Review

Crystallising the role of adrenocorticotrophic hormone in the management of acute gout: a review

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ABSTRACT

Objective. *Acute gout is traditionally treated with NSAIDs, corticosteroids, and colchicine. However, the presence of comorbid conditions and advancing age, often seen in hospitalised patients, may prevent their use. We reviewed the published data on the use of ACTH in the treatment of acute gouty arthritis.*

Methods. *A search was performed up to June 2017. We included clinical trials or case studies/series where ACTH had been administered in human subjects as a treatment for acute gout or pseudogout.*

Results. *Data consistently demonstrated ACTH to be fast-acting, typically relieving the painful symptoms of acute gout within 24 h of treatment. Furthermore, the average number of days needed to achieve 100% resolution of gout symptoms in patients treated with ACTH was similar to those of the corticosteroid triamcinolone. Retrospective data confirm the efficacy of ACTH or the synthetic analogue Synacthen in the treatment of acute gout in patients with comorbidities such as cardiovascular disease, chronic kidney disease, and hypertension, including those who were hospitalised, with all patients responding after 1–3 doses. ACTH appears to be well-tolerated with side effects being minor and transient in nature. Importantly, ACTH/Synacthen has no clinically significant effect on glucose and potassium levels or blood pressure. Clinical evidence from available case studies supports these findings.*

Conclusion. *ACTH is a fast acting, efficacious and well-tolerated option for patients with acute gout when traditional therapies have failed or are contraindicated. However, large, carefully designed, randomised controlled trials are required to confirm these findings.*

Introduction

Gout is a chronic inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues in the presence of elevated urate concentrations (1, 2). The clinical features of gout occur as a result of the inflammatory response to MSU crystals and include severe pain, swelling, and tenderness resulting in difficulty moving the affected joint(s). Importantly, gout pain typically measures >7 on an ascending 1–10 scale (2), negatively impacting on health-related quality of life and resulting in absence from work, increased healthcare use, and reduced social engagement (2-4). Furthermore, there is emerging evidence that gout is an independent risk factor for cardiovascular disease (5 ,6).

The principles of gout management remain the same regardless of a patient's age (7); 1. adequately manage the gout attack or 'flare', while, 2. eliminating MSU crystals deposited in the joints and other sites by normalising serum uric acid levels (2, 7-9). Holistic care of such patients demands that all medical conditions frequently associated with gout occurrence, such as obesity, hypertriglyceridaemia, hypertension, diabetes mellitus, and excessive alcohol consumption should also be addressed (7).

Despite effective treatments, gout management remains suboptimal (9). Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticosteroids are all recommended therapeutic options for acute gout (9-11). However, the choice of drug is dictated by the presence of contraindications, the patient's previous experience with treatments, time after flare onset, the number and type of joint(s) involved, and concomitant medications (9, 11). Patients with gout, particularly those of

advanced age, often harbour multiple comorbidities that result in contraindications to many of the treatments available for gout (12). Thus, the standard goals of treatment for acute gout may be more difficult to accomplish (7). In addition, approximately 25% of gout patients receive inappropriate management for their recurrent gout attacks (13).

Adrenocorticotropic hormone (ACTH), a member of the melanocortin group of proteins, has long been used in the treatment of gout and is an alternative therapeutic option, especially in difficult-to-treat patients (14). A synthetic analogue of ACTH (Synacthen Depot) consists of the first 24 amino acids of ACTH ($ACTH_{1–24}$) and displays the same physiological properties (15, 16). Several studies have demonstrated it to be effective in the treatment of gout, while offering a good safety profile (17-20). However, an assessment of all available evidence for ACTH/Synacthen has not been performed before.

This review aimed to compile all available clinical data related to the therapeutic use of ACTH/Synacthen in the treatment of acute gout.

Methods

We performed am electronic search using the ProQuest tool (www.proquest.com). All the databases searched are present in the Appendix. No date limit was applied to the search to allow any suitable published literature to be identified. The search string used for the initial literature search was '(gout* OR crystal arthritis OR pseudogout) AND (ACTH OR adrenocorticotrop* OR synacthen OR tetracosactide OR corticotropin OR corticotrophin OR tetracosactrin OR cosyntropin)'. The search was undertaken on 5th June 2017 and returned 55 results. The abstracts of these articles were assessed in order to identify case reports, case series, or clinical studies where ACTH has been administered in human subjects as treatment for either acute gout or pseudogout. Articles for possible inclusion were retrieved in full and assessed for inclusion/exclusion. Review papers, editorials, non-research-based articles, and non-English language articles were excluded. Studies which included patients with other crystal arthritidies, *e.g.* pseudogout were analysed separately for completeness as coexisting gout could not be confidently excluded.

Results

Fifteen publications were included in this review. These included four prospective studies, three retrospective studies, and eight case studies/case series. A summary of the key data from the prospective and retrospective studies are shown in Table I. All four prospective studies were small (n<100) with patients typically aged >60 years, male and with acute gouty arthritis/crystal-proven gout (17, 19, 21, 22). Patient comorbidities were not specified. Three of these studies used a single injection of ACTH 40 IU (17, 19, 22), while the fourth used four divided doses per day (21); two studies allowed concomitant use of colchicine (19, 22). Few rebound attacks of gout were reported following treatment with ACTH, each typically responding to a repeat course of therapy. The largest retrospective study assessed the use of single injection ACTH 100 IU in hospitalised patients with acute gout and established comorbidities (n=181), who were predominantly male (78.5%) and elderly (mean age: 74.2 years) (20). Patients in the smaller retrospective study by Ritter *et al*. (18) with acute gout (mean age: 66 years; 55% male) or pseudogout (mean age: 86.2 years; 100% female) along with comorbid conditions received ACTH 40 or 80 IU tid with tapering allowed (18). One small retrospective study assessed the use of single injection ACTH 100 IU in elderly patients (mean age: 80.3 years; 50% male) with pseudogout and at least one comorbidity (n=14) with no rebound attacks reported (23). Case studies/series on the use of ACTH in the treatment of acute gout were published more than 60 years ago (range of publication date: 1945–1952) but provided an important insight into the use of ACTH in individual patients.

