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Adrenocorticotrophic hormone: A powerful but underappreciated therapeutic tool for acute crystal induced arthritis?

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Abstract

Treatment of acute gout is not always an easy task since patients usually have multiple comorbidities that preclude the use of nonsteroidal anti-inflammatory drugs and colchicine, the most widely used therapeutic tools. Adrenocorticotrophic hormone (ACTH) has long been used in the treatment of acute gout and several studies have shown that it is highly effective and exhibits an excellent safety profile. ACTH belongs to a family of proteins called melanocortins; these molecules have strong anti-inflammatory properties and serve as natural inhibitors of inflammatory responses. We have recently reported that treatment of acute gout with 100 IU of synthetic ACTH is highly effective and associates with negligible side effects. It is noteworthy that ACTH did not associate with significant "steroid related" side effects such as hypertension, hyperglycemia and hypokalemia. ACTH appears as a powerful and easy to use therapeutic tool for patients with multiple comorbidities. We believe that the role of ACTH as a treatment for acute gout should be reappraised, especially in light of new experimental data indicating that ACTH

has pleiotropic anti-inflammatory properties and is not just a hormone that stimulates the release of steroids.

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Key words: Adrenocorticotrophic hormone; Gout; Treatment; Melanocortins; Hyperuricemia

Core tip: The treatment of acute gout in patients with multiple comorbidities is problematic. Adrenocorticotrophic hormone (ACTH) is an effective, safe and easy to use therapeutic tool for these patients. ACTH is probably the most attractive choice. Evidence suggests that it is safe and does not seem to associate with immunosuppression; moreover ACTH is a low cost drug at least in Europe.

Daoussis D, Andonopoulos AP. Adrenocorticotrophic hormone: A powerful but underappreciated therapeutic tool for acute crystal induced arthritis? *World J Rheumatol* 2013; 3(2): 6-8 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v3/i2/6.htm> DOI: <http://dx.doi.org/10.5499/wjr.v3.i2.6>

INTRODUCTION

Gout is the most common form of inflammatory arthritis affecting 1% of the male population in Western countries^[1]. The prevalence of hyperuricemia and gout has been constantly rising during the last decades. Many causes have contributed to this increase: dietary changes, widespread use of medications associated with hyperuricemia, increase in life expectancy and most importantly, the metabolic syndrome "epidemic"^[2]. In the majority of cases, gout is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. However, treatment of

gout is not always an easy task, since patients usually have multiple comorbidities that preclude the use of these agents. In difficult to treat patients steroids have been traditionally used; however, this therapeutic option is not ideal, since steroids associate with immunosuppression and metabolic side effects.

ADRENOCORTICOTROPIC HORMONE

Adrenocorticotrophic hormone (ACTH) has long been used in the treatment of acute gout; as a matter of fact, the first relevant report was published more than half a century ago^[3]. Several studies in the 1990's have shown that ACTH is highly effective in the treatment of acute gout and exhibits an excellent safety profile. More specifically these studies have shown that ACTH was equally effective than indometacin and steroids and in some cases faster acting; moreover it was effective and safe in patients with multiple medical problems^[4-6]. ACTH belongs to a family of proteins called melanocortins; these molecules, apart from their pigment inducing capacity, seem to have a regulatory role in a wide range of biologic functions. Evidence suggests that melanocortins have strong anti-inflammatory properties and serve as natural inhibitors of inflammatory responses^[7]. The prevailing hypothesis was that ACTH mainly acts by stimulating the release of endogenous steroids by the adrenal glands. However, experimental evidence, accumulated over the last decade, indicates that ACTH mainly acts in a steroid independent manner. In a rat knee joint model of inflammation where monosodium urate crystals were injected intra-articularly, local administration of ACTH was highly effective without altering systemic corticosterone levels^[8]. More importantly, ACTH was also effective in rats subjected to adrenalectomy indicating that ACTH has a direct anti-inflammatory effect which is not related to endogenous steroid release. This effect was shown to be mediated by stimulation of melanocortin type 3 receptor located on macrophages. The role of melanocortin receptor signalling in modulating inflammatory responses, including gouty inflammation, has been increasingly recognized over the last years^[9]. It is also interesting that melanocortins may even antagonize the action of interleukin (IL)-1, the key cytokine in gout pathophysiology^[10].

In our department we have been using ACTH as a first line treatment for acute gout in hospitalized patients since 1995. We have recently reported that treatment of acute gout with 100 IU of synthetic ACTH is highly effective and associates with negligible side effects^[11]. It is note worthy that ACTH did not associate with significant "steroid related" side effects such as hypertension, hyperglycemia and hypokalemia. ACTH appears as a powerful and easy to use therapeutic tool for patients with multiple comorbidities. We believe that the role of ACTH as a treatment for acute gout should be reappraised, especially in light of new experimental data indicating that ACTH has pleiotropic anti-inflammatory properties and is not

just a hormone that stimulates the release of steroids. However, current therapeutic guidelines either ignore ACTH^[12,13] or recommend it solely for patients unable to receive oral medications^[14].

CONCLUSION

There is a clear need for effective therapies for gout that can be safely administered in patients with multiple medical problems. Recent studies have assessed the efficacy of IL-1 inhibitors; these agents are effective and have been proposed as an alternative therapeutic option for high risk patients. However, we believe that for these difficult to treat patients, ACTH is probably the most attractive choice. Evidence suggests that it is safe and does not seem to associate with immunosuppression^[11]; moreover ACTH is a low cost drug at least in Europe.

