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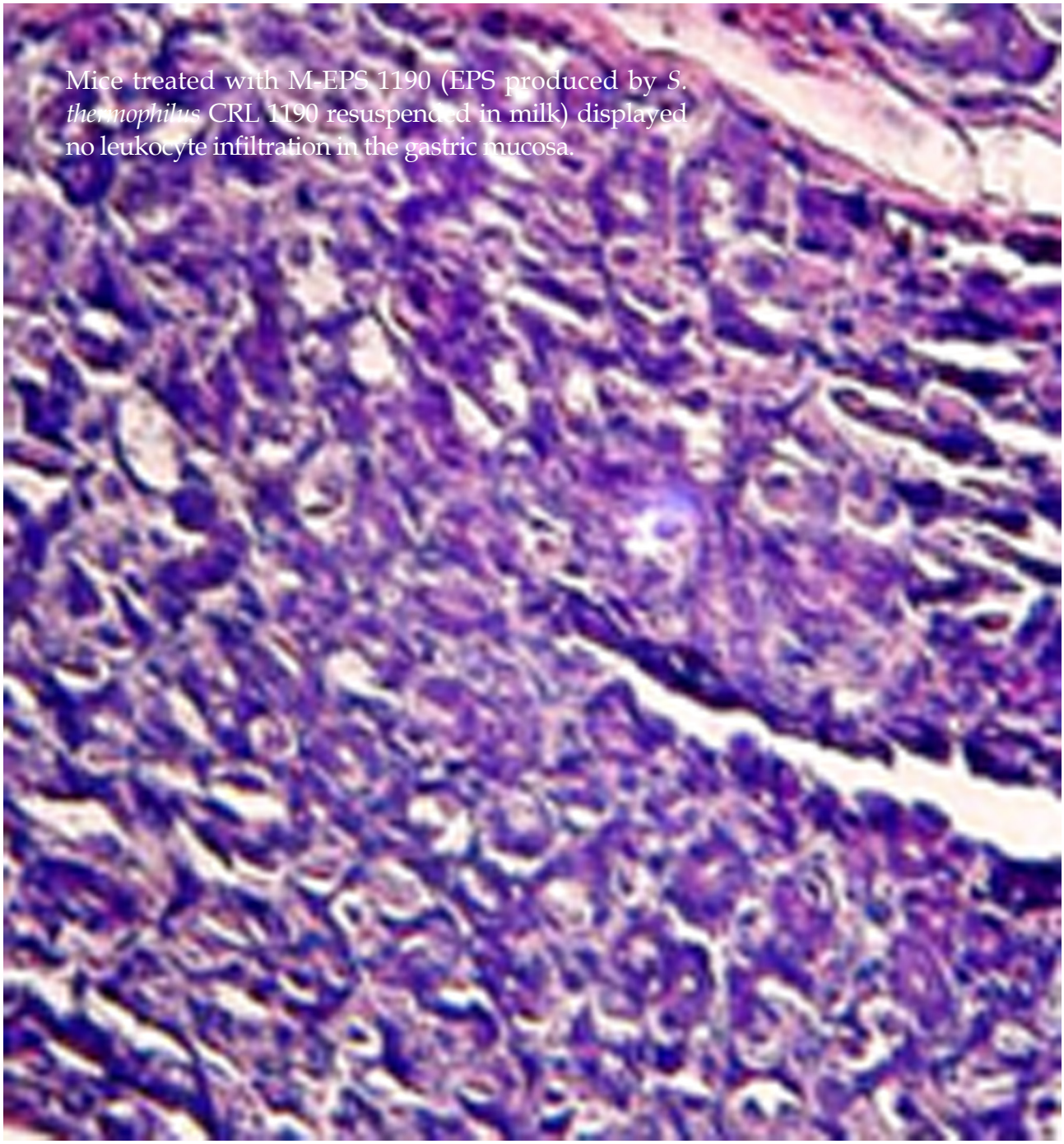

Mice treated with M-EPS 1190 (EPS produced by *S. thermophilus* CRL 1190 resuspended in milk) displayed no leukocyte infiltration in the gastric mucosa.

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EDITORIAL

Recent advances in the management of distal ulcerative colitis

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Abstract

The most frequent localization of ulcerative colitis (UC) is the distal colon. In treating patients with active distal UC, efficacy and targeting of the drug to the distal colon are key priorities. Oral and rectal 5-aminosalicylic acid (5-ASA) preparations represent the first line therapy of mild-to-moderate distal UC for both induction and maintenance treatment. It has been reported that many UC patients are not adherent to therapy and that non-compliant patients had a 5-fold risk of experiencing a relapse. These findings led to the introduction of once-daily oral regimens of 5-ASA as better therapeutic options in clinical practice due to improved adherence. New formulations of mesalazine, including the multi-matrix delivery system, and mesalazine granules, which allow once-daily administration, have been developed. They have been demonstrated to be efficacious in inducing and maintaining remission in mild-to-moderate distal UC in large clinical trials. However, existing data for distal UC are rather insufficient to make a comparison between new and classical 5-ASA formulations. It seems that the new formulations are at least as effective as classical oral 5-ASA formulations. Other treatment options, in the case that 5-ASA therapy is not effective, include systemic corticosteroids, thiopurines (azathioprine or 6-mercaptopurine), cyclosporine, infliximab and surgery. The combination of a prompt diagnostic work-up, a correct therapeutic approach and an appropriate follow-up schedule is important in the management of patients with distal UC. This approach can shorten the duration of symptoms, induce a prolonged remission, improve patient's quality of life, and optimize the use of health resources.

Key words: Aminosalicylates; Azathioprine; Infliximab mesalazine; Ulcerative colitis

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INTRODUCTION

The majority of newly diagnosed adult patients with ulcerative colitis (UC) present with disease limited to the distal or left side of the colon[1], which is also called distal UC. The term "distal UC", therefore, defines disease distal to the splenic flexure, which includes proctitis (involvement of rectum only), proctosigmoiditis (involvement of rectum and sigmoid colon) and left-sided colitis (involvement extending as far as the descending colon or splenic flexure). Cases with proctitis (E1) and left sided colitis (E2), according to the recent Montreal classification[2], are included. Approximately 80% of UC patients present as distal UC and about 20% present with extensive colitis or pancolitis[1]. The literature suggests that the course of distal UC varies. Its onset may be gradual or abrupt, and most patients experience remitting and relapsing symptoms.

As for all cases of inflammatory bowel disease, the aim of medical management of patients with distal UC is to induce remission in active disease and to minimize the risk of relapse. In treating active distal UC, efficacy and targeting of the drug to the distal colon are key priorities. Moreover, for maintenance therapy, long-term toxicity and factors that affect compliance are important. Treatment options include 5-aminosalicylic acid (5-ASA and derivatives), corticosteroids and immunosuppressive therapy. Emerging data suggest that early, aggressive treatment of distal UC may prevent or delay proximal extension, an occurrence that otherwise is common[3].

The main recent advances in conventional therapy for distal UC are once-daily mesalazine therapy, the new delivery system utilizing Multi Matrix System (MMX) technology, the newly developed micropellet formulations of 5-ASA and the reappraisal of high-dose mesalazine and immunomodulators. Especially the recent introduction of novel 5-ASAs provides a wider choice to clinicians of oral therapy for UC patients.

5-ASA is the standard first-line treatment for mild-to-moderate distal UC. Since 5-ASA is believed to act topically, the development of 5-ASA formulations aim to minimize the systemic absorption of 5-ASA from the small intestine and to maximize the delivery of the active drug to the site of inflammation in the colon. Various rectal gels, liquids, and foam enemas have been developed and fulfil these criteria by delivering 5-ASA directly to the site of inflammation, while ensuring minimal systemic absorption. However, these formulations are often associated with adverse events, such as leakage and abdominal bloating. Moreover, many patients find rectal formulations impractical and, as a result, compliance with prescribed dosing regimens is poor. Consequently, rectal formulations are mainly used as add-on therapy[4].

Only 40%-60% of the patients who are newly diagnosed or have longstanding disease are adherent to therapy[5]. It was shown that non-compliant patients had a 5-fold risk of experiencing a relapse as compared to patients taking more than 80% of their prescribed mesalazine medication[6].

Treatment alternatives to 5-ASAs include other topical preparations for rectal administration and oral and intravenous therapies.

This review discusses recent clinical trials pertaining to the management of distal UC. It summarizes the evidence for recent developments in the use of established therapies, as well as emerging novel therapies.

TREATMENT OF THE ACUTE PHASE

Several medications are available for the treatment of the acute phase of distal UC. Oral formulations and topical therapies with aminosalicylates or corticosteroids have shown to be highly effective in this situation. Meta-analysis of the published data and important relative reviews have been published[4,7-10].

In patients with mild-to-moderately active ulcerative proctitis, rectal administration of suppositories of 5-ASA or corticosteroids has been established as first-line therapies. In this setting, suppositories of 5-ASA are more effective than rectal steroids and has been shown to be more effective than oral 5-ASA[11].

Patients with active distal UC can be treated with rectal 5-ASA (enemas, foams, or suppositories), oral 5-ASA, or a combination of both. Several controlled trials have shown that rectal therapies have a more rapid effect than oral treatment[12,13]. Meta-analysis of the published data showed that rectal 5-ASA is superior to placebo and to conventional rectal corticosteroids for inducing remission of symptoms, endoscopy, and histology of distal UC[7]. Moreover, it has been found that the combination of oral and rectal 5-ASA further improves the efficacy and speed of improvement in patients with distal UC without differences in safety[13].

Although a dose response of oral mesalazine for active UC has been suggested, the benefit of mesalamine 4.8 g/d over 2.4 g/d is limited to symptom improvement rather than remission of the disease[10]. The ASCEND Ⅱ trial suggested that 4.8 g is superior to 2.4 g in patients with moderately active UC[14]. However, other recent studies do not suggest a difference[10].

There is evidence that distal active UC of mild-moderate severity should initially be treated with a combination of topical aminosalicylates and oral mesalazine (≥ 2 g/d). Concerning topical treatment alone, steroids or mesalazine are also effective, but mesalazine is more effective than steroids. Each one, as well as oral aminosalicylates alone, is less effective than combination therapy[15]. The response to oral and rectal therapy should be apparent in about 2 wk and, if rectal bleeding persists, then the response is slow and steroid therapy should continue.

In the case that rectal 5-ASA or corticosteroids and oral 5-ASA therapy are not effective, then oral corticosteroids should be administered. Usually, the suggested dose of oral prednisone (or equivalent) is 40 mg daily, which leads to rapid clinical response in the majority of patients[9]. After a clinical response, prednisone is tapered (5 mg to 10 mg/1-2 wk) with the rate of tapering depending on the disease severity and rapidity of improvement. At the same time, oral and rectally administered 5-ASA therapy should be continued with the goal of maintaining remission of UC once prednisone is discontinued.

Patients with severe distal UC should be hospitalized and treated with IV corticosteroids. Another option in these cases is the use of infliximab. Systemic corticosteroids are appropriate if symptoms of active distal UC do not respond rapidly to mesalazine. Severe distal UC is usually an indication for hospitalization for intensive treatment with systemic administration of the therapy[15]. Treatment with corticosteroids intravenously is evaluated after about 5 d.

In cases with moderate-to-severe active disease who have failed therapy with aminosalicylates, corticosteroids, or immunomodulators, the administration of infliximab is indicated. The evidence for this is provided from two large randomized, double-blind, controlled trials: ACT-1

and ACT-2 where 56% of the patients had left-sided or distal UC suggesting that infliximab is effective in this group of patients[16]. However, it should be realized that the steroid-free remission rate after 7 mo (30 wk) on infliximab is only 21%[16]. Furthermore, infliximab seems to be effective as a rescue therapy to avoid colectomy in severe UC unresponsive to intravenous steroids in short-term and long-term follow-up[17,18]. The role of infliximab in cases with severe distal UC that are resistant to therapy, and whether it is an alternative to surgery, remains to be established.

MAINTENANCE TREATMENT

All patients with distal UC are at risk for relapse and should receive maintenance treatment. The vast majority of untreated patients will relapse by 1 year, whereas maintenance therapy significantly decreases the risk of relapse[9]. Therefore, long-term treatment is indicated for reduction of the risk of relapse, but also for decrease of proximal extension of the disease and for reduction in the development of carcinoma. Only a few cases with mild ulcerative proctitis do not require maintenance treatment.

The choice of the appropriate maintenance therapy for a patient with distal UC should be based on the efficacy of the medication in combination with its long-term safety, tolerability, convenience and acceptability to the patient.

The mainstay of maintenance therapy for distal UC has been 5-ASA for the past few decades. Rectally administered 5-ASA preparations are effective for maintenance of remission in most patients with distal UC. The combination of rectal and oral 5-ASA may be the most effective strategy. However, rectal formulations are often associated with undesirable side effects (leakage and abdominal bloating), and many patients find them impractical and compliance with this treatment is poor. Therefore, long-term 5-ASA for oral maintenance treatment of distal UC is usually preferred by patients and doctors. It is of note that using 5-ASA therapy for maintaining remission after patients required prednisone is a common practice, but it is not based on the literature.

