Current and emerging options in treatment of gout: a review

Kubo MN[1], Oyoo GO[2]

[1]Unit of Clinical Pharmacology, Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenya
[2]Associate Professor of Rheumatology, Department of Clinical Medicine and Therapeutics, University of Nairobi, Kenya

Corresponding author:
Dr Mary N Kubo. Unit of Clinical Pharmacology, Department of Clinical Medicine and Therapeutics, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya. Email: nigandimarie@gmail.com

Abstract

Objective: To review current and emerging pharmacologic treatment options for gout, with particular emphasis on the rapidly changing recommendations outlined in the latest treat to target strategy employed in the 2016 European League Against Rheumatism (EULAR) guidelines.
Data source and extraction: Published clinical drug trials, reviews and guidelines for the treatment of gout. Research work published in English and emphasizing pharmacologic management of gout was included after online and library searches.
Conclusion: Research into pharmacologic therapies for gout had largely remained silent after licensing of allopurinol in 1966. Since 2008 however, with approval of febuxostat and pegloticase, the stage has been set for exciting research into new molecules in the management of this largely curable condition. Updated evidence supporting the use of current and emerging agents such as febuxostat, canakinumab, lesinurad and pegloticase is summarized in this review.

Key words: Gout; Acute flare therapy, Urate lowering drugs

Introduction

Recent advances in therapy for gout provide exciting new possibilities in reduction of gout-associated morbidity and disability. With a prevalence of up to 2-4%[1], gout is a common and disabling condition that remains poorly managed. Unlike rheumatoid arthritis, premature mortality associated with gout has remained unimproved over the last decade[2].

Gouty arthritis is a result of deposition of monosodium urate crystals within tissue, with resultant inflammation and joint destruction. Elevated serum uric acid levels contribute to this pathophysiology, either as a result of increased production or reduced renal excretion of urate. Various co-morbid conditions associated with gouty arthritis further complicate its management, with drug interactions commonly encountered when treating patients with concomitant hypertension, diabetes, chronic kidney disease, cardiovascular disease and dyslipidemia[3].

Pharmacologic therapy targets a reduction in uric acid levels, as well as control of inflammation present during acute flares. This review looks at current and emerging therapeutic options available for gout management, in line with the latest treat-to-target strategy recommended by the European League Against Rheumatism (EULAR) and the British Society for Rheumatology[4,5].

Acute flares

Pathogenesis of acute gouty arthritis

Uric acid crystals deposited within the joint cavity are engulfed by synovial phagocytic cells, triggering release of lysosomal enzymes and inflammatory cytokines. Monocytes produce TNF, IL-1, IL-6 and IL-8, while mast cells produce histamine and IL-1, with resultant increased vascular permeability and vasodilatation. Increased IL-8 in phagocytes leads to activation of neutrophils, further exacerbating the inflammatory response.

Pharmacologic management of acute flares is most efficient when began early after flare onset, and includes use of colchicine, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), steroids, and, recently, IL-1 antagonists such as canakinumab.

Colchicine

A first line agent used in management of acute gouty flares, colchicine achieves its antiiflammatory effect via various mechanisms. It concentrates within leukocytes, disrupting microtubule polymerization and inflammasome function, interfering with neutrophil chemotaxis, adhesion, recruitment and superoxide production. Additionally, colchicine inhibits release of IL-1 and 8[6].

Of note, colchicine has a narrow therapeutic window and potential for life threatening drug interactions. Its most common adverse effects include

abdominal pain, nausea, diarrhoea, pharyngolaryngeal pain and blood dyscrasias. GIT adverse effects are usually the first signs of colchicine toxicity and should lead to prompt dose reduction or discontinuation of the drug.

Recent evidence from the AGREE Trial (Acute Gout Flare Receiving Colchicine Analysis) showed that when taken within 12 hours of symptom onset, lower doses of colchicine at 1.8mg (1.2mg then 0.6mg one hour later, self-administered) were as effective and better tolerated than traditional higher doses of 4.8mg[7]. Colchicine is available in 1mg and 0.5mg tablets, therefore recommended dosage is 1mg followed an hour later by 0.5mg, as per the EULAR guidelines[4]. Patient education on self-medication is key to halt flares early, thus physicians are further encouraged to adopt the 'pill in the pocket' approach in fully informed patients.

