Treatment of hyperuricemia in gout: current therapeutic options, latest developments and clinical implications

Sebastian E. Sattui and Angelo L. Gaffo

Abstract: Despite being the most common type of inflammatory arthritis, gout is often poorly managed. Except for febuxostat and pegloticase, research in new therapeutic agents for the management of hyperuricemia in gout remained insufficient for several decades. With emerging evidence of possible roles of hyperuricemia in cardiometabolic comorbidities, as well as more convincing evidence regarding poor outcomes (e.g. disability, recurrent hospital admissions) in patients with uncontrolled gout, several agents are current under development. Increasing knowledge regarding renal urate transporters has resulted in the development of new generation uricosurics such as lesinurad and arhalofenate. This review aims at discussing current therapeutic strategies for gout, as well as their limitations and the possible role of emerging agents in the chronic management of hyperuricemia in gout. Drugs in phases I and II of development will be discussed, along with new agents and therapeutic classes, such as purine nucleoside phosphorylase inhibitors and dual-action drugs. These new developments are encouraging, and will hopefully contribute to a more adequate management of hyperuricemia in gout.

Keywords: arhalofenate, gout, hyperuricemia, lesinurad, ulodesine, URAT1, urate-lowering therapy

Introduction

Gout is the most common type of inflammatory arthritis in adults in the United States [Lawrence et al. 2008; Zhu et al. 2011]. In the UK, gout has an incidence of approximately 2.68 per 1000 person-years and increases significantly with age [Cea Soriano et al. 2011]. Besides its significant frequency, gout has also been associated with poor quality of life and increased healthcare utilization. In addition, poor gout management can result in recurrent hospital admissions and disability [Singh and Strand, 2008; Becker et al. 2009; Hutton et al. 2009; Garg et al. 2013]. Despite this, management of gout is usually overlooked or suboptimal because of different barriers, which include patient and physician misbeliefs, along with lack of knowledge about guideline and evidence-based gout management [Doherty et al. 2012; Spencer et al. 2012].

Hyperuricemia, defined as a serum urate (SU) concentration higher or equal to 6.8 mg/dl (0.408 mmol/l), is the biochemical abnormality underlying the development of gout. Hyperuricemia usually occurs due to overproduction or under excretion of urate, the latter being causative of hyperuricemia in 90% of gout patients [Choi et al. 2005]. The risk of developing gout is strongly associated with the degree of hyperuricemia [Campion et al. 1987]. However, hyperuricemia is not a sufficient causative factor for the development of gout, as demonstrated by multiple studies including the 2007–2008 National Health and Nutrition Examination Survey in the US in which the prevalence of hyperuricemia was 21%, compared with a gout prevalence of only 3.9% [Zhu et al. 2011].

Because of the established association between hyperuricemia, gout development, and the effectiveness of SU reduction in its chronic management, urate-lowering therapy (ULT) represents the main pillar in the chronic management of gout. An insufficient amount of ULT agents has
led to many decades of unmet needs in the treatment of hyperuricemia of gout. Besides, emerging evidence about an association between hyperuricemia with cardiovascular and metabolic comorbidities has raised further interest in the development of the novel ULTs [Kim et al. 2009, 2010; Grayson et al. 2011].

This review will provide an overview of current practice and agents available for ULT in gout as well as data on new agents currently in the development pipeline in different clinical trial phases, including the recently FDA-approved lesinurad. Repercussion of current therapies on other medical comorbidities will also be discussed.

**Current treatment for hyperuricemia in gout**

**General principles**
Based on 2012 American College of Rheumatology (ACR) guidelines, ULT is recommended in the established diagnosis of gout with two or more acute gout attacks per year, presence of tophi, chronic kidney disease (CKD) stage 2 or more, or presence of renal stones [Khanna et al. 2012]. These are consistent with recommendations from other guidelines. SU goal is less than 6 mg/dl (0.36 mmol/l), based on ACR and European League Against Rheumatism (EULAR) recommendations, in comparison to a lower target of less than 5 mg/dl (0.3 mmol/l) recommended by the British Society for Rheumatology (BSR) [Zhang et al. 2006; Jordan et al. 2007; Khanna et al. 2012]. The goal of less than 5 mg/dl is supported by ACR and EULAR in severe cases of gout, defined as patients with tophi, chronic arthropathy, or frequent attacks.