The dose-response of 5-ASA formulations in maintenance therapy of distal UC has not been definitively evaluated.

Where 5-ASA has insufficient efficacy, immune modulation is indicated. Thiopurines (azathioprine and 6-mercaptopurine) have been found to be superior to placebo in maintaining remission in distal UC[19,20]. Overall, oral therapy with azathioprine or 6-mercaptopurine is reserved for patients with steroid-dependent distal UC and those with chronic disease that is refractory to other drugs. Patients with early stage disease have higher steroid-free remission rates on azathioprine compared to patients with late stage disease[21]. Moreover, it has been suggested that increasing the dose of azathioprine up to 2.5 mg/kg appeared beneficial in patients who had not responded to 2 mg/kg per day[20].

The use of azathioprine in distal UC is less indicated than in extensive UC. Moreover, the relapse rate after drug withdrawal is significantly lower in distal UC compared to extensive UC[22]. A recent meta-analysis showed that thiopurine drugs are more effective than placebo for the prevention of relapse in UC, with a number needed to treat of 5 and an absolute risk reduction of 23%[23].

Methotrexate has also been used to maintain remission in patients with steroid-dependent UC who fail to respond to or who are intolerant of thiopurines, but the evidence is mainly based on uncontrolled studies with small sample sizes and heterogeneous doses[24,25]. In a recent study, clinical response to methotrexate was seen in 7 of 9 (78%) of UC patients who were refractory to thiopurines and 15 of 23 (65%) who were intolerant to thiopurines[26]. However, the data are limited and evidence is lacking to recommend methotrexate to maintain remission in UC.

REFRACTORY DISTAL UC

Refractory distal UC is a term with different definitions, but the most accepted is that of the case who failed or has partial therapeutic response to conventional therapy. A patient with refractory distal UC requires a complete evaluation of possible exogenous and endogenous factors contributing to this refractory condition. Enteric infections, such as clostridium difficile, campylobacter jejuni, salmonella, shigella, cytomegalovirus, herpes simplex virus and various parasitic infections, should be excluded. It is of note that the prevalence and case fatality of UC patients complicated by clostridium difficile infection rose significantly during last few years[27].

Moreover, other reasons for refractoriness include poor adherence with therapy, inadequate concentrations of the active drug, unrecognised complications (such as proximal constipation) or inappropriate diagnosis (such as co-existent irritable bowel syndrome, Crohn's disease, mucosal prolapse, or very rarely, cancer)[15]. Medication history should be obtained in detail since some agents, specifically nonsteroidal anti-inflammatory drugs and antibiotics, may play a role in the activity of the disease.

Another parameter that should be taken into account is approximately half of the patients with proctitis or distal UC present with progression of the disease and this possibility should be examined in cases that present with refractoriness. Moreover, possible worsening of the symptoms by 5-ASA preparations, although rare, should be kept in mind and, in this case, aminosalicylates should be discontinued.

Patients with distal UC not responding to rectal and/or oral 5-ASA or corticosteroids present a treatment dilemma. Options for therapy for these refractory patients include infliximab and cyclosporine. Infliximab 5 mg/kg induction (0, 2 and 6 wk) followed by maintenance therapy (every 8 wk) offers an effective treatment option for patients with refractory distal UC. The use of infliximab has also been found to be effective in preventing colecto-

my in some cases with refractory UC[17,18], but in cases that are finally operated on, it seems that there are increases in the risk of short-term postoperative complications. This is supported by the findings of a recent meta-analysis[28].

Intravenous cyclosporine (2-4 mg/kg per Id) is effective in refractory patients with distal UC but is associated with rare and potentially life-threatening side effects, such as nephrotoxicity, opportunistic infections, and seizures. Patients who respond to cyclosporine require azathioprine or 6-mercaptopurine for maintenance of remission[9].

In severe refractory distal UC not responding to intensive treatment, or if the symptoms of the disease have major adverse effects on a patient's quality of life, surgery should be considered. Overall, patients with distal UC are less likely to require surgery than patients with extensive UC. Among patients who have a colectomy for refractory UC, 10%-35% are reported to have distal disease[29,30].

NEW ORAL MESALAZINE FORMULATIONS

The most important aim of treatment for UC with 5-ASA is to deliver high concentrations of the drug topically to areas with active inflammation. Various formulations have been developed to enable release of orally administered 5-ASA in the colon.

Commercially available 5-ASA includes azo-bond prodrugs, such as sulfasalazine, olsalazine and balsalazide, and delayed and controlled-release forms of mesalazine. Although emphasis has been placed on the manner in which different delivery systems may influence responses to 5-ASAs, the evidence in clinical practice for variability in efficacy among these products is rather weak.

Two major problems have appeared during the last decades with the use of oral 5-ASA in UC patients. The first is that azo-bonded and delayed-release formulations may not deliver therapeutically effective doses of 5-ASA to the left colon. There is evidence from clinical studies showing mucosal 5-ASA concentrations using azo-bonded or bolus-release formulations to be highest in the right colon, whereas in the rectum, the concentration of 5-ASA is significantly lower[31,32]. The second is that these formulations were given multiple times daily since this has been considered essential to ensure that therapeutically effective 5-ASA doses are maintained in the colon. This approach has been shown to be efficacious for the treatment of UC in clinical studies, but patient compliance has been demonstrated to be poor in clinical practice, with the result of reduced drug efficacy and poorer disease control[6]. Therefore, the once-daily oral formulations of 5-ASA have been suggested as a better therapeutic option in clinical practice due to improved adherence.

Concerning safety, the majority of oral 5-ASA agents have safety profiles similar to that of a placebo in large clinical trials. Only sulfasalazine is not well tolerated since it is associated with dose-related side effects including nausea, vomiting, dyspepsia, anorexia, and headache.

There are no definitive data suggesting that one 5-ASA preparation is superior to another. The choice of 5-ASA agent for treatment of a patient with distal UC should be based upon tolerability, ability to titrate dose to effect and cost.

New mesalazine formulations have been developed with the aim of both increasing the adherence to oral mesalazine treatment and avoiding topical administration of the drug.

MMX mesalazine

The recently developed MMX technology (in Italy by Cosmo S.p.A. Corp) involves incorporating mesalazine into a lipophilic matrix that is itself dispersed within a hydrophilic matrix to delay and prolong dissolution. There is a gastroresistant polymer film that prevents initial drug release until exposed to a pH of 7 or higher, so the film coat normally starts to dissolve only in the terminal ileum. In this case the hydrophilic matrix is exposed to intestinal fluids and swells, leading to the formation of a viscous gel mass with a slow and gradual release of mesalazine throughout the length of the colon[33].

Initially, the efficacy of MMX mesalazine was compared with mesalazine enema in patients with left-sided active UC. Clinical remission occurred in 60% of patients in the MMX group and in 50% of the enema group. Similar improvement was seen in the endoscopic and histological pattern. In addition, the adherence rate in remission was 92% in the MMX group and 65% in the enema group[34].

In a large randomized, double-blind, placebo-controlled trial, Lichtenstein *et al*[35] investigated the efficacy of MMX mesalazine 1.2 g twice daily and 4.8 g once-daily compared with a placebo for 8 wk, for the induction of remission in patients with mild-to moderate UC. Both MMX mesalazine groups achieved statistically significant clinical and endoscopic remission compared with the placebo (34.1% and 29.2% *vs* 12.9%, 2.4 g/d and 4.8 g/d *vs* placebo, $P < 0.001$ and $P = 0.009$, respectively). Another large double-blind, placebo-controlled, multicenter clinical trial, by Kamm *et al*[36] randomized patients with active, mild-to-moderate UC to receive MMX mesalazine 2.4 g once daily, MMX mesalazine 4.8 g once daily, placebo, or a delayed-release (EUDRAGIT S-coated) mesalazine 800 mg 3 times daily. Significantly more patients achieved clinical and endoscopic remission at week eight in the MMX mesalazine groups compared with the placebo group (40.5% and 41.2% *vs* 22.1% with 2.4 g/d, 4.8 g/d *vs* placebo; $P = 0.01$ and $P = 0.007$). In contrast, the group of delayed-release mesalazine demonstrated only a trend for improvement (32.6% *vs* 22.1%, $P = 0.124$). It is of note that, in the subgroup analysis, no significant difference in the remission rates between extensive and left-sided colitis was found in the four groups of this study.

The efficacy of MMX mesalazine as maintenance therapy was examined in a more recent multicenter study[37]. Patients with UC were randomized to receive MMX mesalazine 2.4 g/d once daily, or delayed-release (EUDRAGIT S-coated) mesalazine 2.4 g/d twice daily, administered in a double-dummy fashion for 12 mo. All

patients were in remission with at least one documented relapse in the previous year. The data from this study indicate that MMX mesalazine 2.4 g/d once daily and delayed-release mesalazine 2.4 g/d twice daily are similarly tolerated and effective in the maintenance of remission of distal UC. However, when only the Italian population was examined, statistically significant treatment differences favouring MMX mesalazine were revealed.

In theory, once-daily dosing with MMX mesalazine may improve patient compliance and have higher remission rates than delayed-release mesalazine in the treatment of patients with distal UC. In order to confirm this theory, future studies evaluating compliance rates in clinical practice and larger studies focused on distal UC are required.

Mesalazine granules

Another new formulation of 5-ASA, which is becoming more widespread, is the micropellet release system, which allows once daily dosing in an easy-to-swallow formulation. It is provided as individual sachets containing a single dose, using granules to effect a delayed and sustained release of 5-ASA with similar delivery properties and systemic exposure to tablets.

Mesalazine granules are a multiparticulate formulation with an enteric acid-resistant film coating. Their dissolution starts approximately at pH > 6.0, leading to a delayed and, due to the inner polymer matrix, prolonged release of the active ingredient throughout the entire colon[38].

The mesalazine micropellet formulation was found to be as effective as tablets (EUDRAGIT L-coated mesalazine) in patients with mild-to-moderate UC, enabling a larger dose to be taken comfortably and conveniently with possible impact on patient compliance[39].

In a recent study, the administration of a 3 g once-daily dose of mesalazine granules was found at least as effective as a divided dose of 1 g given three times daily, leading a substantial proportion of patients with mild-to-moderate active UC into clinical and endoscopic remission. Especially for patients with distal UC, the clinical remission rate was significantly higher in the group using a once-daily dose compared to a three times daily dose (86% *vs* 73%, $P = 0.03$)[40].

In another recent study, after 1 year of treatment, 70.9% of the group given 2 g mesalazine granules once daily remained in remission *vs* 58.9% of the group given 1 g mesalazine granules twice daily; this difference was statistically significant ($P = 0.024$), indicating the increased efficacy of once daily, compared with twice daily, dosing[41].

These findings suggest that once daily treatment with mesalazine granules could be offered as a first choice of induction or maintenance treatment for UC patients.

OTHER NEW MEDICATIONS

Probiotics

VSL#3, a probiotic preparation containing 8 different bacterial strains, has been found to be effective in inducing remission of mild-to-moderate active UC, as well as in maintaining remission[42,43]. Concerning maintenance treatment of UC, *E. coli* Nissle 1917 has been found to be equivalent to mesalazine in maintaining remission in UC, including patients who were treated after an acute episode of UC[44]. The conclusion of a Cochrane review of randomized, controlled trials of probiotics in UC was probiotics added to standard therapy may provide modest benefits in the reduction of disease activity in patients with mild-to-moderately active UC[45].

Beclomethasone diproprionate

Recently, steroids with a colonic release mechanism and low systemic bioavailability, such as beclomethasone diproprionate are becoming available. Oral beclomethasone diproprionate in combination with oral 5-ASA has been found to be significantly more effective than 5-ASA alone in the treatment of patients with extensive or left-sided active UC[46]. In another large study of patients with active left-sided or extensive colitis, beclomethasone diproprionate 5 mg/d had an effect similar to that of mesalazine, but without systemic steroid side-effects[47]. Beclomethasone diproprionate has also been used in an enema with comparable tolerability and efficacy to mesalazine enema in mild active distal UC[48].

Budesonide MMX

The available oral formulations of budesonide have mainly been developed to treat ileocolonic Crohn's disease and not distal colonic lesions, due to their characteristic pattern of drug release in the gut. Budesonide enema is both effective and safe for the treatment of active distal UC[49]. Recently, a budesonide-MMX 9 mg formulation was developed and investigated in patients with UC. In a pilot study, budesonide-MMX induced a fast and significant clinical improvement in active left-sided UC without suppression of adrenocortical functions and without toxicity[50].

Adalimumab

Adalimumab is an anti-TNF agent similar to infliximab, but administered subcutaneously with less immunogenicity. Trials on adalimumab in UC are ongoing. A small series with preliminary data in patients with mild-to-moderate UC who had secondary failure to infliximab showed that adalimumab was well-tolerated and effective in maintaining clinical remission in a subgroup of patients with UC with lost response or intolerance to infliximab[51,52].