Colchicine is a substrate for intestinal and hepatic CYP3A4, as well as the P-glycoprotein 1 reflux transporter. Fatal drug interactions have been reported when colchicine is used concomitantly with P-glycoprotein inhibitors such as cyclosporine, verapamil and ranolazine, as well as CYP3A4 inhibitors including clarithromycin, itraconazole, ketoconazole and some protease inhibitors. In addition, myopathy and rhabdomyolysis have occurred when concomitantly used with statins, fenofibrate, gemfibrozil and digoxin[6].

Excretion of colchicine is predominantly via the hepatobiliary route, thus dose should be reduced in patients with hepatic impairment. About 10-20% of colchicine is cleared through the kidneys, hence will accumulate in patients with impaired renal function. Dose should be limited to 0.5-0.6mg/day in moderate renal insufficiency (eGFR 30-60 mL/min) and 0.5-0.6 mg every 2 to 3 days if eGFR is 15 to 29mL/min. It is contraindicated in stage 5 chronic kidney disease (eGFR<15mL/min or dialysis)[8].

Apart from its anti-inflammatory effect in acute gouty arthritis, colchicine may have additional beneficial effects in reduction of cardiovascular risk, which is increased in patients with gout and hyperuricemia[9,10]. Emerging evidence from recent trials increasingly points towards a possible role of colchicine in reduction of adverse cardiovascular outcomes in patients with gout[11,12].

Non Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs have long been a mainstay of acute gouty flare management, acting via inhibition of cyclooxygenase enzymes, thus reducing production of prostaglandins that mediate pain and inflammation. Indomethacin was the first NSAID used in acute flare treatment[13], and although it has demonstrable efficacy, side effects including headache, nausea and vertigo limit its use[14]. Other traditional NSAIDs, though efficacious, are usually poorly tolerated due to a high incidence of dyspepsia, peptic ulceration, and GI bleeding, prompting the use of concomitant proton pump inhibitor therapy. Indomethacin is considered one of the more GI toxic traditional NSAIDs[15].

Newer COX-2 selective agents may be preferred, due to their selective inhibition of inducible COX-2 that mediates prostaglandin production mainly at sites of inflammation, sparing the constitutive COX-1 responsible for GI tract mucosal integrity. Several trials have confirmed comparable efficacy and better tolerability of celecoxib (200mg to 400mg twice a day) and etoricoxib (120mg once a day) in control of acute gouty flares compared to traditional NSAIDs[16,17].

Lumiracoxib is a novel COX-2 inhibitor with proven efficacy and good tolerability in treatment of chronic pain in osteoarthritis from the TARGET study (Therapeutic Arthritis Research and Gastrointestinal Event Trial)[18]. Lumiracoxib 400mg once a day reduced incidence of serious GI complications by 79% compared to traditional NSAIDs. Additionally, a randomized control trial of lumiracoxib 400mg once a day in acute gout showed comparable anti-inflammatory efficacy to indomethacin, less GI adverse effects, and an additional benefit of reduction of blood pressure levels compared to traditional NSAIDs[19]. NSAIDs should be prescribed for a total of 5 to 10 days, or until symptoms resolve.

Steroids

An alternative to NSAIDs and colchicine in acute gouty flares, steroids such as prednisone are surprisingly prescribed only about 9% of the time for management of acute gout in the US[20]. Evidence from several randomized trials comparing steroids and NSAIDs in acute gout consistently shows similar efficacy of prednisone 30-35mg once a day for five days when compared to NSAIDs such as indomethacin or naproxen[21,22].

Concerns regarding the adverse effect profile of steroids may contribute to the low prescription rates of these agents. No significant adverse effects were encountered with short term oral steroid use in gout[21,22] as well as rheumatoid arthritis[23]. In addition, steroids are a safe alternative in patients with contraindications to NSAID and/or colchicine use, eg patients with significant renal impairment. They should however be avoided in patients with concomitant infection, brittle diabetes or postoperatively due to impaired wound healing. Prednisolone is the steroid of choice in patients with hepatic impairment, since prednisone requires conversion to the active prednisolone form in the liver.

Despite lack of randomised trials to support use of intraarticular glucocorticoid injections[24], two small studies[25,26] and EULAR guidelines[4] consider that this may be an option in select patients with monoarthritis of an easily accessible joint. Options include triamcinolone acetate 40mg for a large joint (eg. knee), 30mg for a medium joint (eg. wrist, ankle, elbow), and 10mg for a small joint. 40 to 80 mg of intraarticular methylprednisolone may also be used[27].