Prospective studies of ACTH

An early prospective study examined the effect of ACTH in patients with monoarticular or polyarticular acute gouty arthritis (21). Ten patients with a total of 11 acute gout attacks ACTH was typically administered for four days in dosages of 100, 55, 30 or 20 mg per day as four divided doses, with most patients receiving 100 mg per day for over a four-day treatment period. Seven of the eleven cases of acute gouty arthritis showed a satisfactory response to ACTH, with symptom relief (joint swelling, pain) typically being reported as early as 12 h after first administration and patients remaining symptom-free after treatment discontinuation (with or without subsequent colchicine). In one patient, a severe attack which resisted two weeks of colchicine therapy responded promptly to ACTH, while two patients with gastrointestinal bleeding and therefore unable to receive colchicine due to the risk of vomiting and/or diarrhoea received ACTH.

More recently, a prospective, open-label, comparative study (17) suggested that a single parenteral dose of ACTH provided more rapid symptom relief than the oral NSAID indomethacin in the treatment of the acute gouty arthritis (17). Patients received either a single IM injection of ACTH 40 IU (n=36) or oral indomethacin 50 mg qid (n=40) until relief from gout pain. Mean patient age was similar across treatment groups and all patients were male. ACTH provided complete pain relief within a mean time of 3 h compared with 24 h with indomethacin (p<0.001). However, the mean interval between gout attacks during the study period was 3 months for both treatments. Likewise, the frequency of gout attacks were also similar between treatment groups during the study period. No adverse events were reported by patients receiving ACTH while those given indomethacin reported abdominal discomfort or dyspepsia (n=22), headache (n=15), and difficulty with mentation (n=12).

A single-blinded prospective study supports findings from (17) by confirming that single-dose parenteral ACTH was more effective in rapidly ending attacks of acute gout, with fewer side effects and a higher benefit to toxicity ratio than indomethacin (22). Male patients (age range: 42–81 years) with acute gouty arthritis received a single

injection of ACTH 40 units (n=15) or indomethacin 50 mg tid tapered over 2 weeks (n=14). In addition, patients received a concomitant daily dose of oral colchicine 0.6 mg. The median time to relief of gout pain was significantly shorter for the ACTH group (8 h) compared with the indomethacin group (48 h; p=0.0003). In addition, ACTH achieved a shorter time to complete resolution of symptoms compared with indomethacin, although this was not statistically significant (3 days *vs*. 7 days, respectively; p=0.0861). Over 6 months of follow-up, only 2 patients (14.3%) in the ACTH group and 3 patients (21.4%) in the indomethacin group had flares of gouty arthritis requiring a repeat of course therapy. No adverse events were reported with ACTH.

A prospective study in patients with crystal-proven gout demonstrated that patients treated with the corticosteroid triamcinolone required fewer reinjections for inadequate pain relief than those treated with ACTH at up to 30 days of follow-up (5 *vs*. 9 patients; p=0.11) (19). Patients received a single injection of triamcinolone acetonide 60 mg (n=16; mean age: 62.4 years) or ACTH 40 IU (n=15; one patient lost to follow-up; mean age: 69.6 years). The average number of days needed to achieve 100% resolution of gout symptoms was 7.92 in the ACTH group and 7.60 in the triamcinolone acetonide group (difference ns). Nine patients in the ACTH group required reinjection: three were reinjected because of <50% resolution, while six had rebound arthritis. Three of the patients reinjected for the rebound arthropathy required a third injection. In contrast, five patients in the triamcinolone acetonide group required reinjection and only one of those reinjected required a third injection; no rebound attacks were reported in the triamcinolone acetonide group. Both treatments were well tolerated.

Retrospective studies

Ritter *et al*. (18) retrospectively assessed the efficacy of ACTH in 33 patients with acute gout and multiple comorbidities (18). Mean patient age was 66 years (range 43–93). Parenteral ACTH 40 IU was administered every 8 h via intravenous, intramuscular, or subcutaneous routes with gradual tapering according to clinical improvement. Prophylactic, low-dose colchicine treatment was used by the majority of patients. Treatment with ACTH was highly effective with 97% resolution of all gout episodes. Complete resolution of gout was achieved by an average of 5.5 days, with improvements reported within days 1–3. Minimal side effects with ACTH included hypokalaemia, hyperglycaemia, and oedema (all 12.1% each); these side effects were mild and easily controlled.