Parnaparin MMX

Parenteral administration of low-molecular weight heparins (LMWHs) has been taken into consideration in the treatment of UC with conflicting results. Recent experimental data proved that parnaparin sodium, a LMWH with a mean molecular mass around 5000, delivered by catheter into the colon of rat was highly effective in ameliorating dinitrobenzene (DNB)-induced colitis[53]. This lead to the suggestion that the administration of parnaparin sodium, contained in tablets delivering the product directly into the

lumen of the colon, could represent a promising approach to treat UC. In a recent study, parnaparin sodium, in the form of colon-released tablets using MMX technology, has been found to be a safe and effective treatment of distal UC[54].

Curcumin (Turmeric)

Curcumin is a biologically active natural phytochemical substance present in turmeric, and since it has anti-inflammatory and antioxidant properties, it has been suggested to be beneficial in UC. In a recent study, UC patients who received curcumin as maintenance treatment had significantly less relapses compared to patients in the placebo group. Moreover, curcumin significantly improved both clinical activity and endoscopic indices, suggesting that it is effective and safe for maintaining remission in patients with quiescent UC[55].

CONCLUSION

Distal UC is the most frequent form of this disease at diagnosis. In treating active distal UC, efficacy and targeting of the drug to the distal colon are key priorities.

Oral and rectal 5-ASA preparations represent the best therapeutic option for most patients with mild-to-moderate distal UC for both induction and maintenance treatment. There is evidence that early and aggressive treatment of distal UC may prevent or delay proximal extension.

The data showing that many UC patients are not adherent to therapy and that non-compliant patients had a 5-fold risk of experiencing a relapse has led to the introduction of once-daily oral regimens of 5-ASA as a better therapeutic option in clinical practice due to improved adherence.

New formulations of mesalazine, including MMX mesalazine and mesalazine granules, have been shown to be efficacious in inducing and maintaining remission in mild-to-moderate distal UC in large clinical trials. However, existing data, especially for distal UC, are rather insufficient to make a comparison between new and classical 5-ASA formulations. It seems that the new formulations are at least as effective as classical oral 5-ASA formulations.

Other treatment options, in the case that 5-ASA therapy is not effective, include systemic corticosteroids, thiopurines (azathioprine or 6-mercaptopurine), cyclosporine, infliximab and surgery.

The combination of a prompt diagnostic work-up, a correct therapeutic approach and an appropriate follow-up schedule is important in the management of patients with distal UC. This approach can shorten the duration of symptoms, induce a prolonged remission, improve patient quality of life, and optimize the use of health resources.

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EDITORIAL

Role of proton pump inhibitors in the management of peptic ulcer bleeding

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Abstract

Peptic ulcer bleeding is a serious medical problem with significant morbidity and mortality. Endoscopic therapy significantly reduces further bleeding, surgery and mortality in patients with bleeding peptic ulcers and is now recommended as the first hemostatic modality for these patients. The efficacy of large-dose proton pump inhibitor (PPI) therapy in reducing re-bleeding after endoscopic therapy has been supported by evidence derived from randomized controlled trials. It may be premature to recommend small-dose intravenous injection PPI after endoscopic hemostasis in patients with bleeding ulcers. An updated systematic review shows that PPI therapy before endoscopy significantly reduces the proportion with major stigmata and requirement for endoscopic therapy at index endoscopy. Some studies show that there is no significant difference between oral and intravenous PPIs in raising intragastric pH. However, clinical data is lacking in patients with peptic ulcer bleeding to date.

Key words: Proton pump inhibitor; Peptic ulcer bleeding; Re-bleeding; Hemostasis; Endoscopic therapy

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Peptic ulcer bleeding remains a serious medical problem with significant morbidity and mortality. Despite advance in management of this life-threatening condition, the mortality rate remains around 5%-10%. Endoscopic therapy significantly reduces further bleeding, surgery and mortality in patients with bleeding peptic ulcers and is now recommended as the first hemostatic modality for these patients[1,2].

Is adjuvant pharmacotherapy effective in reducing re-bleeding following successful endoscopic therapy? From a theoretical point of view, a stable blood clot in a peptic ulcer is crucial to hemostasis. However, in a low pH environment, platelet dysfunction has been observed[3,4]. In addition, pepsin can lyse the blood clots that plug vessels in the ulcer base and induce re-bleeding thereafter[4,5]. Thus, the hypothesis that by suppressing the intragastric acid, the use of proton pump inhibitor (PPI) might benefit patients at risk for further hemorrhage was proposed.

The efficacy of PPI therapy in reducing re-bleeding has been supported by evidence derived from randomized controlled trials[6]. Findings from meta-analyses suggest that histamine receptor 2 antagonists (H2RAs) might not be as effective as PPIs for this indication[6]. We have previously shown that pharmacological tolerance of H2RAs significantly limits their capability to sustain a high intragastric pH[7]. Therefore, we believe that PPIs should be the drug of choice for the prevention of peptic ulcer re-bleeding as far as therapeutic efficacy is concerned.

With regards to PPIs usage as an adjuvant pharma-

cotherapy in the management of peptic ulcer bleeding, the following questions should be answered: the dosage of optimal action, route of administration (oral or intravenous), mode of intravenous route (continuous infusion or bolus), use before or after endoscopic therapy and which is the choice PPI?

To sustain a high intragastric pH, a high dose of omeprazole has been used in previous studies concerning high-risk peptic ulcer bleeding. In our study, we used 40 mg omeprazole intravenous bolus followed by 160 mg/d continuously infusion for 3 d. The mean intragastric pH rose to 6.0 one hour after the initial bolus of omeprazole in the omeprazole group and it was maintained around this value for the rest of the 24 h[7]. The re-bleeding rates were much lower in the PPI group as compared with the H2RA group (Day 3: 0/50 *vs* 8/50, $P < 0.01$; Day 14: 2/50 *vs* 12/50, $P < 0.01$). In a similar study, Lau *et al*[8] used omeprazole 80 mg intravenous bolus followed by 8 mg/h for 3 d and the re-bleeding rates were also much lower in the PPI group as compared with the placebo group (Day 3: 5/120 *vs* 24/120 $P < 0.001$; Day 30: 8/120 *vs* 27/120, $P < 0.001$).

On the other hand, low dose PPI use was supported by some studies. A 2008 multicenter trial by Andriulli *et al*[9] demonstrated a similar efficacy of high dose PPI (80 mg bolus followed by 8 mg/h) and low dose PPI (40 mg bolus daily) in patients with peptic ulcer bleeding. They concluded that 40 mg omeprazole or pantoprazole daily was as effective as a high-dose regimen in reducing the risk of recurrent bleeding. Cheng *et al*[10] used 7-d low-dose omeprazole (3.3 mg/h) and 3-d high-dose omeprazole (8 mg/h) in patients with peptic ulcer bleeding combined with co-morbid illness. They concluded that prolonged low-dose PPI infusion for 7 d reduce re-bleeding during the first 28 d in these patients.

There are some points that deserve discussion in the Andriulli *et al*[9] and Cheng *et al*[10] studies. Dual endoscopic therapy has been proven significantly superior to epinephrine injection alone for bleeding high-risk peptic ulcers[11]. Epinephrine injection alone cannot seal the bleeding vessels immediately. Therefore, a high re-bleeding rate may occur after epinephrine injection alone[11]. This phenomenon has been observed in our previous studies[12]. Therefore, epinephrine injection is not recommended as the only therapeutic modality for these high-risk patients. Unfortunately, over 50% (50% in intensive regimen and 57.6% in standard regimen) of Andriulli *et al*'s[9] study and over one third of the patients (55/142, 38.7%) in Cheng *et al*'s[10] study received epinephrine injection alone. Under these conditions, results and conclusions may be misleading. Therefore, it may be premature to recommend low-dose intravenous PPI after endoscopic hemostasis in patients with bleeding ulcers[13].

How about the route of PPI usage? Which route (oral or intravenous) is the preferred route? Laine *et al*[14] used oral lansoprazole in patients with peptic ulcer bleeding. Patients were randomly assigned to intravenous lansoprazole (90 mg bolus followed by 9 mg/h infusion) or oral lansoprazole (120 mg bolus followed by 30 mg every 3 h). A pH was recorded for 24 h. Mean pH rose above 6 after 2-3 h of intravenous PPI and 3-4 h of oral PPI. They concluded that frequent oral PPI may be able to replace the currently recommended intravenous bolus plus infusion PPI therapy in patients with bleeding ulcers. In one recent article, Javid *et al*[15] also proved that there was no significant difference among various PPIs (omeprazole, pantoprazole and rabeprazole) given through different routes (intravenous and oral routes) on raising intragastric pH above 6 for 72 h after successful endoscopic hemostasis in bleeding peptic ulcer. In our recent study, we have proved that oral rabeprazole and intravenous omeprazole are equally effective in preventing re-bleeding (13/78 in rabeprazole *vs* 12/78 in omeprazole, $P > 0.1$) in high-risk bleeding peptic ulcers[16]. All secondary outcomes between the two groups were similar including the amount of blood transfusion, hospital stay, need for surgery and mortality.

Is it beneficial to use PPI before endoscopic therapy? Lau *et al*[17] concluded that infusion of high-dose omeprazole before endoscopy accelerated the resolution of signs of bleeding in ulcers (active bleeding: 12/187 in omeprazole group *vs* 28/190 in placebo group, $P = 0.01$) and reduced the need for endoscopic therapy (60/314 in omeprazole group *vs* 90/317 in placebo group, $P = 0.007$). An updated systematic review includes six trials of 2223 patients[18]. PPI therapy initiated before endoscopy in bleeding peptic ulcer patients significantly reduced the proportion with major stigmata (37.2% *vs* 46.5%, $P = 0.005$) and requirement for endoscopic therapy at index endoscopy (8.6% *vs* 11.7%, $P = 0.02$). However, there was no evidence that PPI therapy improves clinical outcomes.

How about the mode of intravenous administration? Should PPI be given as a bolus or continuous infusion? A pooled analysis of 16 randomized controlled trials (> 3800 patients) suggested that optimal effect is achieved with an intravenous 80 mg bolus, followed by continuous infusion of 8 mg/h for 3 d, after which therapy may be continued with an oral PPI. Intermittent bolus administration yielded a minimal benefit[18]. This observation is plausible because intermittent bolus of PPI may cause a big fluctuation of intragastric pH.

Is there any benefit in using PPIs for patients with high-risk patients? Recent meta-analyses showed that use of PPIs significantly decreased the risk of further bleeding [odds ratio: 0.4, 95% confidence interval (CI): 0.24-0.67], the need for urgent surgery (odds ratio: 0.5, 95% CI: 0.33-0.76) and the risk of death (odds ratio: 0.53, 95% CI: 0.31-0.91)[6,19,20].

What is the optimal large dose for intravenous PPI usage? It has been demonstrated that the benefit of PPI appears more pronounced in Oriental patients[21]. This phenomenon can be explained by the low gastric acid output, cytochrome P-450 2C19 genetic polymorphism and high prevalence of *Helicobacter pylori* in Asians. In our recent study, we compared two large doses of intravenous PPIs (160 mg/24 h, $n = 60$ mg/24 h and 192 mg/24 h, $n = 60$) in patients with high-risk peptic ulcer bleeding[22]. Bleeding

recurred in a total of 11 (9.2%) patients, with six (10%) in the 192 mg/d group and five (8.3%) in the 160 mg/d group ($P > 0.1$). All secondary outcomes between the two groups were similar including the amount of blood transfusion (mean: 1179 mL *vs* 1203 mL, $P > 0.1$), hospital stay (mean: 9.5 d *vs* 9.9 d, $P > 0.1$), need for surgery ($n = 1$ *vs* $n = 0$, $P > 0.1$) and mortality ($n = 1$ *vs* $n = 0$, $P > 0.1$). Therefore, we believe that dosage of intravenous PPIs in Asians can be lower than that of Occidentals.

In conclusion, in patients with high-risk peptic ulcer bleeding after successful endoscopic therapy, a large intravenous dose of continuous infusion PPI for 3 d is recommended as the management of choice. Whether the oral route can replace the intravenous route in administering PPI remains to be determined.

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TOPIC HIGHLIGHT

Angelo Zullo, MD, Professor, *Series Editor*

Hepatic encephalopathy therapy: An overview

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Abstract

Type-C hepatic encephalopathy (HE) is a severe complication of cirrhosis, which seriously affects quality of life and is strongly related to patient survival. Treatment based on a classical pharmacological approach that is aimed at reducing the production of gut-derived toxins, such as ammonia, is still under debate. Currently, results obtained from clinical trials do not support any specific treatment for HE and our competence in testing old and new treatment modalities by randomized controlled trials with appropriate clinically relevant end-points urgently needs to be improved. On the other hand, patients who are at risk for HE are now identifiable, based on studies on the natural history of the disease. Today, very few studies that are specifically aimed at establishing whether HE may be prevented are available or in progress. Recent studies have looked at non absorbable disaccharides or antibiotics and other treatment modalities, such as the modulation of intestinal flora. In the treatment of severe stage HE, artificial liver supports have been tested with initial positive results but more studies are needed.