Interleukin 1 antagonists

Interleukin 1β, a proinflammatory cytokine whose release is triggered by monosodium urate crystals, plays an integral role in gouty arthritis inflammation. Canakinumab is an anti IL-1β monoclonal antibody with

a long half life of 3 to 4 weeks, that has been approved in Europe for management of acute gouty flares in patients with contraindications, intolerance or non-response to colchicine, NSAIDs or steroids[4].

Evidence from randomized trials including β-RELIEVED and β-RELIEVED-II showed that one dose of subcutaneous canakinumab 150mg was superior to triamcinolone in pain reduction in acute flares as well as prevention of episodes of re-flare[28]. Of particular concern with use of anticytokines is their potent immunosuppressant effect that may increase the risk of serious infections and malignancy. In these studies rates of infection were increased in the canakinumab group, which resolved with standard of care. No opportunistic infections were reported, and only one benign neoplasm (lipoma) was noted[28]. Screening for occult infections is recommended prior to initiation of anticytokines such as canakinumab.

Anakinra, an interleukin 1 receptor antagonist, has also shown promise in management of acute gouty arthritis. Subcutaneous anakinra at a dose of 100mg for 3 days was shown to reduce pain in patients with acute gout[29]. On the other hand, rilonacept, a soluble IL-1α and IL-1β receptor fusion binding protein showed no benefit in pain relief over indomethacin[30].

Role of combination therapy in acute flares

In patients with particularly severe flares of gout involving multiple joints, EULAR guidelines recognize the need for combination therapy using colchicine plus either an NSAID or steroids[4].

Urate Lowering Therapy (ULT)

Unlike previously where Urate Lowering Therapy (ULT) was reserved for patients with recurrent acute gout attacks, presence of tophi, urolithiasis or urate overproduction, ULT should now be considered from the first presentation of gout, particularly for patients with comorbidities (eg. hypertension, ischaemic heart disease, chronic kidney disease) and/or serum uric acid >8mg/dL (480µmol/L). Target serum uric acid level should be <6mg/dL (360µmol/L) and <5mg/dL (300µmol/L) in those with severe gout[4]. Severe gout is characterized by presence of tophi, chronic arthropathy and/or frequent acute attacks (>2 per year).

Urate lowering therapies are key to achievement of gout cure. Lowering serum urate concentrations below the saturation point of monosodium urate (6.8mg/dL) leads to dissolution of existing monosodium urate crystals and retards new crystal formation, preventing further attacks of gout and joint damage. ULT also reduces the size and number of tophi, and improves patient quality of life.

Of note however is that as the serum uric acid levels fall, there is mobilization of uric deposits from tissues, leading to flares of acute gout in the initial weeks to months after initiation of urate lowering therapy. Prophylaxis against such flares should thus be initiated using low-dose colchicine (0.6mg/day) or naproxen (250mg twice a day) for up to 6 months, rather than 8 weeks as previously recommended[4,31]. Emerging evidence also points towards a combination of patient education and slow upward titration of urate lowering therapy (specifically allopurinol) possibly obviating the need for flare prophylaxis[32].

Urate lowering therapy should be initiated at least two weeks after resolution of an acute attack, although two small trials have pointed towards minimal risk of worsened or prolonged flares with immediate (during flare) versus delayed (after two weeks) allopurinol initiation[33,34]. ULT should be started at a low dose and titrated upwards, with a goal of lifelong maintenance of serum uric acid at less than 6mg/dL (360µol/L).Urate lowering therapies include xanthine oxidase inhibitors, uricosuric agents and recombinant urate oxidases.

Xanthine oxidase inhibitors

Xanthine oxidase is an integral enzyme in human purine metabolism. It is responsible for oxidation of hypoxanthine and xanthine, with subsequent production of uric acid. Inhibition of this enzyme by allopurinol and febuxostat allows uric acid lowering to target levels.

Allopurinol

A structural isomer of hypoxanthine, allopurinol is a purine analog that is the recommended first line urate lowering agent in patients with gout and normal kidney function[4]. It is rapidly converted to its active metabolite, oxypurinol, by xanthine oxidase. Oxypurinol is excreted mainly via the kidneys, thus accumulating in patients with renal impairment. Increased body weight and use of diuretics will increase dose requirements of allopurinol[35].

