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*EDITORIAL*

# Adrenocorticotropic 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. Adrenocorticotropic 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 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.



**Key words:** Adrenocorticotropic hormone; Gout; Treatment; Melanocortins; Hyperuricemia

**Core tip:** The treatment of acute gout in patients with multiple comorbodities is problematic. Adrenocorticotropic 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 immunussupperssion; moreover ACTH is a low cost drug at least in Europe.

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## 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

Adrenocorticotropic 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 no 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 immunussupperssion[11]; moreover ACTH is a low cost drug at least in Europe.

## REFERENCES


1 **Terkeltaub RA**. Clinical practice. Gout. *N Engl J Med* 2003; **349**: 1647-1655 [PMID: 14573737]
2 **Neogi T**. Clinical practice. Gout. *N Engl J Med* 2011; **364**: 443-452 [PMID: 21288096]
3 **Gutman AB**, Yu TF. Effects of adrenocorticotropic hormone (ACTH) in gout. *Am J Med* 1950; **9**: 24-30 [PMID: 15425530]
4 **Axelrod D**, Preston S. Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum* 1988; **31**: 803-805 [PMID: 2454635 DOI: 10.1002/art.1780310618]
5 **Siegel LB**, Alloway JA, Nashel DJ. Comparison of adrenocorticotropic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. *J Rheumatol* 1994; **21**: 1325-1327 [PMID: 7966077]
6 **Ritter J**, Kerr LD, Valeriano-Marcet J, Spiera H. ACTH revisited: effective treatment for acute crystal induced synovitis in patients with multiple medical problems. *J Rheumatol* 1994; **21**: 696-699 [PMID: 8035395]
7 **Brzoska T**, Luger TA, Maaser C, Abels C, Böhm M. Alpha-melanocyte-stimulating hormone and related tripeptides: biochemistry, antiinflammatory and protective effects in vitro and in vivo, and future perspectives for the treatment of immune-mediated inflammatory diseases. *Endocr Rev* 2008; **29**: 581-602 [PMID: 18612139]
8 **Getting SJ**, Christian HC, Flower RJ, Perretti M. Activation of melanocortin type 3 receptor as a molecular mechanism for adrenocorticotropic hormone efficacy in gouty arthritis. *Arthritis Rheum* 2002; **46**: 2765-2775 [PMID: 12384937 DOI: 10.1002/art.10526]
9 **Getting SJ**, Lam CW, Chen AS, Grieco P, Perretti M. Melanocortin 3 receptors control crystal-induced inflammation. *FASEB J* 2006; **20**: 2234-2241 [PMID: 17077300]
10 **Brzoska T**, Kalden DH, Scholzen T, Luger TA. Molecular basis of the alpha-MSH/IL-1 antagonism. *Ann N Y Acad Sci* 1999; **885**: 230-238 [PMID: 10816656 DOI: 10.1111/j.1749-6632.1999.tb08680.x]
11 **Daoussis D**, Antonopoulos I, Yiannopoulos G, Andonopoulos AP. ACTH as first line treatment for acute gout in 181 hospitalized patients. *Joint Bone Spine* 2013; **80**: 291-294 [PMID: 23195793]
12 **Zhang W**, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, Gerster J, Jacobs J, Leeb B, Lioté F, McCarthy G, Netter P, Nuki G, Perez-Ruiz F, Pignone A, Pimentão J, Punzi L, Roddy E, Uhlig T, Zimmermann-Gòrska I. EULAR evidence based recommendations for gout. Part II: Management.

Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; **65**: 1312-1324 [PMID: 16707532 DOI: 10.1136/ard.2006.055269]

13 **Jordan KM**, Cameron JS, Snaith M, Zhang W, Doherty M, Seckl J, Hingorani A, Jaques R, Nuki G. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology* (Oxford) 2007; **46**: 1372-1374 [PMID: 17522099 DOI: 10.1093/rheumatology/kem056a]

14 **Khanna D**, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, Pillinger MH, Merill J, Lee S, Prakash S, Kaldas M, Gogia M, Perez-Ruiz F, Taylor W, Lioté F, Choi H, Singh JA, Dalbeth N, Kaplan S, Niyyar V, Jones D, Yarows SA, Roessler B, Kerr G, King C, Levy G, Furst DE, Edwards NL, Mandell B, Schumacher HR, Robbins M, Wenger N, Terkeltaub R. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res* (Hoboken) 2012; **64**: 1447-1461 [PMID: 23024029 DOI: 10.1002/acr.21773]

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