Key words: Complications of cirrhosis; Porto-systemic shunts; Ammonia; Nitrogen metabolism; Transjugular intrahepatic portosystemic shunt

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INTRODUCTION

Hepatic encephalopathy (HE) is a neurological syndrome that occurs as a consequence of severe liver damage and portal hypertension. HE is divided into three types: (1) encephalopathy associated with acute liver failure [type-A (= acute) HE], occurring in patients with fulminant hepatitis; (2) encephalopathy associated with portal-systemic bypass [type-B (= bypass) HE], observed in patients with portal-systemic bypass and no intrinsic hepato-cellular disease; and (3) [type-C (= cirrhosis) HE][1] most frequently observed in patients with cirrhosis and portal hypertension. This review is on the treatment of the latter type of HE only.

In cirrhotic patients, HE may be clinically overt or minimal. The term minimal HE (MHE) includes a number of cognitive deficits such as alterations of psychomotor speed and executive functions[2], detectable in patients with liver cirrhosis only by psychometric[3-5] or electrophysiological techniques[6,7]. Clinically, overt HE (OHE) may be further divided into episodic (developing over a short period of time and fluctuating in severity), or persistent (with continuous neurological symptoms negatively affecting the patient's self-sufficiency). Both episodic and persistent HE may be induced by a precipitating event or may occur apparently

spontaneously[1]. Some HE precipitating events are: constipation, hypo- or hyperkalemia, alkalosis, hyponatremia, dietary indiscretion, hypovolemia, gastrointestinal bleeding, dehydration, infections, surgery, renal failure, anaemia, diuretics and psychoactive medications. Defining type-C HE into minimal or overt, episodic or persistent and precipitated or spontaneously occurring is clinically relevant since the management of each category is very different. Moreover, in planning clinical trials on HE treatment, including patients that are homogeneous according to the above classifications is of crucial importance.

Type-C HE represents a major clinical problem. In cirrhotic patients who were followed from a time when the disease was compensated, HE represents, in fact, the second most frequent cause of decompensation after ascites and before variceal bleeding[8]. HE is particularly frequent in patients undergoing portal-systemic shunt[9-11], and is considered an important prognostic factor for survival[12-15]. Both overt and MHE have a detrimental effect on the overall quality of life[15], since even MHE impairs the execution of simple and complex tasks, such as driving[16-18]. For these reasons, research searching for a better treatment is ongoing.

At present, many aspects of HE remain a matter of debate and are seen as "beyond treatment". The current recommendations are based on the generic hypothesis that the symptoms are caused by the loss of a "protective" mechanism exerted by the liver on brain functions. As an effect of liver failure and porto-systemic shunting, substances arising from the gut are able to reach the systemic circulation and the central nervous system, where they can exert a "toxic effect" on brain function. This concept goes back to the beginning of the last century and is supported by: (1) the high incidence of HE after surgical, radiological or spontaneous porto-systemic shunting[9,10,19-22]; (2) the improvement of HE after bowel cleansing by enema[23] or gut irrigation[24]; (3) the improvement of HE by decreasing the stent diameter of transjugular intrahepatic porto-systemic shunts (TIPS)[22,25], and consequently, increasing the amount of intestinal blood shunted into the systemic circulation; and (4) the improvement of HE by closing large spontaneous porto-systemic shunts[26]. Any attempt to clarify the nature of the substances involved in the pathogenesis of HE, as well as the exact mechanism affecting brain function, have been unsatisfactory until now. Ammonia is still incriminated more often, but several other compounds, such as mercaptans, short-chain fatty acids amines, γ-aminobutyric acid (GABA), endorphins, glutamate, endogenous benzodiazepine agonists, tryptophan and several of its metabolites have also been investigated.

However, the role of these factors is still a matter of debate. As far as the mechanism involved in the central nervous system is concerned, in the last few years, astrocyte swelling has been identified as an important process negatively influencing neuronal neurotransmission as well as the brain energy production rate. Moreover, astrocyte swelling may affect the function of important brain proteins by causing oxidative and nitrosative stress with evidence of protein tyrosine nitration and, more recently, ribonucleic acid (RNA) oxidation[27]. The astrocyte swelling hypothesis is able to explain one of the key features of HE, namely that the syndrome is precipitated by heterogeneous factors. Many of these factors have been shown to induce the swelling of astrocytes by different mechanisms[28]. The infection may, for example, induce astrocyte swelling by endotoxins and pro-inflammatory cytokines[29]. Moreover, it has been recently proposed that neutrophils, in addition to ammonia, may be involved in the pathogenesis of HE. Thus, neutrophils can be a target for future anti-inflammatory therapeutic strategies in addition to ammonia lowering therapies[30].

Uncertainties on the pathogenesis of HE limit the development of specific pharmacological therapies. Nevertheless, treatments such non-absorbable disaccharides or antibiotics, gut cleansing by enemas or nasogastric tubes, general measures such as nutritional supports, correction of the precipitating events and of electrolyte imbalance have been used empirically for a long time and are considered standard treatments[31] in patients with HE. Unfortunately, their efficacy cannot be considered as "evidence-based". In fact, most studies were performed before the era of rigorous randomized controlled trials (RCTs) and well-designed therapeutic trials on HE are warranted. It can be difficult to objectively stage HE's severity and to appropriately select clinically relevant end-points[32].

PREVENTION OF HE

A number of observational studies on the natural history of HE and on risk factors for its development are in the literature. These studies allow the identification of patients at risk for developing this complication of liver cirrhosis with sufficient confidence. Therefore, prevention of HE is possible. Preventive treatments are above all needed by patients at high risk of HE, such as those with more advanced liver disease (Child C or ascites)[33], those undergoing radiological[9,11,19-22] or surgical porto-systemic shunts, as well as those bearing large spontaneous shunts in whom episodes of HE are very frequent or persistent[21]. Other patients likely to be selected for preventive measures are those who have already had at least one episode of HE in the past[34] and those with MHE at their first observation[4,35,36]. These two conditions are in fact associated with bouts of HE at follow up.

Given the large prevalence of patients at risk of HE, the possible advantages of a life- long preventive treatment should be balanced against possible adverse events and costs and should be tested by appropriate RCTs. These studies should be specifically aimed at establishing whether HE can be prevented. Their design should be different from that used in HE treatment studies. In fact, the ideal preventive study should include patients without HE at entry, and the main end-point should be the occurrence of any overt episode of HE during follow-up. This end point is very objective and easily identifiable. Each study should include patients with a given risk factor for HE. For exam-

Table 1 RCTs on the prevention of episodes of overt hepatic encephalopathy

Ref.	Type and NO. of patients included	Aim of the study	Tested treatment (s)	Control treatment	Results
Riggio *et al*[38] 2005	Patients submitted to TIPS (75)	Prevention of post TIPS HE	Lactitol (60 g/d) rifaximin (1200 mg/d)	No treatment (25)	No difference between treatment and control groups
Sharma *et al*[39] 2009	Patients who recovered from HE (140)	Prevention of recurrence of HE (secondary prophylaxis)	Lactulose (30-60 mL in 2 or 3 divided doses)	No treatment (70)	Lactulose effective
Kanematsu *et al*[42] 1988	Patients submitted to surgery (56)	Prevention of HE precipitated by surgery	BCAA enriched solution, (29)	Conventional AA solution (27)	No difference between treatment and control groups
Rolachon *et al*[24] 1994	Patients bleeding from varices	Prevention of HE precipitated by bleeding	Gut cleansing using mannitol by naso-gastric tube	No treatment	Gut cleansing effective
Bass *et al*[53] 2009	History of HE	Prevention of recurrence of HE (secondary prophylaxis)	Rifaximin 550 mg twice daily for 6 mo	Placebo	Rifaximin effective

TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; BCAA: Branched-chain amino acid.

ple, all patients who survived a first episode of HE or, as another example, all patients submitted to a transjugular intrahepatic portosystemic shunt (TIPS) The sample size for the study could be estimated from the incidence of HE in the population at risk (for example, from the incidence of HE occurring in patients submitted to a TIPS). The inclusion of a "no-treatment" or a "placebo" group is mandatory. Cost/benefit ratios, as well as data on tolerability and safety, should be considered. Survival should be a secondary end point of the study. Since a prophylactic treatment should be prolonged life-long, the ideal therapy should be extremely safe and well tolerated.

In clinical practice, measures to reduce the nitrogenous load from the gut, such as long-term administration of non-absorbable disaccharides, are commonly applied in patients with advanced cirrhosis[37]. However, their efficacy in preventing HE has been specifically tested only very recently; one RCT report is now available on patients submitted to a TIPS and another has been reported on patients who recovered from an episode of OHE (secondary prophylaxis) (Table 1).

In post-TIPS patients, a recent RCT demonstrated that there was no difference in the incidence of OHE during the first month after TIPS placement, regardless of whether the patients received a prophylaxis with lactitol, rifaximin or no treatment[38]. On the contrary, lactulose has been shown to be able to significantly prevent the occurrence of a second episode of HE in patients who recovered from the first episode[39]. In both studies, a control group receiving no treatment was included. Therefore, low-absorbable disaccharides (lactitol or lactulose) resulted in effective prevention of recurrence of HE after a first episode but not in the prevention of HE after a TIPS. These different results underline the need for including homogeneous patients with specific risk factors in studies aimed at HE prophylaxis. In fact, HE in the first month after TIPS placement may be particularly difficult to prevent. Further compromise of first-pass hepatic clearance of ammonia is to be expected after TIPS placement. Additionally, splanchnic blood flow increases when there is a major reduction of the porto-systemic pressure gradient. Thus, delivery of ammonia to the systemic circulation may increase. Another factor to consider is upregulation of intestinal glutaminase activity, which has been reported to increase after porto-systemic shunt procedures[40]. This enzyme is responsible for the large amount of ammonia generated by the small intestine. Accordingly, one might anticipate that in the immediate aftermath of a TIPS procedure, more "intense" HE therapy might be needed to prevent overt episodes of HE.

Another RCT aimed at studying the effect of a probiotic yoghurt on the psychometric performance of cirrhotic patients with MHE showed that the episodes of OHE at follow up were significantly lower that those observed in the no-treatment arm of the study[41].

Concerning the prevention of precipitant induced HE, a series of specific treatments may be adopted, such as blood aspiration by a nasogastric tube, gut cleansing (by means of gut lavage, oral laxatives or enemas), parenteral/enteral nutrition (in case of bleedings or infections that may lead to a negative energy balance), diet (e.g. no proteins, low proteins, vegetable proteins) and specific drugs [e.g. branched-chain amino acids (BCAAs), ornithine aspartate, non-absorbable disaccharides, antibiotics]. However, until now, RCTs specifically aimed at testing these prophylactic approaches are very few. The only examples are a RCT showing that gut cleansing by means of a solution of mannitol can reduce the incidence of post-hemorrhagic HE[24] and another study on post-operative parenteral nutrition that showed no differences in the rate of occurrence of HE between patients treated with BCAAs-enriched and conventional amino acid solutions[42] (Table 1).

TREATMENT OF HE

MHE

The diagnosis and treatment of MHE are still active matters of discussion[43]. Computerized tests have been recently proposed (and validated) in patients with MHE[44,45] and may represent an amelioration of our diagnostic capacity. Most studies available in the literature have shown that several pharmacological approaches seemed to ameliorate patient psychometric performances. However, MHE affects quality of life and is a risk factor for the development of episodes of OHE[4,35,36]. In the last few years, it has been repeatedly suggested that it may seri-

Table 2 RCTs on the treatment of MHE

Ref.	Type of study	Type of HE/ patients (*n*)	Tested treatment	Control treatment	Results
Prasad *et al*[46] 2007	RCT	MHE (61)	Lactulose (30-60 mL of lactulose in 2 or 3 divided doses)	No treatment	Lactulose improved the quality of life
Bajaj *et al*[41] 2008	Prospective randomized trial	MHE (25)	Probiotic yoghurt	No treatment	Probiotic improved the psychometric performance
Liu *et al*[73] 2004	Double blind, randomized study	MHE (55)	Bioactive, fermentable fibers and lactic acid bacteria	Placebo	Synbiotic treatment improved the psychometric performance and the Child-Turcotte-Pugh class
Malaguarnera *et al*[74] 2009	Randomized study	MHE (125)	Bioactive, fermentable fibers Bifidobacterium + fructo-oligosaccharides	Lactulose	Both treatments improve blood ammonia and psychometric performance

MHE: Minimal hepatic encephalopathy.

ously impair the driving capacity of cirrhotic patients[16,18], which can be evaluated by driving simulators[17].

