, low dose oral curcumin for 8 wk is not effective in inducing clinical remission or response in patients with mild to moderate UC. A multicenter collaborative trial using newer formulations of curcumin with higher bioavailability and a dose defining study design is required to conclusively answer this research question.

COMMENTS

Background

There is a therapeutic gap in inducing clinical remission in patients with ulcerative colitis (UC) with the available treatment options. Curcumin, an active ingredient of turmeric powder, because of its anti-inflammatory properties, can decrease the mucosal inflammation in patients with active UC. The present study was designed to evaluate the role of curcumin in inducing clinical remission in patients with mild to moderate UC.

Research frontiers

Oral 5-aminosalicylates (5-ASA) compounds are the first line therapy used for inducing clinical remission in mild to moderate UC. Treatment options for patients not responding to oral 5-ASA include oral corticosteroids, immunomodulators such as 6-mercaptopurine and azathioprine, topical agents like 5-ASA and steroid enemas, and biologicals. However, each of these agents is associated with its own side-effects and is not effective in every patient. Therefore, there is a need for an agent which is safe, efficacious and cheap and can be added with 5-ASA to increase the remission rates, especially in developing countries like India, where the incidence of inflammatory bowel disease is on the rise.

Innovations and breakthroughs

This was the first dose ranging study to evaluate the efficacy of oral curcumin

in patients with mild to moderate UC. They compared oral curcumin (450 mg/d) with mesalamine (2.4 g/d) vs placebo with mesalamine in inducing remission in patients with mild to moderate UC and found that oral curcumin at a dose of 450 mg/d was ineffective in inducing remission in mild to moderate UC.

Applications

The results of this study indicate that low dose curcumin is ineffective in mild to moderate cases of UC. Therefore further studies with higher doses of curcumin or with better drug delivery systems are required to evaluate the efficacy of curcumin in UC.

Terminology

Low dose oral curcumin is ineffective in patients with mild to moderate UC.

Peer-review

This is a good study to point out Low dose oral curcumin at a dose of 450 mg/d, which was ineffective in inducing remission in mild to moderate cases of UC.

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