Whereas the half life of allopurinol is 1 to 2 hours, oxypurinol has a relatively longer half life of about 15 hours, allowing once daily dosing. Recommended starting dose is 100mg/day, uptitrated every two to four weeks to a maximum dose of 800 to 900mg/day. It should be noted that the commonly used standard dose of 300mg/day failed to achieve target serum uric acid levels in upto 50% of patients with normal kidney function[36], thus uptitration of its dose should be considered for maximal benefit.

Allopurinol should be started at a low dose to reduce risk of Serious Cutaneous Drug Reactions (SCARs) including toxic epidermolysis/Steven Johnson syndrome and Drug Related Eosinophilia with Systemic Symptoms (DRESS) syndrome. Carriers of the HLA*B5801 allele are at higher risk of these cutaneous manifestations. Additionally, patients with impaired renal function are at higher risk of SCARs, thus allopurinol dose should be adjusted according to creatinine clearance. Although rare, allopurinol-associated SCARs carry a high mortality rate of 25-30%[37].

In patients who do not achieve target serum uric acid levels despite allopurinol dose adjustment, one can switch to febuxostat or a uricosuric, or allopurinol can be combined with a uricosuric agent[4].

Febuxostat

A nonpurine xanthine oxidase inhibitor, febuxostat is eliminated predominantly via hepatic pathways, thus can be used in patients with mild to moderate renal failure. Several randomized controlled studies[38,39] have shown superior urate lowering efficacy of febuxostat 80mg or 120mg compared to standard dose allopurinol at 300mg. Incidence of adverse effects was similar across all groups. It should however be noted that allopurinol dose was not titrated upwards to maximal doses in these trials.

The febuxostat versus Allopurinol Controlled Trial (FACT) further highlights the importance of flare prophylaxis using colchicine or low dose naproxen for a prolonged duration[38]. Prophylaxis in this study was only given for eight weeks, with a high rate of gout flare in all treatment groups on withdrawal of prophylaxis. Febuxostat does not need to be discontinued if a flare occurs. Additionally, low dose febuxostat at 40mg was shown to be non-inferior to allopurinol 300mg in the CONFIRMS trial[39].

Liver function tests should be monitored in patients on febuxostat as it may cause abnormalities in liver function. Other adverse effects include nausea, arthralgia and cutaneous reactions. It exhibits no cross sensitivity with allopurinol. Like allopurinol, febuxostat may increase levels of theophylline, mercaptopurine and azathioprine, resulting in toxic levels of these drugs.

There have been concerns raised regarding adverse cardiovascular outcomes in patients on febuxostat[39]. The recently published CARES trial (Cardiovascular Safety of Febuxostat or Allopurinol in patients with gout) compared cardiovascular outcomes in over 6,000 patients with gout and coexisting cardiovascular disease, who were on either febuxostat or allopurinol[40]. There was no difference in the rates of major adverse cardiovascular events between the two groups, which was the primary end point. However in the analysis of secondary end points, risk of cardiovascular mortality was higher in the febuxostat group (HR 1.49, 95% CI 1.01 - 2.22). The study was carried out on patients at high risk of cardiovascular mortality due to pre-existing major cardiovascular disease, and results may not be generalizable to patients without coexistent cardiovascular disease. Febuxostat should however be prescribed with caution in patients with history of cardiovascular disease.

Uricosuric agents

Since impaired renal excretion of urate is a significant contributor to increased serum uric acid levels, uricosuric agents continue to play an important role in management of gout. About 90% of filtered urate is reabsorbed in the kidneys via urate transporters such as uric acid transporter 1, glucose transporter 9 and organic anion transporters 1, 3 and 4. These are the targets for the uricosuric agents probenecid, benzbromarone and the novel agent lesinurad.

Uricosuric agents are recommended alone (except for lesinurad) or in combination with allopurinol in patients unable to achieve serum uric acid target levels with maximal doses of allopurinol. They may precipitate urate stones in the kidney and patients should be advised to have high fluid intake to prevent urolithiasis.