Daoussis *et al*. (20) identified 181 cases of acute gout in hospitalised patients where Synacthen Depot (1mg IM, 100IU) was used as first-line treatment and found that all patients responded following 1–3 doses (20). This patient group had a mean (SEM) age of 74.24 (3.38) years and were predominantly male (78.5%). Synacthen was utilised in this 'difficult-to-treat' patient population due to other treatments being contraindicated. No patients received steroids, NSAIDs, or colchicine at the time of the attack. A treatment response was seen in the majority (77.9%) of patients within 24 h of Synacthen administration. The majority (87.50%) of non-responders were retreated with a further single dose the day following the first injection, with most (82.85%) responding to treatment. For the small percentage (11.3%) of responders who suffered a second gouty attack, at a median of 4 days from the initial attack, all responded after one more dose of Synacthen. Importantly for patients with established comorbidities, only very few adverse events were reported, including local, mild skin reactions (2.2%) and flushing (0.6%). This study was unique in that it also investigated potential steroid-related effects of ACTH, which included glucose and potassium levels, along with blood pressure. Diabetic patients who received Synacthen treatment showed an increase in fasting glucose levels 24 h following the injection compared with baseline (mean [SEM]: 174.8 [14.5] *vs*. 151.8 [19.9] mg/dL, respectively, p=0.02), although this increase was not evident 24 h later (mean [SEM]: 161.2 [21.3] mg/dL, p=ns *vs*. baseline) and did not require modification of antidiabetic treatment. Of particular note, a similar transient increase in glucose levels was also seen in non-diabetics. Potassium levels at 24 and 48 h following treatment did not change compared with baseline, and both systolic and diastolic blood pressure remained stable, even in those patients with hypertension.

Case studies

The earliest published case series of the use of ACTH in the treatment of acute gouty arthritis was in 1945 (24). Four brief cases were included, where after a control period of four days, ACTH 150 mg IM was administered each day in divided doses for a total of four days. Administration of ACTH to two patients during an attack of acute gouty arthritis produced a prompt disappearance of the acute arthritis and the author suggested stimulation of adrenal cortical function as the common pathway in the aetiology of acute gouty arthritis by non-specific stress, adding that adrenocorticotropin had potential as a therapeutic agent in gout.

Spies & Stone (25) reported on a 45-year-old male with an 18-year history of gout who received a single dose of ACTH 25 mg for an attack of acute gout (25). While gout symptoms were reduced within 3 h post-injection and full resolution of gout was achieved within 24 h, the patient severely relapsed within 7 days of treatment. In contrast, Leopold (26) reported on a 40-year-old female with acute gout affecting the metatarsal joints of both feet. The patient reported marked relief of pain within 4 h after three injections of ACTH 50 mg and ongoing colchicine use, with approximately 90% relief of pain being achieved within 12 h. The prompt resolution of acute gouty arthritis in three patients treated with a single injection of pituitary ACTH was reported by Margolis & Caplan (27).

Wolfson *et al*. reported on the administration and subsequent withdrawal of ACTH, studied simultaneously in a father with tophaceous gout and his son with genetic hyperuricaemia (28). Each patient received one dose of 100 mg ACTH for three days, both reported weakness and malaise, and the father

Table I. Summary of key data from prospective and retrospective studies of the therapeutic use of ACTH in the treatment of acute gout.

Prospective studies

Reference	No. of patients	Age and gender	Comorbidities	Gout type	Treatment	Time to onset of action	Time to symptom resolution	Time to rebound attack (number of patients)	Adverse events
Gutman & Yu 1950	n=10 (11 attacks in total, two in one patient)	Not specified	Not specified	Acute gouty arthritis	ACTH was usually given for four days in dosages of 100, 55, 30 and 20 mg per day (four divided doses per day)	Not specified	Not specified – treatment response reported in 7/10 patients	Not specified	Not specified
Axelrod & Preston 1988	n=76	Age (mean) at study entry ACTH: 63 years Indomethacin 66 years: Male (100%) for both treatment groups	Not specified	Acute gouty arthritis	Single injection of ACTH 40 IU IM (n=36) Oral indomethacin 50 mg qid (n=40)	ACTH: 3 (1) h Indomethacin: 24 (10) h p<0.0001	ACTH: 3 (1) h Indomethacin: 24 (10) h p<0.0001	ACTH: 3 (1.8) mo Indomethacin: 3 (2.2) mo p=ns	ACTH: None Indomethacin: 22 patients experienced abdominal discomfort or dyspepsia, 15 experienced headaches, and 12 developed difficulty with mentation
Mikdashi *et al*.1994	ACTH Indomethacin	Age range 42–81 years Male (100%)	Not specified:	Acute gouty arthritis	Single ACTH injection 40 IU (n=15) Indomethacin 50 mg tid tapered over 2 weeks (n=14) Daily use of 0.6 mg oral colchicine allowed	Median interval to relief of pain was significantly shorter for the ACTH group (8 h) compared with the indomethacin group (48 h); p=0.0003	Time to complete resolution of symptoms was shorter for the ACTH group, though not statistically significant (3 days vs. 7 days, respectively); p=0.0861	Over 6 months of follow-up, only 2 patients (14.3%) in the ACTH group and 3 patients (21.4%) in the indomethacin group had flares of gouty arthritis requiring a repeat of course therapy	No adverse events reported with ACTH. For indomethacin, 3 patients (21.4%) required use of a H2-blocker for dyspepsia, 2 patients (14.3%) had an increase in blood pressure, and 1 patient (7.1%) developed change in mentation
Siegel *et al*. 1994	n=31	Age (mean) ACTH group: 69.6 years Triamcinolone acteonide group: 62.4 years Gender not specified	One patient in the ACTH group had polycythemia vera and one patient in the triamcinolone acetonide group had both uric acid and calcium pyrophosphate crystals	Crystal-proven gout	ACTH 40 IU injection: n=15 (one patient was lost to follow-up) Triamcinolone acteonide 60 mg: n=16 Patients receiving allopurinol, colchicine, or a uricosuric continued the medication during the study	Not specified	Average number of days to 100% resolution of the symptoms was 7.92 in the ACTH group and 7.60 in the triamcinolone acteonide group (ns)	Nine patients in the ACTH group required reinjection. Three were reinjected because of <50% resolution and 6 had rebound arthritis Three of the patients reinjected for the rebound arthropathy required a third injection There were no rebound attacks in the triamcinolone acteonide group	Both treatments were well tolerated