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B cell depletion in scleroderma lung disease: A promising new treatment?

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Core tip: Rituximab (RTX) may be an effective treatment for systemic sclerosis (SSc)-associated interstitial lung disease (ILD). A large scale study assessing the efficacy of RTX in SSc associated ILD is warranted. If RTX turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

Daoussis D, Andonopoulos AP. B cell depletion in scleroderma lung disease: A promising new treatment? *World J Rheumatol* 2013; 3(2): 9-11 Available from: URL: <http://www.wjgnet.com/2220-3214/full/v3/i2/9.htm> DOI: <http://dx.doi.org/10.5499/wjr.v3.i2.9>

Abstract

Evidence suggests that B cells may participate in the fibrotic process. Based on this experimental evidence, treatment with rituximab (RTX) has been tried in systemic sclerosis (SSc) with promising results. In a randomized controlled study from our research group it was shown that treatment with 2 courses of RTX leads to a significant improvement of lung function at 1 year compared to baseline. All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis something that adds further evidence in favor of a disease modifying role of RTX in SSc. It is more than obvious that novel therapies for SSc-associated lung disease are needed. A large scale, randomized, controlled study assessing the efficacy of RTX in SSc associated interstitial lung disease is warranted. If RTX turns out to be effective it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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Key words: Rituximab; Scleroderma; Systemic sclerosis; Interstitial lung disease; Treatment

INTRODUCTION

Lung involvement, especially in the form of interstitial lung disease (ILD), is nowadays the leading cause of mortality in patients with systemic sclerosis (SSc). So far, treatment of this fearful complication has been disappointing. Therapy has been relied on intense immunosuppression in the form of cyclophosphamide (CYC). Administration of CYC leads to a modest reduction in the rate of pulmonary function decline but this effect wanes following drug discontinuation. Therefore, continuous treatment is needed; however long term treatment with CYC is not feasible due to its toxicity. It is more than obvious that we need to develop effective, less toxic therapies that can be safely administered over a long time.

A PROMISING NEW TREATMENT

Evidence suggests that B cells may be actively involved in the fibrotic process^[1]. B cells are overactivated in both experimental models of fibrosis^[2] as well as in humans with SSc^[3]. Moreover, treatment with rituximab (RTX), a monoclonal antibody that depletes B cells was effective in

Table 1 All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis

Study	Participants (n)	Evaluation time point (mo)	Clinical assessment skin	Histologic improvement-skin	Lung function tests
Smith <i>et al</i> ^[9]	8	6	Improved	Yes	Stable
Lafyatis <i>et al</i> ^[8]	15	6/12	Stable	Yes	Stable
Bosello <i>et al</i> ^[10]	9	6-36	Improved	Not reported	Stable
Daoussis <i>et al</i> ^[11]	8	12	Improved	Yes	Improved

an animal model of fibrosis^[4]. Based on this experimental evidence, RTX has been tried in SSc with promising results. In a randomized controlled study from our research group it was shown that treatment with 2 courses of RTX leads to a significant improvement of lung function at 1 year compared to baseline^[5]. Based on this clinical improvement, patients remained on this treatment and received 2 additional courses of RTX. The beneficial effect on lung function was still evident with patients exhibiting an almost linear improvement of lung function parameters throughout the 2 years of treatment^[6]. A favorable effect on lung function has also been recently reported by another research group^[7]. Of note, patients with SSc associated ILD tend to worsen over time; improvement in lung function tests is something not usually seen within the natural course of the disease.

All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis, something that adds further evidence in favor of a disease modifying role of RTX in SSc^[8-11]. Additional information is provided in Table 1.

So far, we do not know exactly how RTX mediates its beneficial effects in SSc (if indeed this treatment turns out to be effective). Our research group has recently shown that treatment with RTX associates with a significant decrease in platelet derived growth factor (PDGF) receptor expression and activation in the skin^[12]. This is an important finding, taking into account the pivotal role of PDGF in fibrosis. Of note, agonistic auto-Abs against PDGF receptor have been found in patients with SSc^[13]; one may hypothesize that RTX acts by eliminating these auto-Abs. However, RTX seems to have a broad effect on the immune system, beyond B cell depletion, and therefore other mechanisms may apply.

CONCLUSION

We believe that all efforts should focus on a large scale, randomized, controlled study assessing the efficacy of RTX in SSc associated ILD. Recently, the Rituximab group of EUSTAR reported encouraging results in 72 patients with SSc treated with RTX^[14]. Taking into consideration that the beneficial effect of RTX on lung function in our study was evident at 12 mo, following two consecutive treatment courses, we propose that this scheme is the most appropriate if a randomized controlled study is to be performed (*i.e.*, at least 1 year duration, administration of two consecutive RTX courses). Based on the calculations made in the Scleroderma Lung Study^[15], at least 160 patients (80 in the RTX group and 80 in the control

group) will need to be recruited so that the study can have sufficient statistical power to detect significant differences between groups. If RTX turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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Books

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

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- 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

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

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- 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

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- 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

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- 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/index.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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *ν* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 $24.5 \mu\text{g/L}$; CO_2 volume fraction, 50 mL/L CO_2 , not 5% CO_2 ; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindI*, *BamHI*, *Kho I*, *Kpn I*, *etc.*

Biology: *H. pylori*, *E. coli*, *etc.*

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