Probenecid

An organic anion transporter inhibitor, probenecid was the first commercialized urate lowering drug. It is started at a dose of 250mg twice daily, increased weekly up to 1g twice a day. In patients without proper control on allopurinol 300mg/day, 65% of patients reached target serum uric acid levels when switched to probenecid 2g daily[36]. Further, a combination of allopurinol-probenecid was more effective than allopurinol alone in lowering serum uric acid[41].

Adverse effects associated with use of probenecid include renal calculi, gastrointestinal intolerance and skin rash. Concomitant use with allopurinol prolongs the half life of probenecid. Excretion of penicillin, NSAIDs and methotrexate is reduced when administered together with probenecid.

Benzbromarone

A more potent uricosuric agent compared to probenecid, benzbromarone achieves it's urate lowering effect via an active metabolite, 6 hydroxybenzbromarone. This metabolite inhibits renal urate reabsorption via inhibition of urate transporter 1 (URAT1). Initially licensed for use in the 1970's, benzbromarone was withdrawn in 2003 after reports of serious hepatotoxicity, but is still available in some countries outside of the US (eg in Europe and Southeast Asia)[42].

It is one of the uricosuric agents recommended in the EULAR guidelines for management of gout, either alone or in combination with allopurinol[4], at a dose of 50-200mg/day. In patients unable to achieve adequate urate lowering with allopurinol 300 mg, upto 92% were able to reach target serum uric acid levels when switched to benzbromarone 200mg[36]. Benzbromarone can be used in patients with moderate renal impairment, but is not recommended once the eGFR falls below 30mL/min.

Lesinurad

A novel Selective Uric Acid Reabsorption Inhibitor (SURI), lesinurad achieves its uricosuric effect via inhibition of renal urate transporter 1 (URAT1). Lesinurad 200mg was approved (in combination with xanthine oxidase inhibitors) for therapy of gout by the US Food and Drug Administration as well as the European Medicines Agency in 2015.

At doses of 200mg and 400mg, lesinurad showed superior urate lowering effect when combined with allopurinol in the phase III multinational CLEAR-2 study (Combining Lesinurad with Allopurinol Standard of

Care in Inadequate Responders), compared to allopurinol alone[43]. These findings were further mirrored when lesinurad was combined with febuxostat[44].

Though more efficacious in urate level reduction, the higher 400mg lesinurad dose was associated with more adverse effects, including a reversible elevation in serum creatinine levels. Notably, there was no increased risk of urolithiasis seen in the CLEAR-2 study, perhaps due to the fact that concomitant allopurinol use reduces uric acid production. Additionally, lesinurad was prescribed as a once daily dose in the morning, a time when the potential for uric acid precipitation is lowest due to high urine volume and urine pH.

Arhalofenate

A novel uricosuric agent, arhalofenate is the first agent to have both urate lowering and anti-flare effects. It reduces uric acid reabsorption in the proximal tubules via inhibition of uric acid transporter 1 (URAT1). Additionally, in murine models, it had anti-inflammatory activity through suppressed release of proinflammatory cytokines such as Interleukin 1β, a key cytokine in promoting gout flares[45].

In a phase IIb clinical trial, arhalofenate 800mg decreased gout flares significantly compared to placebo, and had no significant difference in reduction of gout flares when compared to allopurinol plus colchicine[46]. It additionally decreased serum uric acid levels by 16%, with a favourable safety profile. Arhalofenate as an oral, once daily fixed dose combination with febuxostat is currently in phase III clinical trials.

Urate oxidases

In most mammals, uric acid is metabolized by uricase enzyme to the more soluble allantoin that is readily excreted by the kidneys. Mutational inactivation of this enzyme in humans occurred in the Miocene era (5-23 million years ago), possibly to maintain an evolutionary advantage associated with antioxidant properties of high levels of serum uric acid.

Rasburicase, a recombinant fungal urate oxidase, was the first recombinant uricase developed for management of tumourlysis syndrome in children. It has however not been licensed for use in gout, due to its short half life and high immunogenicity.

Pegloticase

Produced by a genetically modified strain of *Escherichia coli,* pegloticase is a recombinant uricase that is covalently conjugated to monomethoxypoly(ethylene glycol). This conjugation reduces its immunogenicity and increases its solubility as well as serum half life to approximately 2 weeks[47]. It is administered intravenously and remains in circulation, degrading uric acid and resulting in a urate concentration gradient that draws further uric acid from tissues.