Retrospective studies

Reference	No. of patients	Age and gender	Comorbidities	Gout type	Treatment	Time to onset of action	Time to symptom resolution	Time to rebound attack (number of patients)	Adverse events
Ritter *et al*. 1994	n=38	Patients with acute gout Mean age: 66 years (range 43–93) 15 female, 18 male Patients with pseudogout Mean age: 86.2 years (range 65–104) 100% female	Congestive heart failure (18 gout, 4 pseudogout), chronic renal insufficiency (20 gout, 2 pseudogout), gastrointestinal bleeding (10 gout, 2 pseudogout), or no response to NSAIDs/ colchicine (6 gout, 1 pseudogout)	Acute crystal induced synovitis: 33 patients had documented acute gout and 5 patients had documented acute pseudogout. A total of 43 episodes of acute crystal induced synovitis were treated.	Parenteral ACTH 40 or 80 units IV, IM, or SC tid with tapering	Improvement was seen between days 1–3 following ACTH injection	Resolution of symptoms seen between 1–14 days Average number of days to resolve gout: 5.5 Average number of days to resolve pseudogout: 4.2	Four episodes of relapse of acute gouty arthritis despite the use of prophylactic colchicine in three of these	Gout Hypokalaemia: 4 Worsened glycaemic control: 4 Fluid overload: 4 Pseudogout Hypokalaemia: 1 (the same patient developed hypokalaemia and mild fluid overload) Worsened glycaemic control: 0 Fluid overload: 1
Daoussis *et al*. 2013	n=181	Mean (SEM) age: 74.2 (3.4) years Male: 78.5%	Hypertension (146 (80.7%), cardiovascular disease 99 (54.7%), myocardial infarction 31 (17.1%), CKD (stages 3, 4, and 5) 63 (34.8%), diabetes mellitus 42 (23.2%), oral anticoagulant therapy 21 (11.6%), atrial fibrillation 19 (10.5%), hyperuricaemia 164 (90.6%), gout 152 (84.0%)	Acute gout (hospitalised patients)	Single injection of synthetic ACTH 1 mg (100 IU) IM	<24 h in 77.9% of patients The majority (87.5%) of non-responders were retreated with a single ACTH course the day following the first injection; most of these patients (82.9%) responded		A relatively small percentage of responders suffered a second gouty attack (11.3%) at a median of 4 days from the initial attack. They were retreated once more with ACTH and all responded	Four cases (2.2%) of local, mild skin reactions and one case (0.55%) of flushing
Daoussis et al. 2014	n=14	Mean (SD) age: 80.3 (3.9) years Male: 50%	All patients had at least one comorbidity that represented a contraindication to the use of NSAIDs, steroids or colchicine	Acute calcium pyrophosphate crystal arthritis	Synthetic depot ACTH 1 mg (100IU) IM (single dose); one patient received a second ACTH injection on the day after the first injection	Treatment response in 13/14 patients within 24 h	Symptom resolution in 13/14 patients within 24 h; 1 patient achieved symptom resolution within 48 h	No rebound attacks	None

subsequently developed severe acute gout.

A review of therapeutic outcomes in 51 cases of acute gouty arthritis treated with colchicine and ACTH suggested that a good therapeutic response was not achieved until ACTH evoked a robust increase in adrenal function (29). The authors of this case series noted that aqueous ACTH every 6 h typically enabled 75–90% improvement in gout symptoms within 24 h. For long-lasting ACTH, ≥75% relief of symptoms was typically achieved in 9 h in patients who had not previously received colchicine, and 13 h in those with colchicine-resistant attacks.

Three cases of severe, recurrent, acute gouty arthritis were reported by Kauffman (30), two of which responded promptly to ACTH administration after lack of response to accepted therapeutic measures.

Finally, a case study of a 49-year-old male patient with polyarticular acute gout and comorbidities of hypertension, essential lipaemia, and peripheral neuritis reported pain relief within 24 h of the first ACTH 20 mg dose (administered every 6 h for a total dosage of 560 mg), complete resolution of gout symptoms within 72 h, and no relapse within 7 days (31). As previous treatment with colchicine had limited effect, ACTH 20 mg was administered every 6 h for a total dosage of 560 mg in the absence of any other medication. The patient reported pain relief within 24 h of the first ACTH dose, complete resolution of gout symptoms within 72 h, and no relapse within 7 days, allowing the patient to restart preventative colchicine therapy.

ACTH/Synacthen in the treatment of calcium pyrophosphate disease (pseudogout)

As with acute gout, patients affected by acute calcium pyrophosphate (CPP) crystal arthritis are typically elderly with established comorbidities, such as cardiovascular disease, diabetes mellitus, and hypertension, thus recommended treatments may be contraindicated (14). Current EULAR guidelines for CPP crystal arthritis mentions ACTH as a possible alternative to standard treatment (32), and the limited clinical evidence appears to support this suggestion (18, 23).