The recent demonstration that lactulose in patients with MHE is able to induce an amelioration in the quality of life[46] raised a new prospective in the therapeutic approach of this clinical condition (Table 2). In fact, the demonstration that a given treatment can ameliorate patient psychometric performances, although obtained in RCTs (Table 2), is meaningless because MHE is by definition a subclinical condition. Future studies on the treatment of MHE should be aimed a ameliorating the clinical consequences of this alteration. In addition to quality of life, possible end-points in these studies could be the prevention of overt episodes of HE, which are particularly frequent in patients with MHE, and the improvement of skills such as driving capacity. Nevertheless, the modification of psychometric tests should not be chosen as the main end-point of the study, but as criteria to include comparable patients. Since a treatment of MHE should be prolonged life-long, the ideal therapy should be extremely safe and well tolerated. The modulation of intestinal bacterial flora can be a valid therapeutic approach for MHE.

Precipitant-induced episodic HE

The cornerstones of treatment for precipitant-induced episodic HE are the identification and treatment of the precipitating events and the general support of patients. In fact, the prevention of falls or body injuries in disorientated patients, the care of bladder and bowel functions, the care of intravenous lines, the monitoring of fluid balance, the monitoring of blood glycaemia and electrolytes (such as of arterial blood gases), the correction of acid/base disorders, blood pressure monitoring and the avoidance of aspiration pneumonia are the strategies commonly applied to support patients with episodic HE. The nutritional status of the patient is also considered to be useful. An energy intake of 35/40 kcal/kg body weight per day and a protein intake of 1.2/1.5 g/kg body weight per day are recommended. Energy should be provided by glucose and fat in a ratio of 50%-65%/35%-50% of non-protein calories, according to the european society of parenteral and enteral nutrition guidelines for nutrition in liver disease[47].

Moreover, in patients with severe HE (grades Ⅲ to Ⅳ), solutions with an increased content of BCAAs and a reduced amount of aromatic amino acids can ameliorate neurological symptoms by ensuring, at the same time, an adequate protein intake.

The action of a well-recognized precipitating factor acts as a trigger in precipitant-induced HE. Multiple precipitating events may coexist in the same patient. Although not specifically evaluated, the identification and correction of the precipitating event is considered the first-line effort in patients with this type of HE. If the symptoms do not ameliorate once the identified precipitating event is resolved, a well-known clinical rule is to search for a second complication, for example, a superimposed infection in a patient who has recently bled. Some strategies that are commonly applied to stop precipitating events are the following: (1) in patients with HE induced by gastrointestinal hemorrhage, stop the bleeding with vasoactive drugs, an endoscopic therapy or an angiographic shunt (TIPS), correct the anemia with a blood transfusion and use a nasogastric tube to facilitate upper gastrointestinal cleansing; (2) infections (e.g. pulmonary, of the urinary tract, spontaneous bacterial peritonitis) should be promptly treated with appropriate antibiotic therapies; (3) constipation should be resolved by cathartic and/or bowel enema, electrolyte abnormalities by discontinuing diuretics and correcting hypo- or hyperkalemia; (4) deterioration of renal function should be corrected, if possible, by stopping diuretics, treating dehydration and discontinuing nephrotoxic drugs; and (5) if HE is precipitated by the administration of exogenous sedatives, benzodiazepines should be discontinued and flumazenil, the competitive benzodiazepine antagonist that binds with the benzodiazepine receptor with a high affinity, should be initiated, thus inhibiting the action of these drugs[48] (Table 3).

Recurrent/persistent HE

Searching for possible identifiable and correctable precipitating events is important also in recurrent/persistent HE. The presence of large spontaneous porto-systemic shunts is demonstrable in some patients with persistent HE[21]. In selected cases, the diameter of such large shunts have been reduced by surgical or radiological techniques, resulting in an amelioration in HE[49-52]. Since

Table 3 Treatment strategies in patients with precipitant-induced episodic HE

General supportive care	
	Prevention of falls or body harm in disorientated patients
	Care of bladder and bowel function
	Care of i.v. lines
	Monitor fluid balance
	Monitor glycaemia and electrolytes
	Monitor arterial blood gases
	Correct acid/base disturbances
	Monitor blood pressure
	Avoid aspiration pneumonia
	Prevent causes of sepsis
Support nutritional needs	An energy intake of 35-40 kcal /kg BW/d and a protein intake of 1.2-1.5 g/kg BW/d are recommended. Energy should be provided by glucose and fat in a ratio of 65-50: 35%-50% of non protein calories according to the ESPEN guidelines for nutrition in liver disease (31)
	In patients with severe hepatic encephalopathy (Grade Ⅲ-Ⅳ), solutions with an increase content of BCAAs and reduced amount of aromatic amino acid can ameliorate neurological symptoms ensuring adequate protein intake
Treatment of the precipitating event	
GI bleeding	Stop bleeding with vasoactive drugs, endoscopic therapy or angiographic shunt (TIPS)
	Correct anaemia with blood transfusion
	Nasogastric tube to facilitate upper GI cleansing
Infection (pulmonary, urinary tract, spontaneous bacterial peritonitis)	Appropriate antibiotic terapie
Exogenous sedatives	Discontinue benzodiazepines
Electrolyte abnormalities	Discontinue diuretics
	Correct hypo or hyperkalemia
Constipation	Cathartic
	Bowel enema
Deterioration of renal function	Discontinue diuretics
	Correct dehydration
	Discontinue nephrotoxic antibiotics

large spontaneous shunts are similar to a well-functioning surgical or radiological anastomosis, this approach must be balanced against the possibility of a significant increase in portal hypertension and liver transplantation should always be considered as the first option in these patients. Refractory post-TIPS HE may also be successfully treated by reducing the stent diameter[22,25]. Since the treatment should be prolonged life-long, the ideal therapy should be extremely safe and well tolerated.

PHARMACOLOGICAL APPROACHES TO THE TREATMENT OF HE

The following pharmacological approaches have been used in the treatment of HE (Table 4).

Low-absorbable antibiotics

One of the first strategies applied in patients with HE aimed to suppress bacteria involved in colonic ammonia genesis. In fact, more than 25 trials evaluated the use of a large series of antibiotics (i.e. neomycin, paromomycin, metronidazole, vancomycin, rifaximin) in patients with minimal, persistent and episodic HE. Currently, however, the use of antibiotics is only recommended for short periods of time. However, a recent study suggested that rifaximine may be given for prolonged periods safely and this drug may be able to prevent HE recurrence in patients with previous episodes of OHE[53].

Non-absorbable disaccharides

Lactulose and lactitol administered per os, reaching the colon unmodified, act by reducing the production and absorption of ammonia through several mechanisms. A recent systematic review concluded that "there is insufficient evidence to determine whether non-absorbable disaccharides are of benefit in patients with HE"[54]. Although this analysis can be criticized on several aspects[55], it has raised the issue of non-absorbable disaccharide efficacy and, more generally, the need for placebo-controlled trials in the therapy of HE[56]. An open label RCT that was recently published concluded that lactulose is effective for secondary prophylaxis of HE; i.e in patients who recovered after a first episode[39].

Interestingly, in the group of patients treated with lactulose, significantly fewer patients developed an overt episode of HE precipitated by infections. Non-absorbable disaccharides were able to reduce bacterial translocation in cirrhotic patients, thus reducing the occurrence of spontaneous bacterial peritonitis and other infections. By the same mechanism, these drugs were able to reduce the inflammation, which had been proposed as a pathogenetic mechanism for astrocyte swelling in the brain.

Association between intestinal antibiotics and non-absorbable disaccharides

From a pathophysiological point of view, the association between intestinal antibiotics and non-absorbable disaccharides should not provide additive benefits because

Table 4 Some of the RCTs available on the treatment of hepatic encephalopathy

Ref.	Type of study	Type of HE/ patients (*n*)	Tested treatment	Control treatment	Results
Uribe *et al*[23] 1987	Double-blind, controlled trial	Episodic overt HE (20)	Lactitol and lactose enemas	Nonacidifying enemas	Acidifying agents like lactose and lactitol are effective and superior to tap-water enemas for the treatment of HE
Hassanein *et al*[31] 2007	Prospective, randomized, controlled, multicenter trial	Severe episodic overt HE (70)	Molecular adsorbent recirculating system (MARS) and standard medical therapy	Standard medical therapy	MARS is associated with an earlier and more frequent improvement of HE
Kircheis *et al*[57] 1997	Randomized, double-blind, placebo-controlled, multicenter trial	MHE (53) and mild overt HE (grade Ⅰ-Ⅱ, 53)	L-ornithine-L-aspartate, 20 g/d i.v.	Placebo	Therapy improves psychometric performance and is safe and effective in HE treatment
Stauch *et al*[58] 1998	Randomized, double-blind, placebo-controlled clinical trial	MHE (23) and mild overt HE (43)	L-ornithine-L-aspartate, 9 g/d orally	Placebo	Therapy improves psychometric performance, blood ammonia levels and is safe and effective in HE treatment
Ahmad *et al*[59] 2008	RCT	Overt HE (80)	L-ornithine-L-aspartate, 20 g/d i.v.	Placebo	Treatment improves blood ammonia and mental state
Sushma *et al*[62] 1992	Prospective randomized double-blind study	Overt HE (74)	Sodium Benzoate, 5 g	Lactulose	Improvement in portal-systemic encephalopathy parameters occurred in both treatment groups and was similar
Reding *et al*[66] 1984	Double-blind randomised trial	Chronic HE (22)	Zinc acetate 600 mg/d	Placebo	Treatment improves psychometric performance
Riggio *et al*[67] 1991	Double-blind, crossover trial	Chronic HE (15)	Zinc sulfate 600 mg/d and lactitol	Lactitol	Zinc was significantly raised after oral administration, but no modification in the parameters included in Conn's index were observed
Loguercio *et al*[72] 1995	Double blind parallel trial	HE (40)	SF-68	Lactulose	SF-68 improves blood ammonia and psychometric performance
Gentile[75] 2005	Randomized, double-blind, crossover study	HE (107)	Acarbose 300 mg/d	Placebo	Acarbose improves blood ammonia levels and HE clinical parameters

the former are supposed to act against the intestinal flora, which are responsible for the efficacy of the latter. Nonetheless, some clinical observations support a role for this association in the sub-group of patients with a scarce response to each agent separately. The efficacy of the association can be monitored through the measurement of faecal pH, which should be maintained as lower than 6.

Ornithine aspartate

L-ornithine-L-aspartate (LOLA) is a stable salt composed of two natural amino acids, both important substrates in the metabolic conversion of ammonia to urea and glutamine. LOLA induces an increase of liver and muscle ammonia metabolism, leading to a decrease in blood levels, and is able to cross the blood-brain barrier, increasing the cerebral ammonia disposal. The drug can be administrated both intravenously and orally[57-60]. According to the results of published studies, LOLA is more effective than placebo in reducing blood ammonia and in ameliorating patient mental status and psychometric performance. It should be noted that additional studies have been completed but the publication of results was not allowed by the company producing the drug[55]. Moreover, LOLA is not available in several countries. Recently LOLA showed similar results to placebo in patients with acute liver failure and HE[61].

Drugs favoring alternative pathways of nitrogen metabolism

Sodium benzoate (SB) is able to bind ammonia to form hippurate, a non-toxic substance that can be eliminated in urine and is widely used in patients with a congenital deficit in the urea cycle. SB has the advantage of being particularly inexpensive (1/30 of the cost of lactulose). SB showed an efficacy similar to lactulose in patients with episodic precipitant-induced HE[62], but a note of caution in the use of SB in cirrhotic patients derives from the observation that its administration (10 g/d) induced an increase in both basal blood ammonia and glutamine-induced ammonia levels[63]. Moreover, the prolonged use of SB can interfere with the management of ascites because it induces a significant sodium load. Sodium phenylacetate and SB (Ammonul) is the only drug approved by the Food and Drug Administration for the treatment of acute hyperammonemia and associated encephalopathy in patients with urea cycle disorders[64]. Ammonul *via* intravenous injections is able to promote the synthesis of non-urea nitrogen-containing metabolites, which can be excreted in the urine. A RCT on cirrhotic patients with severe (grade Ⅲ-Ⅳ) HE is currently ongoing. HPN-100 is a pro-drug of phenylbutyrate and a pre-pro-drug of phenylacetic acid (dosed orally in a liquid form). HPN-100 provides an alternative pathway to the urea cycle for the disposal of waste nitrogen through renal excretion of phenylacetylglutamine. The drug is under investigation in patients with urea cycle diseases but has never been used in patients with liver failure.

Zinc

Zinc deficiency has been reported in patients with liver cirrhosis and related neurologic dysfunction. Moreover, reduced zinc concentrations inversely correlate with blood

Table 5 Possible future approaches to HE treatment

Objectives	Approaches currently used	Proposed approaches under evaluation
To reduce the production of Gut-derived toxins	Disaccharides	Probiotics
	Low-absorbable antibiotics	Fermentable fibers, acarbose
		Spherical adsorptive carbon (AST 120)
To favor nitrogen metabolism	Liver transplantation	Artificial liver support
	Reduction of TIPS diameter	Sodium benzoate + phenylacetate (Ammonul)
	Closure of a spontaneous portal systemic shunt	L-ornithine phenylacetate
	Ornithine Aspartate	HPN-100 (Phenylbutyrate + phenylacetic acid)
	Zinc	
	Sodium benzoate	
To correct the alterations in neurotransmission	BCAA	
	Flumazenil	

ammonia and experimental studies showed that zinc supplementation improves ammonia detoxification through urea genesis by increasing liver ornithine transcarbamylase activity[65]. Existing RCTs on oral zinc supplementation to cirrhotic patients, however, have shown conflicting results[66,67].