Pegloticase is highly effective, dramatically reducing serum uric acid levels to as low as 1mg/dl within 24-72 hours[48]. It is FDA approved at a dose of 8mg every two weeks in patients with refractory gout, defined as clinically severe crystal-proven gout not properly treated with conventional urate lowering therapy, including a combination of a xanthine oxidase inhibitor and a uricosuric agent[4]. In addition to urate lowering effect, pegloticase use also leads to more rapid resolution of tophi compared to conventional urate lowering therapy[47].

Whereas pegloticase is highly effective in lowering uric acid levels in some patients, there exists a small subset of patients who are either partial responders, or non-responders. This is due to generation of antipegloticase antibodies (titres typically above 1:2340), leading to loss of response after a mean period of about 6 weeks of therapy[49]. These antibodies may occur in upto 40% of patients, resulting in increased drug clearance, sub-therapeutic drug levels, and higher risk of infusion reactions[49]. Serum uric acid levels should be measured in the 24 hours preceding reinfusion, and the drug stopped if uricemia is not decreased. Importantly, no other urate lowering drug should be prescribed concomitantly so as to maintain this warning signal[8].

Probably due to its rapid lowering of serum uric acid levels, the most common adverse effect associated with pegloticase is gout flare, occurring in upto 70% of patients, despite flare prophylaxis with colchicine or NSAIDs[47]. Additionally, infusion reactions, anaphylaxis and haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency may occur.

Other agents with urate lowering effect

Losartan

An angiotensin II receptor blocker used in hypertensive patients, losartan has been shown to have a probenecid-like uricosuric effect due to its high affinity for, and inhibition of the urate transporter URAT1[50]. Its urate lowering effect approaches 20-25%[50], and appears to be unrelated to angiotensin II receptor blockade, as other drugs in this class do not have a similar effect on uric acid levels. It thus presents a useful pharmacologic tool in hypertensive patients with comorbid gout.

Calcium channel blockers

Due to their effect on increasing glomerular filtration rate, calcium channel blockers may consequently enhance renal clearance of uric acid. Specifically, nifedipine[51] and amlodipine[52] have been shown to reduce serum uric acid levels, with a consequent reduction in risk of gout by 13% and 21% respectively[50].

Statins and fenofibrate

Primarily useful for their lipid lowering effect, statins and fenofibrate have additional beneficial effects on uric acid levels. Fenofibrate lowers serum uric acid by upto 20%, via an increase in renal uric acid excretion[53]. Statins exhibit a more modest serum uric acid reduction of between 3% (rosuvastatin) and 6.5% (atorvastatin)[54].

Canagliflozin

A sodium-glucose co-transporter 2 inhibitor used for management of diabetes mellitus, canagliflozin reduced serum uric acid levels to <6mg/dl in 20-30% of type 2 diabetic patients with concomitant hyperuricemia[55]. A postulated mechanism of its urate lowering effect may involve the renal GLUT9 transporter that exchanges glucose for uric acid. Due to higher glucose concentration in urine with cangliflozin treatment, GLUT9 may release more uric acid into the urine in exchange for glucose.

Future directions in pharmacologic therapies for gout

With robust research into newer molecules ongoing, physicians can look forward to possibly more efficacious agents in the near future. These include single agents with dual mechanism of action targeting both xanthine oxidase and renal urate handling, newer xanthine oxidase inhibitors such as topiroxostat and extended release febuxostat (phase III trials), novel uricosuric agents like verinurad (phase II trials), as well as the orally administered Interleukin 1β inhibitor bucillamine. Additionally, to improve immune tolerance, trials combining a nanoparticle-encapsulated pegsiticase (a pegylateduricase) with the immune modulator rapamycin are also underway[56].

Conclusion

With such a wide armamanterium of pharmacologic agents, clear management guidelines and a treat to target approach, cure for a majority of gout patients is now possible. Gout need not be the chronic, debilitating disease it once was.