The study by Ritter *et al*. (18) included five patients with acute CPP crystal arthritis and reported that treatment with parenteral ACTH 40 IU administered every 8 h resulted in complete resolution of symptoms within 4.2 days (18). More recently, Daoussis *et al*. (23) assessed the use of Synacthen Depot in 14 hospitalised patients (mean [SD] age: 80.3 [3.9] years) with acute CPP crystal arthritis and ≥1 comorbidity which prevented use of NSAIDs, glucocorticoids, or colchicine (23); all cases were monoarticular in nature. All patients were treated with a single injection of Synacthen Depot 1 mg (100IU) IM apart from one patient who received a second Synacthen injection 24 h later. A treatment response was seen in 13 patients with attenuation of signs of inflammation within 24 h without the use of NSAIDs, colchicine or steroids. One patient had a partial response and received a second ACTH injection the day following the first injection; response with complete resolution of gout was seen. Of note, no patient suffered a rebound attack during hospitalisation. No significant changes in systolic blood pressure, fasting glucose or potassium levels were reported following treatment.

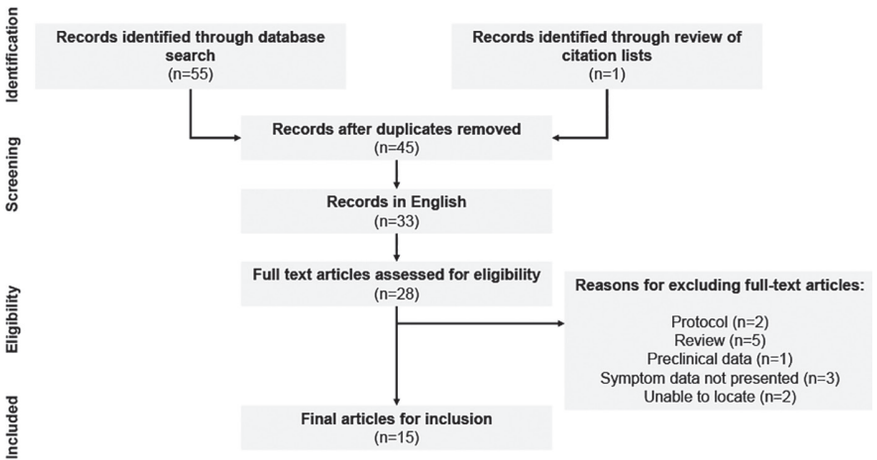

Fig. 1. Flow of information through the different phases of this review.

Discussion

This systemic review confirms the role of ACTH in the management of gout, providing clinicians with another agent in their therapeutic armamentarium. It has, for the first time, comprehensively evaluated all available data for the efficacy and safety of ACTH/Synacthen in this area.

ACTH/Synacthen Depot is a fast-acting anti-inflammatory agent which relieves the painful symptoms of acute gout typically within 24 h of the first injection and appears to have a good tolerability profile with few adverse events. As therapeutic decisions should be based on individualised risks and benefits, ACTH/Synacthen offers an alternative to corticosteroids and NSAIDs which may not be suitable for patients with comorbidities or on multiple drug regimens (12). ACTH provides an additional therapeutic option for elderly patients with acute gout and established comorbidities. The presence of such comorbidities in these patients often limit the use of recommended gout therapies (8). One of three overarching principles recently developed by EULAR for the treatment of gout is that every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout (9). However, Robinson *et al*. (4) reported that hospitalised patients with gout typically have multiple comorbidities and are admitted multiple times for gout management, suggesting that these patients are suffering from treatment

refractory gout, that they are not being treated adequately or that their adherence to treatment may be low or a combination of these factors (4). In addition, Keenan *et al*. (12) reported a high rate of prescribing gout medications that were potentially contraindicated (12); for example, of patients with acute gout and ≥1 contraindication to NSAID use, 18% were nonetheless prescribed these agents, including 9% with strong contraindications to their use (12).

Adverse event profiles of NSAIDs, glucocorticoids, and colchicine, along with potential drug-drug interactions with ongoing polypharmacy may also prevent the use of these agents in elderly or hospitalised patients with multiple comorbidities. Drug-drug interactions for NSAIDs include warfarin, with subsequent increased risk of gastrointestinal bleeding, and ACE inhibitors, with subsequent risk of hypertension and potential for deterioration of renal function (11). Recognised adverse effects observed with NSAID use include nausea, diarrhea, dyspepsia, headaches, confusion, increases in blood pressure and elevations of serum potassium and creatinine, which can pose severe problems for the elderly patient (7). Thus, NSAIDs are relatively contraindicated in patients with renal insufficiency and congestive heart failure, and are best avoided in patients with peptic ulcer disease or gastrointestinal bleeding (7, 33). Side effects of glucocorticosteroid use include congestive heart failure exacerbations, uncontrolled diabetes, elevation in blood pressure, electrolyte shifts, and increased susceptibility to infection (7). Concern about concomitant anticoagulant therapy may also preclude the intra-articular administration of corticosteroids (33). Colchicine is poorly tolerated in the elderly, particularly in those with renal and/or hepatic impairment, and is best avoided (33). In addition, interactions between colchicine and CYP3A4 and P-glycoprotein inhibitors are well recognised, requiring the dose of colchicine to be modified accordingly (11). Thus, ACTH would be a useful alternative treatment for use in such patients.