Benzodiazepine antagonists

Endogenous benzodiazepine (BZD)-like substances have been involved in HE pathogenesis. Flumazenil is a competitive BZD antagonist. One meta-analysis of six RCTs[68] showed that flumazenil induced a clinical improvement in 27% of the patients versus 3% of the placebo group, and an improvement of the EEG tracing (19% *vs* 2%). Another meta-analysis, including 12 trials for a total of 756 patients, led to the conclusion that flumazenil had no significant effect on recovery or survival from HE[69]. No side effects were observed during flumazenil treatment.

BCAAs

Several RCTs and reviews have assessed the effects of BCAAs in patients with HE. In fact, solutions with an increased content of BCAAs and a reduced amount of aromatic amino acids can ameliorate neurological symptoms by ensuring an adequate protein intake at the same time. One meta-analysis[70] concluded that BCAA increased recovery rates from episodic HE without definite effects on mortality, and a more recent review[71], based on 11 RCTs, where BCAAs were either parenterally or orally administered and given alone or as part of solutions containing other amino acids, confirmed that BCAAs significantly increased the number of patients improving from HE as compared with control treatments, without any convincing evidence of any effect on survival. The authors remarked that most trials were small, with a short follow-up, and were of low methodological quality.

Modulators of intestinal bacterial flora

Probiotics, synbiotics (when combined with fermentable fibres), and prebiotics can reduce ammonia production by modifying the gut bacterial flora. The effect of these products in the treatment of HE are currently under investigation: two RCTs have been reported on the effect of probiotics on minimal[41] and OHE[72]; two on synbiotics in MHE[73,74] and one on prebiotic acarbose in patients with OHE[75]. Table 5 shows an overview of the new therapeutic approaches for HE treatment.

FURTHER APPROACHES

Artificial devices

Artificial devices have been shown to improve HE symptoms in patients with decompensated cirrhosis, probably by favoring the disposal of toxins accumulated as the result of a failing liver. Extra-corporeal albumin dialysis (ECAD), using the molecular adsorbent re-circulating system (MARS), has been recently tested by a RCT. Seventy patients with grade-Ⅲ or grade-Ⅳ HE were randomised to receive ECAD plus standard medical therapy (SMT) or SMT alone. The improvement of HE was significantly more frequent and faster in the ECAD group as compared with the SMT group[31].

Correction of electrolyte disturbances

Hyponatremia, commonly found in patients with cirrhosis and ascites, may increase brain edema, a typical condition in case of acute liver failure. A "low-grade brain edema" leading to astrocyte swelling has been also hypothetically thought to be involved in the pathogenesis of type-C HE[29,76]. In rats with a portacaval shunt, chronic hyponatremia exacerbated ammonia-induced brain edema[77]. Hyponatremia was related, in patients with cirrhosis, to the comparison of electroencephalographic abnormalities, known as a risk factor for the development of OHE[22] and a well-known precipitating factor for the development of episodic HE. In this direction, Aquaretic drugs have been proposed in the treatment of hyponatremia in cirrhotic patients[78]. Unfortunately, their use in the prevention of HE in cirrhotic patients with low sodium levels or in the treatment of episodic HE precipitated by hyponatremia can be only hypothesized, since it was never tested until recently. No data are available on the evolution of HE in patients treated with aquaretic drugs.

CONCLUSION

The efficacy of most pharmacological approaches tradi-

tionally used in the treatment of HE is still a matter of intense debate. The empirically developed strategies for the treatment of HE, such as the identification and treatment of the precipitating event and the general support of the patients with episodic HE or the reduction of the blood flow thought a large portal-systemic shunt in the patients with recurrent/persistent HE, make this complication treatable in the majority of patients.

Therapy for HE remains strongly based on the pathophysiological assumption that nitrogen substances coming from the gut are not cleared by the failing liver and are relevant for the modifications occurring in the central nervous system. Improvement in our knowledge of the pathogenesis of HE suggests that several new therapies for HE will emerge (Table 5). These new approaches are likely to be derived from: (1) a better understanding of the cause of astrocyte swelling in the brain as well as the role of inflammation in the pathogenesis of HE; and (2) new knowledge on ammonia trafficking and on the role of intestine and kidney in nitrogen handling. At the same time, our competence in testing old and new treatment modalities should be enhanced urgently. Novel, well designed studies are needed. In particular, RCTs of the new era should have the following characteristics: (1) Homogeneous patients should be included. For example, the inclusion of patient groups with both minimal and OHE in the same study is to be avoided, as it is now clear that these two types of patients are not comparable and the methodology used to stage their symptoms is completely different; (2) Appropriate end points for the study need to be chosen, such as improvement in quality of life or the prevention of future OHE manifestations; and (3) It is necessary to standardize and objectively stage the severity of OHE. In fact, the development of a simple and clinically applicable standardized grading scale, useful for both diagnosing and staging, is essential to obtain a diagnostic tool that is easily applied in practice and sufficiently accurate to offer precise end-points for controlled therapeutic trials.

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REVIEW

Treatment of psychological co-morbidities in common gastrointestinal and hepatologic disorders

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Abstract

Anxiety and depressive disorders frequently coexist with gastrointestinal and hepatologic conditions. Despite their high prevalence, approach to treating these co-morbidities is not always straightforward. This paper aims to review the current literature into etiology of psychological co-morbidities and their treatment in three conditions commonly encountered at gastroenterology outpatient clinics, namely inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and chronic hepatitis C (HepC). The paper demonstrates that although psychotherapy (and cognitive-behavioural therapy in particular) has been established as an effective treatment in IBS, more studies are needed in HepC and IBD. Antidepressants have been recognized as an effective treatment for psychological and somatic symptoms in IBS and for depression in HepC, but good quality studies in IBD are lacking despite the promising preliminary findings from animal models and case studies. Further studies in this area are needed.

Key words: Inflammatory bowel disease; Irritable bowel syndrome; Hepatitis C; Psychological co-morbidities; Antidepressants; Psychotherapy

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INTRODUCTION

Anxiety, depression and poor quality of life are highly prevalent in the chronically ill[1-3]. They can also interact with each other. For example, psychological status is known to independently impact on health-related quality of life[4]. Moreover, there is a positive relationship between the presence of anxiety and depression[5]. All these associations are common among people suffering from chronic gastrointestinal and hepatologic disorders. Indeed, there is evidence that anxiety and depressive disorders frequently coexist with gastrointestinal[6,7] and hepatologic[8,9] conditions. In the case of gastrointestinal diseases this may perhaps be explained by the fact that the gut, while responding to environmental and physiological factors, also directly cooperates with the brain through the so-called brain-gut axis[10]. In the case of hepatologic disorders the etiology seems much more complex and this will be explained in more detail below.

Although psychological co-morbidities are highly prevalent in gastrointestinal and hepatologic disorders, the approach to treating these co-morbidities is not always straightforward. This paper aims to review the current literature into etiology of psychological co-morbidities and their treatment in three conditions commonly encountered at gastroenterology outpatient clinics, namely inflammatory

bowel disease (IBD), irritable bowel syndrome (IBS) and chronic hepatitis C (HepC). These three conditions were selected from among many gastrointestinal and hepatologic disorders due to their commonness but also due to their etiological differences and thus possible different origins of psychological difficulties. For example, IBD is a chronic, disabling and only rarely life threatening condition, which significantly impacts on patients' quality of life and which has been controversially associated with psychological problems. IBS is a very common chronic functional and non-life threatening condition of the gastrointestinal tract where the psychological burden is not obviously proportional to the severity of its presentation, while HepC is a chronic and potentially life threatening hepatologic disorder with a significant psychological burden, present mainly in those sufferers aware of their diagnosis.

IBD

Epidemiology

IBD is a generic term used to describe a group of chronic and usually relapsing inflammatory disorders of the gastrointestinal tract, of which Crohn's disease (CD) and ulcerative colitis (UC) are the most common. The prevalence of IBD ranges from 37 cases to 246 cases per 100 000 persons for UC and from 26 cases to 199 cases per 100 000 persons for CD depending on the region of the world[11]. The disease's prevalence is not equally distributed among races, with the Jewish and Caucasian populations at highest risk[12]. Both sexes have been observed to be equally affected by IBD, however, UC is slightly more common in men, and CD in women[13].

Presentation, etiology and psychological co-morbidities

IBD is characterised by an inappropriate immune response that causes characteristic inflammatory lesions in the gut wall. Both CD and ulcerative colitis involve inflammation of the bowel wall and both have a relapsing course. CD causes inflammation of the full thickness of the bowel wall anywhere along the digestive tract (from mouth to anus) in a discontinuous fashion, whereas ulcerative colitis affects the colon only, causing inflammation which is continuous, commencing in the rectum and extending proximally along the bowel for a variable distance. In UC, only the mucosal layer of the bowel is inflamed. Although CD may involve the gut anywhere along its length, it mainly affects the distal small intestine (ileum) and colon. Common symptoms of CD include: abdominal pain; diarrhoea; urgency; fever; weight loss and anemia. Ulcerative colitis similarly involves symptoms such as diarrhoea and abdominal pain. However, rectal bleeding and the passage of mucous per rectum are also commonly experienced, with weight loss and anemia being less common than in CD[14].

The etiology of IBD is unknown. Nonetheless, genetic, immune and environmental factors have all been implicated in its causation[15]. Studies also report that stressful life events exacerbate the disease[16]. More specifically, it has been conceptualized that psychological stress may be linked to the exacerbation of IBD, and UC in particular, by inducing systemic and mucosal pro-inflammatory responses[17]. IBD is at present an incurable condition and its course is unpredictable. As the disease is usually diagnosed in young adults, sufferers must often cope with their disease for many years. Their quality of life and psychosocial wellbeing may be profoundly impaired as a consequence of systemic symptoms, surgery, medication side effects and prevalent fatigue. Both CD and UC have a significant impact on patients' self-image, social relationships and sexual functioning[15,18]. Moreover, IBD is often associated with IBS[19]. According to researchers, up to 60% of IBD patients in remission, concurrently suffer symptoms of IBS[20]. Therefore, for these patients, quality of life and psychosocial well-being remain impaired regardless of whether IBD is active or quiescent. Furthermore, in population-based studies, more than 50% of IBS patients have reported psychiatric symptoms[21]. Thus, anxiety and depression in patients with IBD may be partly explained by co-existent IBS. In view of the above findings, it is not surprising that the rate of anxiety and depression in patients with IBD is around 30% during remission[22] and as much as 70% during relapse[23]. However, the etiology of these psychological co-morbidities in IBD is associated with a number of controversies, as reported by the present author elsewhere[24].

Standard treatment

Common treatment options for IBD include aminosalicylates (e.g. sulfasalazine, mesalazine), glucocorticoids (e.g. prednisolone), immunomodulators (e.g. azathioprine 6MP, methotrexate), and antibiotics (e.g. metronidazole, ciprofloxacin). Less common treatments for severe disease include cyclosporine and monoclonal antibodies (e.g. infliximab)[25,26]. Aminosalicylates and immunomodulators are mainly used to maintain remission of IBD. However, they can also be used to control mild to moderately active disease. Immunomodulators become effective after 10-12 wk of treatment whereas corticosteroids are used when a rapid response is required and they are typically a first-line treatment to induce remission. However, it should be acknowledged that corticosteroids cannot be used as a maintenance therapy as they have been commonly associated with many serious side effects when taken for a long time[25]. However, all listed treatment options are associated with some side effects and, importantly for the purpose of this paper, some of these side effects may be of psychological nature (e.g. mood changes, mania, depression and psychoses induced by corticosteroids)[27].

Treatment of psychological co-morbidities

Psychotherapy including supportive-expressive, interpersonal and psychodynamic modalities as a treatment for psychological problems in patients with IBD has been examined in a small number of studies[28-31] and by-and-large proved ineffective for treating psychological co-morbidities.

The few studies that examined cognitive-behavioural therapy showed more encouraging results. Schwarz and Blanchard (1991), in a randomised controlled trial with 29 participants, found cognitive behavioral therap (CBT) to be an ineffective way to treat psychological problems in a mixed IBD group of CD and UC patients[32]. However, others[33], in a prospective but uncontrolled study with 28 IBD participants, identified CBT as a highly useful tool in a short- and long-term treatment for psychological distress in IBD. Other investigators[34] in a prospective non-controlled study with 11 adolescents with IBD, also found CBT to be effective as a long-term treatment for anxiety and/or depression as assessed by DSM-IV-TR criteria when additionally supported by antidepressants. The same group of researchers subsequently conducted a randomized controlled trial with 41 adolescents with subsyndromal depression and showed reduction in depression and anxiety at 3 mo in the experimental but not the control group[35]. Moreover, 15.4% of the CBT group *vs* 25% of the comparison group had moderate/severe disease activity at 2 wk post treatment, with a drop from 28.6% and 29.4% at baseline, respectively. However, this group difference was not statistically significant. Further, in the most recent randomised controlled trial, Diaz Sibaja *et al*[36] showed CBT to be an effective treatment for anxiety and depression in IBD, the effect of which was maintained at 12 mo follow-up. However, this study did not measure the impact of CBT on the course of the disease. Moreover, small studies into hypnotherapy have indicated its significant potential in improving the course of the disease[37,38].