References

1. Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol.* 2015; **11**(11):649–662.
2. Fisher MC, Rai SK, Lu N, Zhang Y, Choi HK. The unclosing premature mortality gap in gout: a general population-based study. *Ann Rheum Dis.* 2017; **76**(7):1289–94.
3. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. *BMC Med* [Internet]. 2017; **3**:15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5494879/
4. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, *et al.* 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis.* 2017; **76**(1):29–42.
5. Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, *et al.* The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology.* 2017; **56**(7):1246–1246.
6. Leung YY, Hui LLY, Kraus VB. Colchicine --- update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum.* 2015; **45**(3):341.
7. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* 2010; **62**(4):1060–68.
8. Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective – A review. *J Adv Res.* 2017; **8**(5):495–511.
9. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res.* 2010; **62**(2):170–180.
10. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation.* 2007; **116**(8):894–900.
11. Hemkens LG, Ewald H, Gloy VL, Arpagaus A, Olu KK, Nidorf M, *et al.* Colchicine for prevention of cardiovascular events. *Cochrane Database Syst Rev.* 2016;(**1**):CD011047.
12. Solomon DH, Liu C-C, Kuo I-H, Zak A, Kim SC. The effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with medicare claims. *Ann Rheum Dis.* 2016; **75**(9):1674–79.
13. Pittman JR, Bross MH. Diagnosis and management of gout. *Am Fam Physician.* 1999; **59**(7):1799–806.
14. Thompson M, Percy JS. Further experience with indomethacin in the treatment of rheumatic disorders. *Br Med J.* 1966; **1**(5479):80–83.
15. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet(Lond Engl.)* 1994; **343**(8900):769–772.
16. Schumacher HR, Berger MF, Li-Yu J, Perez-Ruiz F, Burgos-Vargas R, Li C. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. *J Rheumatol.* 2012; **39**(9):1859–66.
17. Li T, Chen S, Dai Q, Han X-H, Li Z-G, Wu D-H, *et al.* Etoricoxib versus indometacin in the treatment of Chinese patients with acute gouty arthritis: a randomized double-blind trial. *Chin Med J (Engl).* 2013; **126**(10):1867–71.
18. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet (Lond Engl.)* 2004; **364**(9435):665–674.

19. Willburger RE, Mysler E, Derbot J, Jung T, Thurston H, Kreiss A, *et al.* Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. *Rheumatology.* 2007; **46**(7):1126–32.
20. Krishnan E, Lienesch D, Kwoh CK. Gout in ambulatory care settings in the United States. *J Rheumatol.* 2008; **35**(3):498–501.
21. Janssens HJEM, Janssen M, van de Lisdonk EH, van Riel PLCM, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet(Lond Engl.)* 2008; **371**(9627):1854–60.
22. Man CY, Cheung ITF, Cameron PA, Rainer TH. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute goutlike arthritis: a double-blind, randomized, controlled trial. *Ann Emerg Med.* 2007; **49**(5):670–677.
23. Gotzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database Syst Rev.* 2004;(**3**):CD000189.
24. Wechalekar MD, Vinik O, Schlesinger N, Buchbinder R. Intra-articular glucocorticoids for acute gout. *Cochrane Database Syst Rev.* 2013;(**4**):CD009920.
25. Andrés M, Begazo A, Sivera F, Vela P, Pascual E. AB0815 Intraarticular triamcinolone plus mepivacaine provides a rapid and sustained relief for acute gouty arthritis. *Ann Rheum Dis.* 2016; **75** (Suppl 2):1182.
26. Fernández C, Noguera R, González JA, Pascual E. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J Rheumatol.* 1999; **26**(10):2285–86.
27. Suresh E. Diagnosis and management of gout: a rational approach. *Postgrad Med J.* 2005; **81**(959):572–579.
28. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, *et al.* Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. *Ann Rheum Dis.* 2012; **71**(11):1839–48.
29. Ottaviani S, Moltó A, Ea H-K, Neveu S, Gill G, Brunier L, *et al.* Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. *Arthritis Res Ther.* 2013; **15**(5):R123.
30. Terkeltaub R, Sundy JS, Schumacher HR, Murphy F, Bookbinder S, Biedermann S, *et al.* The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. *Ann Rheum Dis.* 2009; **68**(10):1613–17.
31. Wortmann RL, MacDonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase iii trials. *Clin Ther.* 2010; **32**(14):2386–97.
32. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis.* 2013; **72**(6):826–30.
33. Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med.* 2012; **125**(11):1126–1134.e7.
34. Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis.* 2015; **21**(3):120–125.
35. Wright DFB, Duffull SB, Merriman TR, Dalbeth N, Barclay ML, Stamp LK. Predicting allopurinol response in patients with gout. *Br J Clin Pharmacol.* 2016; **81**(2):277–289.
36. Reinders MK, Roon EN van, Jansen TLTA, Delsing J, Griep EN, Hoekstra M, *et al.* Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann Rheum Dis.* 2009; **68**(1):51–56.
37. Ramasamy SN, Korb-Wells CS, Kannangara DRW, Smith MWH, Wang N, Roberts DM, *et al.* Allopurinol hypersensitivity: A systematic review of all published cases, 1950–2012. *Drug Saf.* 2013; **36**(10):953–980.
38. Becker MA, Schumacher HR, Wortmann RL, MacDonald PA, Eustace D, Palo WA, *et al.* Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005; **353**(23):2450–61.
39. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, *et al.* The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther.* 2010; **12**(2):R63.
40. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, *et al.* Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med.* 2018; **378**(13):1200–10.
41. Stocker SL, Graham GG, Mclachlan AJ, Williams KM, Day RO. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in patients with gout. *J Rheumatol.* 2011; **38**(5):904–910.
42. Lee M-HH, Graham GG, Williams KM, Day RO. A benefit-risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? *Drug Saf.* 2008; **B**(8):643–665.
43. Bardin T, Keenan RT, Khanna PP, Kopicko J, Fung M, Bhakta N, *et al.* Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). *Ann Rheum Dis.* 2017; **76**(5):811–820.