Corticosteroids increase blood pressure through volume retention, and blood pressure elevation due to the chronic use of NSAIDs is also well recognised (34). While acute ACTH administration is a short-term stimulator of aldosterone, prolonged use can ultimately lead to transient or suppressed secretion, subsequently increasing the risk of hypertension (35–37). Thus, the duration of ACTH administration requires careful consideration, particularly in patients with chronic crystal-induced arthritis where longer term management is required. For acute gout in hospitalised patients, Daoussis *et al*. (20) reported that both systolic and diastolic blood pressure remained stable following the use of Synacthen, even where hypertension was present.

Historical reports of ocular side effects with long-term corticosteroid or ACTH use include an increased risk of developing steroid cataracts or macular exudates, respectively (38). More recently, it has been recognised that corticosteroids increase the risk of glaucoma by raising the intraocular pressure when administered exogenously and in certain conditions of increased endogenous production (39). Of note, patients aged >40 years with certain diseases, such as diabetes mellitus, appear more vulnerable to corticosteroid-induced glaucoma. In contrast, no available published evidence appears to suggest that the use of ACTH/Synacthen increases the risk of developing glaucoma.

The use of corticosteroids can increase the risk of acute pancreatitis, with possible direct injurious effect on the exocrine pancreas and increased levels of the pancreatic enzymes (40, 41). Chronic use of corticosteroids can produce undesired diabetogenic side effects through interactions with the regulation of glucose homeostasis and lead to insulin resistance (42). Thus, glucose tolerance disorders are well documented in patients receiving corticosteroids, although this risk appears to be less when low to moderate doses are administered for a short period (43). In addition, single, local soft tissue and intra-articular musculoskeletal corticosteroid injections can be used even in patients with well-controlled diabetes mellitus (44). Daoussis *et al*. (20) reported that while non-diabetic and diabetic patients who received Synacthen treatment showed an increase in fasting glucose levels 24 h following the injection compared with baseline, this increase was not evident after a further 24 h period and did not require modification of antidiabetic treatment, where used.

While newer first-in-class drugs might be discovered in the future for the treatment of gout, the repurpose of older drugs, such as synthetic ACTH clearly offers therapeutic efficacy and good tolerability, particularly in elderly or hospitalised patients with established comorbidities (45). ACTH has been FDA-approved and used in patients since 1952, but typically regarded as the last therapeutic option for acute gout when other medications, cannot be used or when oral treatment cannot be administered (45). It is widely understood that ACTH is a major component of the hypothalamic-pituitary-adrenal axis and acts by stimulating the release of endogenous steroids (45). However, improved understanding of the mechanism of action of ACTH, along with new insights on melanocortin receptor biology, have revived interest in its use (45). Melanocortins are natural pro-resolving mediators in the inflammatory process, which act to provide control and balance (45). Getting *et al*. (46) discovered that the intrinsic anti-inflammatory effect of ACTH is related to its ability to bind and stimulate melanocortin (MC) receptors (46). ACTH activates the receptor MC2 on the adrenal cortex, leading to the production of corticosteroids, which explains the glucocorticoid-dependent anti-inflammatory actions of ACTH (45). However, the effect of ACTH is also mediated by receptor MC3, which is expressed in immune cells and in the brain, explaining the glucocorticoid-independent anti-inflammatory actions of ACTH (45). Bone, cartilage, and other joint cells highly express MC receptors, highlighting the relevance of ACTH treatment in inflammatory joint conditions (45). The discovery of this novel mode of action, involving the recruitment of the body's natural pro-resolution inflammatory response, appears unique to ACTH and requires further research.

While available data support the use of

ACTH in the treatment of acute gout, it is important to highlight several limitations of the current systematic review. Firstly, and most importantly, there appears to be a limited amount of published literature on the use of ACTH in the treatment of acute gout. All case studies included were all reported more than 60 years ago and some provide limited information on patient characteristics, treatment approach and gout symptoms. In addition, the retrospective studies included lacked any control arm and some adverse events may not have been reported due to the study design; however, the study by Daoussis *et al*. (20) did include data from 181 patients (20). The retrospective study by Ritter *et al*. (18) included a relatively low number of patients and also allowed concomitant use of colchicine (18). In addition, the prospective studies included in this systematic review were non-randomised and non-blinded, preventing any robust conclusions (17, 19). Thus, there is an absolute need for a carefully designed randomised controlled trial to robustly establish the efficacy and safety of ACTH.

Summary/conclusions

Available clinical evidence, while limited, suggests that ACTH may provide an efficacious, fast acting, and well tolerated therapeutic option for patients with acute gout in whom other traditional therapies have failed or are contraindicated. However, carefully designed randomised controlled trials are still required to definitively establish the efficacy and safety of ACTH in patients with acute gout.