A review evaluating evidence arising from these studies concluded that psychotherapy has little impact generally on the course of disease in IBD, although it may be beneficial for patients with anxiety and depression[39]. A more recent paper reviewing psychological co-morbidity and treatment in IBD suggested that, based on initial evidence, CBT has a potential to treat anxiety and depression in IBD effectively[40]. There is however only limited evidence on the impact of CBT on the course of the disease and this should be further explored. Larger studies measuring both psychological status and disease activity are clearly needed in this area as CBT seems to be a promising pathway for psychological treatment in patients with IBD. Larger controlled studies into the influence of hypnosis on clinical outcomes could also be of interest as preliminary findings are encouraging and hypnosis has also been found effective in IBS[41].

With respect to pharmacological treatment of depression and anxiety in patients with IBD, to date, there has been little formal research on the use of antidepressants in IBD, with most published data being uncontrolled and anecdotal. In the systematic review co-authored by the present author, it was observed that even though antidepressants seem to improve both mental and somatic status of IBD patients, the low quality of available studies makes it impossible to make a definitive statement on their efficacy[42]. In the review, 12 relevant publications were identified, all presenting non-randomised studies. In 10 papers, paroxetine, bupropion and phenelzine were found effective for treating both psychological and somatic symptoms in patients with IBD. In the subsequent qualitative interview study we showed that gastroenterologists commonly treat IBD patients with antidepressants for pain, anxiety and/or depression, and insomnia[43]. Gastroenterologists reported that tricyclic antidepressants (i.e. amitriptyline, dothiepin, prothiaden, doxepin, imipramine, nortriptyline) were successful in reducing pain, gut irritability, and urgency of defecation. However, only a few doctors had experience of treating IBD patients with newer antidepressants. The most recent update to the systematic review on the role of antidepressants in IBD[44] found a positive impact of antidepressants (i.e. desipramine and fluoxetine) on inflammation in IBD. However, the evidence came mostly from animal trials. Good quality human data are lacking and randomized controlled trials are warranted. They are especially needed as antidepressants may offer a yet relatively unexplored contribution to the management of IBD.

IBS

Epidemiology

Functional disorders account for up to 50% of referrals to gastroenterologists in outpatient clinics[45,46], with IBS alone accounting for 20% of gastroenterology output practice[47]. The prevalence of IBS has been estimated at 17 per 100[48], making it one of the most common disorders in gastroenterological practice[49].

Presentation, etiology and psychological co-morbidities

IBS is a chronic relapsing condition in which there is abdominal pain or discomfort associated with altered bowel habits (constipation and/or diarrhoea)[50]. Other common symptoms include flatus and bloating. IBS is classified as a functional gastrointestinal disorder (FGID), meaning that it presents with non-structural symptoms and is identified only by symptoms[51]. In line with other FGIDs, the etiology of IBS is controversial. IBS is considered to be a disorder in which sensory and motor[50] and inflammatory[52] changes can play a role. It is conceptualized that the symptoms of IBS can be the result of altered motility, impacted on by such factors as psychological difficulties, food, infections and hormones. From a clinician's perspective, according to a renowned survey study involving 704 members of the American Gastroenterological Association, FGIDs are defined as conditions in which no known structural abnormalities, or infectious or metabolic causes, can be found[46]. However, in the same survey, 57% of practitioners and 34% of academics claimed that FGIDs are associated with stress and 43% of practitioners and 26% of academics saw them as motility disorders. A more recent study reports that doctors perceive FGIDs as psychological disorders or merely the absence of organic disease, quite often revealing pejorative attitudes towards FGID sufferers[53]. However, FGID is perhaps best understood as a product

of interaction between psychological factors and altered gut physiology *via* the brain-gut axis[10]. Because of this, the biopsychosocial model has been found useful in effectively understanding FGIDs and their treatment[54-55]. Interestingly, in population-based studies, more than 50% of IBS patients have reported psychiatric symptoms[21]. These findings lend support to the notion that the patient's psyche plays an important role in the etiology and course of IBS.

As previously stated, IBS commonly co-exists with IBD and both disorders additionally co-exist with psychological problems such as anxiety and depression. Some investigators have explained this co-existence by hypothesizing that chronic inflammation (IBD) may lead to persistent gut dysfunction (IBS)[56] and that psychological factors are likely to be involved in this process[20]. Although, traditionally, IBD was treated as an inflammatory disorder and IBS as a functional disorder, it has become increasingly difficult to separate the two conditions, as the current research provides evidence on the existence of pathological abnormalities in the gut in patients with IBS[57].

Standard treatment and treatment of psychological co-morbidities

As IBS symptoms may result from disturbed functions of intestine, brain, or in neurological links between intestine and the brain, treatment can be targeted at multiple levels of the brain-gut axis[58]. Conventional pharmacological treatment includes bulking agents, antidiarrhoeals, antispasmodics, prokinetics, serotoninergic agents and antidepressants[58,59]. Non-drug treatments such as probiotics and peppermint have also been found effective in IBS[60].

As IBS has been considered a partly psychological disorder, it is not surprising that psychological (psychotherapy) and psychiatric treatments (antidepressants) for IBS have been the subject of many studies, as evidenced by systematic reviews and meta analysis[59,61,62]. In the most recent high quality meta analysis including 32 randomised controlled trials, tricyclics and SSRIs have been found equally effective for symptoms of IBS, with no serious adverse events[61].

In the same study the researchers observed that while antidepressants are effective in the treatment of IBS, there are few high-quality studies on the use of psychological therapies in IBS. Nevertheless, they showed that a range of different psychological therapies were able to significantly reduce physical symptoms in patients with IBS, with studies on CBT providing greatest evidence[61]. Another important observation has been made by researchers working on the role of hypnosis in treating IBS[41,62]. In a systematic review comprising 14 trials (eight without and six with a control group), Tan *et al*[41] observed that hypnosis improves both the cardinal symptoms of IBS and non-colonic symptoms in the majority of patients. Wilson *et al*[62] reported on 18 trials of which four were randomized, two controlled and 12 uncontrolled and showed that hypnotherapy was effective in the management of IBS. However, these authors also recommended better quality trials. Although pharmacological treatment with antidepressants has been found effective in IBS, some researchers claim the superiority of psychological treatments over antidepressants in terms of long-term reduction in health care costs[63]. However, there is a scarcity of studies comparing antidepressants to psychotherapy and such studies could shed some light on which treatment modality is more effective in patients with IBS.

HEPC

Epidemiology

Hepatitis C is a chronic disorder which carries a mortality risk, being a major cause of cirrhosis, end-stage liver disease and liver cancer[64]. The current typical modes of acquisition for acute hepatitis C in Western countries are intravenous drug use and sexual intercourse[65]. Drug use *via* injection accounts for up to 60% of cases and another 20% of cases are probably sexually acquired. Other known exposures (occupational, hemodialysis, household, perinatal) together account for about 10% of infections and in the remaining 10%, no recognized source of infection can be identified[66]. For HepC, the acquisition patterns differ, with injection drug use accounting for 50% of cases, blood transfusion for 20% and sexual exposure for a small number of cases. Interestingly, up to 30% of cases report an unknown acquisition source, which can probably be partly attributed to patients' denial of high-risk behaviors[67]. In a recent population-based survey, the prevalence of chronic HepC in Australia was estimated at about 2 per 100[68], with the 20-24 years age group having the highest HepC prevalence of around 5% (95% CI: 3.3%-8.1%) with a male to female ratio of 1.8:1.0.

Presentation, etiology and psychological co-morbidities

HepC is a viral infection. Typically, within 2 wk of exposure to the hepatitis C virus, antibodies to the virus (HCV RNA) appear in the blood. Approximately 85% of acutely infected patients subsequently develop HepC. In 15% of patients, HCV RNA in serum becomes undetectable and these patients either do not develop the disease or develop it later[14]. The majority of patients experience no clinical symptoms[69] but up to 25% of patients may develop jaundice, and 10%-20% report non-specific symptoms such as fatigue, nausea and vomiting[14]. In some studies, up to 90% of patients had documented psychiatric and/or substance abuse diagnoses[70]. Particular research on military veterans, showed that approximately 50% of patients with HepC have been diagnosed with depression, 40% with anxiety, 30% with post-traumatic stress disorder and 20% with psychosis[70,71]. In another study with patients awaiting treatment with interferon α, depression was diagnosed in only 28% of patients and anxiety in 24%[8]. A recent Canadian population-based study showed that, in 1995, 22% of all HepC population had some mental health condition and this rate increased to 32% by 2000 and 35% by 2005, with depression being most prevalent[9]. The discrepancies

in the prevalence of anxiety and depression in patients with HepC may depend on many factors such as age differences of participants or concurrent treatment with interferon α. Some researchers, however, have also recommended caution when interpreting the meaning of high rates of psychological and psychiatric problems as well as poorer quality of life[72] in patients with HepC. This is because patients' scores on psychological measures appear to vary depending on whether they are aware or unaware (many patients may spend years with occult infection) of their HepC positivity[73,74]. This may suggest that the psychological impact of diagnosis knowledge may play an important role in these patients' psychological outcomes. Moreover, because in some studies up to 80% of patients with HepC have been classified as substance and alcohol users, addiction and other high risk behaviors are likely to be confounding factors contributing to the level of psychological problems in HepC[70,73]. Notwithstanding the controversy about the reasons for and the exact level of psychological problems in patients with HCV, their psychological burden is clearly significant.

The psychological burden may also be multiplied by the stigma attached to HepC[75], as the disease is stereotypically associated with alcoholism, drug addiction and the human immunodeficiency virus. Moreover, according to some researchers, HepC itself may contribute to the psychological morbidity through pathophysiological events resulting from infection[76], which may impact on cognitive functioning[77].

Standard treatment

Until this decade, the disease had a very low success rate from antiviral monotherapy with standard interferon α, with only about 6% to 13% of patients achieving virological clearance when treated for 24 and 48 wk, respectively[78]. A major improvement in therapy has resulted from a combination therapy comprising interferon α and ribavirin, which has given a response rate of 35% during a 24-wk therapy and 43% during a 48-wk therapy[79]. This response rate has further increased after the recent development of pegylated forms of interferon α, which in combination with ribavirin produces a 56% response rate after a 48-wk therapy[80].

Although the combined pegylated interferon and ribavirin treatment gives higher viral clearance rates, treatment related depression is still a significant issue in as many as 30% of patients, compared with 34% for non-pegylated interferon and ribavirin therapy[81]. According to Manns and colleagues (2001), in the case of both treatment modalities, about 35% of patients suffer from irritability and 40% from insomnia.

Treatment of psychological co-morbidities

There is some general agreement, based on clinical practice, on how to treat depression and other psychiatric conditions in HepC[82]. These researchers found most psychotropic medications (antidepressants, mood stabilizers, antipsychotics, and neuroleptics) to be safe to use in the management of patients with HepC and psychiatric illness, and for the management of interferon-induced neuropsychiatric adverse effects. In their recent systematic review, Sockalingam *et al*[83] evaluated 9 trials on antidepressants in HepC and found SSRI antidepressants safe and efficacious in treatment of depression after interferon therapy.

In contrast to IBS, but consistent with a limited number of relevant high quality studies in IBD, psychotherapy has not been widely studied in HepC and no randomized controlled trials or systematic reviews are available. Only two studies that used psychotherapy have been found[84,85]. Lang *et al*[84] conducted a small retrospective survey of 29 HepC patients treated with interferon and suffering depression who were about to discontinue the treatment. Twenty three of these patients were provided with a psychiatric care comprising antidepressants and psychotherapy which improved their treatment compliance. However, the study was not randomized and it applied supportive psychotherapy together with pharmacological treatment using antidepressants. It is, therefore, hard to estimate whether the positive result was achieved due to the effectiveness of antidepressants or psychotherapy or the combination of the two. Skibinski[85] in their non-randomized controlled study showed that short-term group cognitive-behavioural therapy does not improve quality of life whilst individual therapy does. However, groups were not directly compared as the researchers used Spearman correlation as their only type of analysis and correlated a particular group with symptoms. As HepC patients commonly suffer from mental disorders and as antidepressants may not be as effective as psychotherapy in preventing long-term relapses of these problems, studies into efficacy of psychotherapy are needed. Randomised controlled trials are clearly warranted.

CONCLUSION

Psychological co-morbidities are highly prevalent in patients with chronic gastrointestinal and hepatologic disorders. Although psychotherapy (and CBT in particular) has been established as an effective treatment in IBS, more studies are needed in HepC and IBD. Antidepressants have been recognized as an effective treatment for psychological and somatic symptoms in IBS and for depression in HepC, but the good quality studies in IBD are lacking despite the promising preliminary findings from animal models and case studies. Further studies in this area are needed.