44. Dalbeth N, Jones G, Terkeltaub R, Khanna D, Kopicko J, Bhakta N, *et al.* Lesinurad, a selective uric acid reabsorption inhibitor, in combination with febuxostat in patients with tophaceous gout: Findings of a phase iii clinical trial. *Arthritis Rheumatol.* 2017; **69**(9):1903–13.
45. Arhalofenate is a novel dual-acting agent with uricosuric and anti-inflammatory properties [Internet]. ACR Meeting Abstracts. [cited 2018 Oct 2]. Available from: https://acrabstracts.org/abstract/arhalofenate-is-a-novel-dual-acting-agent-with-uricosuric-and-anti-inflammatory-properties/
46. Poiley J, Steinberg AS, Choi Y, Davis CS, Martin RL, McWherter CA, *et al.* A Randomized, double-blind, active- and placebo-controlled efficacy and safety study of arhalofenate for reducing flare in patients with gout. *Arthritis Rheumatol Hoboken Nj.* 2016; **68**(8):2027–34.
47. Sundy JS, Baraf HSB, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, *et al.* Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA.* 2011; **306**(7):711–720.
48. Sundy JS, Ganson NJ, Kelly SJ, Scarlett EL, Rehrig CD, Huang W, *et al.* Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. *Arthritis Rheum.* 2007; **56**(3):1021–28.
49. Lipsky PE, Calabrese LH, Kavanaugh A, Sundy JS, Wright D, Wolfson M, *et al.* Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. *Arthritis Res Ther.* 2014; **16**(2):R60.
50. Choi HK, Soriano LC, Zhang Y, Rodríguez LAG. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *Br Med J.* 2012; **344**:d8190.
51. Ruilope LM, Kirwan B-A, de Brouwer S, Danchin N, Fox KAA, Wagener G, *et al.* Uric acid and other renal function parameters in patients with stable angina pectoris participating in the ACTION trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome. *J Hypertens.* 2007; **25**(8):1711–18.
52. Chanard J, Toupance O, Lavaud S, Hurault de Ligny B, Bernaud C, Moulin B. Amlodipine reduces cyclosporin-induced hyperuricaemia in hypertensive renal transplant recipients. *Nephrol Dial Transplant.* 2003; **18**(10):2147–53.
53. Derosa G, Maffioli P, Sahebkar A. Plasma uric acid concentrations are reduced by fenofibrate: A systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacol Res.* 2015; **102**:63–70.
54. Ogata N, Fujimori S, Oka Y, Kaneko K. Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides Nucleotides Nucleic Acids.* 2010; **29**(4–6):321–324.
55. Davies MJ, Trujillo A, Vijapurkar U, Damaraju CV, Meininger G. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2015; **17**(4):426–429.
56. Dalbeth N, Choi HK, Terkeltaub R. Review: Gout: A roadmap to approaches for improving global outcomes. *Arthritis Rheumatol.* 2017; **69**(1):22–34.