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References

1. NEOGI T: Gout. *N Engl J Med* 2011; 364: 443-52.
2. DALBETH N, MERRIMAN TR, STAMP LK: Gout. *Lancet* 2016; 388: 2039-52.
3. KHANNA PP, NUKI G, BARDIN T *et al*.: Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. *Health Qual Life Outcomes* 2012a; 10: 117.
4. ROBINSON PC, MERRIMAN TR, HERBISON P, HIGHTON J: Hospital admissions associated with gout and their comorbidities in New Zealand and England 1999-2009. *Rheumatology* (Oxford) 2013; 52: 118-26.
5. CHOI HK, CURHAN G: Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; 116: 894-900.
6. PEREZ-RUIZ F, MARTÍNEZ-INDART L, CARMONA L, HERRERO-BEITES AM, PIJOAN JI, KRISHNAN E: Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. *Ann Rheum Dis* 2014; 73: 177-82.
7. HOSKISON KT, WORTMANN RL: Management of gout in older adults. Barriers to optimal control. *Drugs Aging* 2007; 24: 21-36.
8. BERNAL JA, QUILIS N, ANDRÉS M, SIVERA F, PASCUAL E: Gout: optimizing treatment to achieve a disease cure. *Ther Adv Chronic Dis* 2016; 7: 135-44.
9. RICHETTE P, DOHERTY M, PASCUAL E *et al*.: 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis* 2017; 76: 29-42.
10. KHANNA D, KHANNA PP, FITZGERALD JD *et al*.: 2012 American College of Rheumatology Guidelines for Management of Gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res* 2012b; 64: 1447-61.
11. STAMP LK: Safety profile of anti-gout agents: an update. *Curr Opin Rheumatol* 2014; 26: 162-68.
12. KEENAN RT, O'BRIEN WR, LEE KH *et al*.: Prevalence of contraindications and prescription of pharmacologic therapies for gout. *Am J Med* 2011; 124: 155-63.
13. NEOGI T, HUNTER DJ, CHAISSON CE, ALLENSWORTH-DAVIES D, ZHANG Y: Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. *J Rheumatol* 2006; 33: 104-9.
14. DAOUSSIS D, ANTONOPOULOS I, ANDONOPOULOS AP: ACTH as a treatment for acute crystal-induced arthritis: Update on clinical evidence and mechanisms of action. *Semin Arthritis Rheum* 2014b; 43: 648-53.
15. Synacthen Depot Ampoules 1 mg/mL SPC. Mallinckrodt Specialty Pharmaceuticals Ireland Limited. November 2015.
16. ANON: Medicines Compendium. Datapharm Communications, Epsom, UK, 2003: 2054-55.
17. AXELROD D, PRESTON S: Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum* 1988; 31: 803-5.
18. 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: 696-99.
19. SIEGEL LB, ALLOWAY JA, NASHEL DJ: Comparison of adrenocorticotropic hormone and triamcinolone acetonide in the treatment of acute gouty arthritis. *J Rheumatol* 1994; 21: 1325-27.
20. DAOUSSIS D, ANTONPOULOS I, YIANNOPOULOS G, ANDONOPOULOS AP: ACTH as first line treatment for acute gout in 181 hospitalized patients. *Joint Bone Spine* 2013; 80: 291-94.
21. GUTMAN AB, YU TF: Effects of adrenocorticotropic hormone (ACTH) in gout. *Am J Med* 1950; 9: 24-30.
22. MIKDASHI JA, HOCHBERG MC, MOY EM, WHITE B, HANDWERGER BS: Single dose parental ACTH in the treatment of acute gouty arthritis: a high benefit to toxicity ratio. *Arthritis Rheum* 1994; 37 (Suppl.): S428 (Abstract 1593).
23. DAOUSSIS D, ANTONOPOULOS I, YIANNOPOULOS G, ANDONOPOULOS AP: ACTH as first-line treatment for acute calcium pyrophosphate crystal arthritis in 14 hospitalized patients. *Joint Bone Spine* 2014; 81: 93-101.
24. HELLMAN L: Production of acute gouty arthritis by adrenocorticotropin. *Science* 1945; 109: 280-81.
25. SPIES TD, STONE RE: Relief of the symptoms of acute gout and rheumatoid arthritis by means of pituitary adrenocorticotropic hormone (ACTH). *South Med J* 1949; 42: 720-22.
26. LEOPOLD HN: ACTH and colchicine in therapy of gout. Report of a case of acute gouty arthritis. *Texas State J* 1950; 46: 710-12.
27. MARGOLIS HM, CAPLAN PS: Treatment of acute gouty arthritis with pituitary adrenocorticotropic hormone (ACTH). *JAMA* 1950; 142: 256-58.
28. WOLFSON WQ, COHN C, WISE W, SIDEMANS: Administration and subsequent withdrawal of ACTH, studied simultaneously in a gouty father and his hyperuremic son. *J Clin Encocrin 1950*: 835. Abstract 62.
29. WOLFSON WQ, HUNT HD, COHN C, ROBINSON WD, DUFF IF: ACTH and colchicine in the clinical treatment of acute gouty arthritis. Physiological considerations and review of therapeutic results in fifty-one attacks. *J Mich State Med Soc* 1950; 49: 1058-64.
30. KAUFFMAN F: Diagnosis and treatment of gout: effects of pituitary adrenocorticotropic hormone (ACTH) in the acute attack. *Am Pract Dig Treat* 1951; 2: 146-50.
31. FULTON JK: Essential lipemia, acute gout, peripheral neuritis, and myocardial disease in a Negro man; response to corticotropin. *Arch Int Med* 1952; 89: 303-38.
32. ZHANG W, DOHERTY M, PASCUAL E *et al*.: EULAR recommendations for calcium pyrophosphate deposition. Part II: management. *Ann Rheum Dis* 2011; 70: 571-75.
33. FAM AG: Gout in the elderly. Clinical presentation and treatment. *Drugs Aging* 1998; 13: 229-43.
34. LOVELL RA, ERNST MA: Drug-induced hypertension: Focus on mechanisms and management. *Curr Hypertens Rep* 2017; 19: 39.
35. MANTERO F, BOSCARO M, SCARONI C *et al*.: Effect of a synthetic substituted alpha1-18 ACTH on mineralocorticoid secretion. *Horm Metab Res* 1980; 12: 464-70.
36. ARMANINI D, ANDRISANI A, AMBROSINI G, BORDIN L, SABBADIN C: Role of adrenocorticotropic hormone in essential hypertension and primary aldosteronism. *J Clin Hypertens* (Greenwich) 2017; 19: 287-89.