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CASE REPORT

Cryoglobulinemia in elderly patients with HCV-related chronic hepatitis

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Abstract

Hepatitis C virus (HCV) infection affects about 3% of the world's population and often leads to chronic liver disease. In some industrialized countries, HCV prevalence increases with age, but the optimal management of older patients has not been accurately defined. HCV infection can also lead to lymphoproliferative disorders, the most common being mixed cryoglobulinemia (MC), and also for this condition that frequently affects elderly patients, the optimal therapeutic strategy is still debated. We report the case of a 77-year-old Caucasian woman with HCV-related chronic hepatitis and cutaneous manifestations consisting of urticaria and pruritus related to MC resistant to antihistamines. The patient underwent a treatment with interferon and ribavirin. Such a treatment led to early biochemical and virological response associated with the resolution of cryoglobulinemia and cutaneous symptoms. After the end of treatment, HCV replication relapsed, but cryoglobulinemia and cutaneous symptoms did not recur. In the absence of definite treatment guidelines in this particular context, our experience suggests that the presence of symptoms related to HCV-infection that deeply affect patient quality of life warrants antiviral therapy even beyond the age limits that currently exclude patients from treatment.

Key words: Cryoglobulinemia; Elderly patients; Hepatitis C virus chronic hepatitis; Antiviral treatment

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INTRODUCTION

Hepatitis C virus (HCV) infection affects about 3% of the world's population and often leads to chronic liver disease. HCV infection can also lead to lymphoproliferative disorders, the most common being mixed cryoglobulinemia (MC)[1].

In some industrialized countries, such as Japan and Italy, the prevalence of HCV infection increases with age[2]. Unfortunately, antiviral therapy with PEG-interferon alpha and ribavirin, which represents the current treatment of choice, often fails in older patients, especially in those affected by HCV-related MC. Moreover, in this context,

neither the optimal therapy strategy nor prognostic criteria have been accurately defined[1].

We report the case of an elderly woman with HCV-related chronic hepatitis associated with MC, presenting with severe urticaria and itching resistant to antihistamines, who underwent PEG-interferon and ribavirin treatment.

CASE REPORT

In January 2007, a 77-year-old Caucasian woman with HCV-related chronic hepatitis, diagnosed in the early 1990s, was referred to our outpatient clinic because of urticaria and itching resistant to antihistamines. The most common causes of urticaria had been previously excluded, such as allergic and haematologic diseases, other gastrointestinal infections, parasitosis, autoimmune diseases (other than MC), and tauopathies. In 1998, she had undergone treatment with interferon 3 times a week with no benefit. The patient was not able to report either type or dosage of interferon or treatment duration. When we first saw the patient, she was in good physical condition and was not affected by heart, lung, renal or neurological diseases. Physical examination revealed urticaria and scrabble signs. Laboratory tests are listed in Table 1.

Liver, renal and thyroid functions were normal, as well as serum immunoglobulins, anti-DNA, anti-mitochondrial, anti-nuclear antibodies and anti-neutrophil cytoplasmic antibody, lactate dehydrogenase and β-2–microglobulin. The serological markers of HBV and HIV infections were negative. Physical examination and laboratory tests excluded renal or neurologic involvement of MC; purpura was absent. Ultrasound examination showed moderate hepatosplenomegaly, without evidence of cirrhosis and portal hypertension. No focal liver lesions were detected. A reactive lymph node of about 1 cm was present at the hepatic hilus.

After written informed consent, the patient was treated with PEG-interferon α-2a (180 μg/wk) plus ribavirin 800 mg/d. After 3 wk, PEG-interferon α-2a was shifted to human leucocyte interferon-α at the dosage of 6 MU thrice a week, because of progressive reduction of neutrophil granulocyte count and profound weakness. Thereafter, the treatment was well tolerated and did not require further dosage adjustment. Overall treatment lasted 6 mo.

The patient's cutaneous manifestations resolved in 10 d, and HCV-RNA and cryoglobulins were negative 1 mo from the beginning of treatment. After 3 mo from the end of treatment, ALT and AST again increased and HCV-RNA became detectable. However, the relapse of viral replication was not accompanied by the recurrence of cryoglobulinemia, and serum cryoglobulins were negative after a 2 year follow-up.

DISCUSSION

Chronic HCV infection is the most common cause of MC. 70% to 80% of patients with MC are infected by HCV[2]. Conversely, cryoglobulinemia is detected in a third of patients with HCV infection, although most are asymptomatic[2]. The close association between HCV and MC is witnessed by the finding of HCV-RNA in both cryoprecipitate and supernatant[3], but the mechanism (s) through which HCV may induce MC remains unclear.

Cryoglobulinemia is defined by the presence of circulating immunoglobulins, which precipitate with cold temperature and re-solubilise when reheated. The most common symptoms are weakness, arthralgias and purpura (Meltzer and Franklin triad). Raynaud phenomenon, peripheral neuropathy, sicca syndrome, renal involvement, lung disorders, fever and thrombocytopenia can also be observed[1]. In addition to purpura, MC-associated dermatological disorders include the presence of leukocytoclastic vasculitis, leg ulcer, pruritus and urticaria[4]. In a retrospective study on 62 MC patients, pruritus was reported in 8% of cases and urticaria in 6%[5]. Moreover, pruritus was the most frequent (15%) cutaneous manifestation in 2000 consecutive HCV patients, 40% of whom presented with cryoglobulinemia, even though the extent of association between pruritus and MC was not reported[6]. Indeed, even in the absence of MC, it should not be forgotten that several other dermatological manifestations may result from disorders potentially associated with HCV infection, such as porphyria cutanea tarda, linchen planus (LP), psoriasis, polyarteritis nodosa, systemic lupus erythematosus, sarcoidosis, xerosis, pruritus and non-specific excoriation[4].

Although a wide spectrum of dermatological disorders have been described in association with HCV infection, their pathophysiological relationship with HCV is still a matter of debate[4,5]. In any case, HCV particles have been localized within skin lesions in MC, LP, pruritus and psoriasis. Moreover, parallel improvement in HCV viremia and some dermatological symptoms under antiviral treatment suggests a close correlation.

In our case, the absence of other common causes of urticaria claims a relationship between HCV virus and this dermatological manifestation. Skin biopsy has an essential role in the diagnosis of urticaria vasculitis, and the lack of this information does not allow us to know for certain the exact mechanism of urticaria in our case, but the presence of MC suggests an immune mediated pathogenesis.

The treatments that can be offered to patients with MC include corticosteroids, cyclophosphamide, plasmapheresis, cryoapheresis, low-antigen continent diets and anti-CD20 antibodies. However, antiviral treatments are first line therapy in HCV-related MC[1,3], even though the lack of standardized protocols, the high rate of relapses, and general or MC-specific contraindications to antiviral treatments (i.e. old age, severe liver disease, acute nephritis, and widespread vasculitis) render such treatments rather difficult[1].

A main problem with our patient was associated with her age. Whether to treat patients older than 65 years with interferon and ribavirin is highly debated, especially in terms of cost/benefit ratio. In addition, the natural history of chronic hepatitis C in elderly patients is scarcely known, as the presence of comorbidities can affect illness progression and life expectancy.

Data favoring treatment are represented by the reduction in liver-related mortality and risk of developing hepatocellular carcinoma achieved by treatment in HCV-

Table 1 Laboratory tests of the patient

WBC (nr 4-10 × 1000/mmc)	7.18	Gamma glutamyl transpeptidase (nr 6-35 U/L)	25
Hb (nr 12-15 g/dL)	11.4	Anti-cyclic citrullinated peptide	Negative
PLT (nr 140-400 × 1000/mmc)	135	Rheumatoid factor	Positive
ESR (nr < 36 mm/h)	24	HCV RNA U/mL	754823
AST (nr 4-40 U/L)	53	HCV genotype	2a
ALT (nr 4-37 U/L)	58	C3 (nr 0.9-1.8 g/L)	1.24
Total bilirubin (nr 0.1-1.2 mg/dL)	1.2	C4 (nr 0.1-0.4 g/L)	0.06
Alkaline phosphatase (nr 80-280 U/L)	191	Cryoglobulin	Type 3 (IgG-IgM) 10% cryocrit

related chronic hepatitis[7], while resistance to treatment, due to either advanced liver fibrosis or reduced interferon immunomodulatory activity, and frequent comorbidities, which limit indications and reduce tolerance, militate against treatment. In any case, it should be pointed out that the prevalence of HCV infection in elderly patients is increasing in industrialized countries[2], and, therefore, physicians will more often face this condition.

Our 77-year-old patient did not have remarkable liver damage, and laboratory and ultrasound evidence of cirrhosis was lacking. Therefore, the risk to develop frank cirrhosis or hepatocellular carcinoma in the short run was theoretically low. However, she suffered from severe cutaneous symptoms due to HCV-related MC, which were not responsive to symptomatic therapy and deeply affected her quality of life. This was the reason that prompted us to undertake antiviral therapy. In the lack of precise guidelines for the treatment of elderly patients and, in particular, elderly patients with cutaneous manifestation of HCV-related MC, we decided to start with PEG-interferon and ribavirin as indicated for adult patients with a favourable genotype[8,9].

Treatment led to a rapid resolution of the cutaneous symptoms. However, intolerance to treatment induced us to shift PEG-interferon α-2a to leukocyte interferon-α after 3 wk. The decision to continue with treatment was supported by fast improvement of the cutaneous symptoms, strong patient motivation, and the available and convincing data on the tolerability of this type of interferon[10,11].

The main reason for the rapid resolution of the cutaneous symptoms we achieved in the present case is likely the concomitant virological response. Available data about treatment efficacy on MC-related cutaneous manifestations are conflicting[4], even though the resolution of itching with antiviral treatment has already been reported[3,4]. It is of interest to note that MC and cutaneous symptoms did not reappear for 2 years despite the relapse of viral replication. We do not have a definite explanation for this, but it may be somewhat related to the antiproliferative and immunomodulatory properties of interferon[12] along with low immunoreactivity that characteristic elderly subjects.

In conclusion, we think that undertaking antiviral treatment with interferon and ribavirin in elderly patients in the attempt to resolve particular conditions, such as MC-induced pruritus and urticaria, can be taken into account. Treatment should be offered after full disclosure of risks and benefits, and close patient monitoring is warranted to avoid complications. In this context, leukocyte interferon-α seems to be better tolerated than PEG-interferon.

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Meetings

Events Calendar 2010

January 15-16, 2010
AGA Clinical Congress of Gastroenterology and Hepatology
Las Vegas, United States
http://www.gilearn.org/clinicalcongress

February 4, 2010
New Developments in Pain Therapy sponsored by the Swiss Society of Pharmacology and Toxicology
Bern, Switzerland
http://pharmacology.unibe.ch/SSPT2010

February 5-9, 2010
Cancer Genomics, Epigenomics & the Development of Novel Therapeutics
Waikoloa, United States

February 7-10, 2010
53rd Annual Meeting of the Western Pharmacology Society
San Diego, United States
http://www.medicine.nevada.edu/wps/annualmeeting.html

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
London, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 16-18, 2010
83rd Annual Meeting of the Japanese Pharmacological Society
Osaka, Japan
http://www2.convention.co.jp/83jps/english/english_top.html

March 17-20, 2010
Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics
Atlanta, United States
http://www.ascpt.org/annualmeeting2010/index.cfm

March 23-25, 2010
51st Annual Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology
Mainz, Germany
http://www.pharmakologie.uni-mainz.de/JTG/JTG.html

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

May 15, 2010
Digestive Disease Week 2010
New Orleans, United States
http://www.ddw.org/

June 2-4, 2010
Annual meeting of the Canadian Society of Pharmacology and Therapeutics
Toronto, Canada
http://www.pharmacologycanada.org

July 16-17, 2010
WorldPharma2010 Satellite Meeting: The role of clinical pharmacology in therapeutic drug monitoring and clinical pharmacogenetics
Copenhagen, Denmark

July 17-23, 2010
16th World Congress on Basic and Clinical Pharmacology (WorldPharma2010)
Copenhagen, Denmark
http://www.WorldPharma2010.org

September 12-14, 2010
39th Annual Meeting of the American College of Clinical Pharmacology
Baltimore, United States
http://www.accp1.org

September 23-26, 2010
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases
Prague, Czech

October 15-20, 2010
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting
San Antonio, United States

October 20-23, 2010
Australian Gastroenterology Week
Melbourne, Australia
http://www.gesa.org.au/agw.cfm

November 11-12, 2010
20th Neuropharmacology Conference co-organized by the Nomenclature Committee of IUPHAR (NC-IUPHAR): Receptor Structure and Drug Design
San Diego, United States
http://www.neuropharmacology-conference.elsevier.com

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Acknowledgments

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer

disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http//www.cdc.gov/ncidod/EID/eid.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean ± SD or mean ± SE.

Statistical expression

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