37. EL GHORAVEB N, BOURDEAU I, LACROIX A: Role of ACTH and other hormones in the regulation of aldosterone production in primary aldosteronism. *Front Endocrinol* (Lausanne) 2016; 7: 72.
38. WILLIAMSON J: New look at the ocular side-effects of long-term systemic corticosteroid and adrenocorticotrophic therapy [Abridged]. *Proc R Soc Med* 1970; 63: 791-92.
39. TRIPATHI RC, PARAPURAM SK, TRIPATHI BJ, ZHONG Y, CHALAM KV: Corticosteroids and glaucoma risk. *Drugs Aging* 1999; 15: 439-50.
40. DANDONA P, JUNGLEE D, KATRAK A, FONSECA V, HAVARD CW: Increased serum pancreatic enzymes after treatment with methylprednisolone: possible evidence of subclinical pancreatitis. *Br Med J* (Clin Res Ed) 1985; 291: 24.
41. SADR-AZODI O, MATTSSON F, SJÖBERG BEXLIUS T, LINDBLAD M, LAGERGREN J, LJUNG R: Association of oral glucocorticoid use with an increased risk of acute pancreatitis. A population-based nested case-control study. *JAMA Intern Med* 2013; 173: 444-49.
42. RAFACHO A, ORTSÄTER H, NADAL A, QUESADA I: Glucocorticoid treatment and endocrine pancreas function: implications for glucose homeostasis, insulin resistance and diabetes. *J Endocrinol* 2014; 223: R49-62.
43. DABROWSKI P, MAJDAN M: Glucose tolerance disorders during treatment with glucocorticoids in patients with inflammatory diseases of the musculoskeletal system - based on the analysis of data from the literature and own research results. *Postepy Hig Med Dosw* (Online) 2017; 71: 307-14.
44. WATERBROOK AL, BALCIK BJ, GOSHINSKA AJ: Blood glucose levels after local musculoskeletal steroid injections in patients with diabetes mellitus: A clinical review. *Sports Health* 2017; 9: 372-74.
45. MONTERO-MELENDEZ T: ACTH: The forgotten therapy. *Semin Immunol* 2015; 27: 216-26.
46. GETTING SJ, KANEVA M, BHADRESA Y *et al*.: Melanocortin peptide therapy for the treatment of arthritic pathologies. *Sci World J* 2009; 9: 1394-414.

Appendix
Databases used in the literature search

ABI/INFORM® Professional Advanced, Abstracts in New Technology & Engineering, AdisInsight: Drugs, AdisInsight: Safety Reports, AdisInsight: Trials, Adis Pharmacoeconomics & Outcomes News, AGRICOLA, AGRIS, Allied & Complementary Medicine™, Analytical Abstracts, Australian Education Index, BIOSIS® Toxicology, BIOSIS Previews®, British Library Inside Conferences, British Nursing Index, Business & Industry, CAB ABSTRACTS, Chemical Business Newsbase, Chemical Engineering & Biotechnology Abstracts, Chemical Safety Newsbase, Civil Engineering Abstracts, Current Contents® Search, Derwent Drug File, Derwent Drug Registry, DH-DATA: Health Administration, Medical Toxicology & Environmental Health, DIOGENES® FDA Regulatory Updates, Drug Information Fulltext, Earthquake Engineering Abstracts, EconLit, Ei Compendex®, Ei EnCompassLIT, Embase®, EMCare®, ESPICOM Pharmaceutical & Medical Device News, FDAnews, FLUIDEX (Fluid Engineering Abstracts), Foodline®: MARKET, Foodline®: PRODUCT, Foodline®: SCIENCE, FSTA®, Gale Group Computer Database™, Gale Group Health Periodicals Database, Gale Group New Product Announcements / Plus®, Gale Group Newsletter Database™, Gale Group PharmaBiomed Business Journals, Gale Group PROMT®, Gale Group Trade & Industry Database™, GEOBASE™, Global Health, HSELINE: Health and Safety, ICONDA - International Construction Database, IMS Company Profiles, IMS New Product Focus, IMS Pharma Trademarks, IMS R&D Focus, IMS R&D Focus Drug News, Incidence & Prevalence Database, Inspec®, International Pharmaceutical Abstracts, Jane's Defense & Aerospace News, King's Fund, KOSMET: Cosmetic Science, Lancet Titles, Material Safety Datasheets -OHS™, Mechanical & Transportation Engineering Abstracts, MEDLINE®, New England Journal of Medicine, NTIS: National Technical Information Service, PAIS International, Paperbase, PAPERCHEM, PIRABASE, Polymer Library, ProQuest Advanced Tech & Aerospace Professional, ProQuest Biological & Health Science Professional, ProQuest Dissertations and Theses Professional, ProQuest Environmental Science Professional, ProQuest Materials Research Professional, ProQuest Newsstand Professional, Prous Science Daily Essentials, Prous Science Drug Data Report, Prous Science Drugs Of The Future™, PsycINFO, Registry of Toxic Effects of Chemical Substances (RTECS®), SciSearch®: a Cited Reference Science Database, Social SciSearch®, Thomson Reuters Embargoed Research Collection®, ToxFile®, Transport Research International Documentation, TULSA™ (Petroleum Abstracts), UBM Computer Full Text, Weldasearch®, Zoological Record Plus