Xanthine oxidase inhibitors (XOIs) still remain the first line of treatment as recommended by all guidelines. Among these, allopurinol is the first-line agent in all but the ACR guidelines, which recommend allopurinol or febuxostat interchangeably. Uricosurics are still second-line or alternative agents, and all recent guidelines also support the combination of agents (e.g. XOIs and uricosurics) when monotherapy is not effective [Zhang et al. 2006; Khanna et al. 2012]. Benefits of management of asymptomatic hyperuricemia are still unclear, but the Japanese guidelines do recommend treatment in nongout patients with SU above 8 mg/dl (0.44 mmol/l) under the concern of increased risk of development of gout or development of other comorbidities such as CKD [Yamanaka, 2011].

**XOIs**
XOIs are the oldest agents, and still first-line for the treatment of hyperuricemia in gout (see Figure 1). Allopurinol and febuxostat are the two agents available in this category; the former being still the more established and commonly used medication for ULT.
Allopurinol

Allopurinol remains as first-line agent for ULT due to its efficacy, availability, and low cost. It is a nonspecific competitive XOI that is later converted to oxypurinol for its renal excretion. Starting dose, as recommended by ACR guidelines, is usually 100 mg with slow-up titration of the dose every 2–4 weeks until target SU is achieved [Khanna et al. 2012]. Doses up to 800 mg/day are approved in the US, in comparison with up to 900 mg/day in Europe [Jordan et al. 2007].

Despite the wide availability of allopurinol, target SU concentrations are not always achieved due to multiple factors, including failure to monitor SU, low adherence to medication, and inadequate dosing [Horsburgh et al. 2014; Stamp et al. 2014]. A study that randomized patients to fixed doses of 100 and 300 mg of daily allopurinol based on renal function, showed that only 39–41% achieved a target SU of 6 mg/dl [Schumacher et al. 2008]. Another trial that titrated allopurinol up to 300 daily mg showed that only 56% of patients reached a target SU of 6 mg/dl [Reinders et al. 2009].

Inadequate up-titration and dosing is partly influenced by lack of knowledge by physicians, but to some extent by the concern of possible side effects. Besides gastrointestinal side effects, the main concern is development of rashes, Steven–Johnson’s syndrome, and allopurinol hypersensitivity syndrome (AHS) [Arellano and Sacristan, 1993]. AHS is a rare side effect that carries a mortality rate of approximately 27% and is more common in individuals of Thai or Han Chinese descent who carry the HLA-B*5801 haplotype [Hung et al. 2005; Ryu et al. 2013; Yun et al. 2014]. Under the concern that high allopurinol doses increased the risk of AHS, allopurinol titration was guided by dosing recommendations given by Hande and colleagues [Hande et al. 1984] Recent evidence however, has showed that risk of AHS is mostly related to allopurinol starting dose rather than the maintenance dose [Stamp et al. 2012]. In this case-control study, those who developed AHS were more likely to be started on a higher than creatinine clearance-based allopurinol dose, Odds Ratio (OR) 16.7 (95% CI 5.7–47.6). Moreover, in patients who tolerated allopurinol initiation uneventfully, no association between AHS risk and allopurinol maintenance dose was observed. Safety and efficacy of allopurinol dose escalation in combination with education and lifestyle advice was subsequently proved in a trial of 106 participants in which 92% of participants reached a SU target of 6 mg/dl [Rees et al. 2013]. Allopurinol starting dosing needs to be adjusted in CKD patients. Despite previous concerns about the risk of AHS in this population, a recent investigation has described effective and safe up-titration of allopurinol with 88% of patients reaching a goal SU of 6 mg/dl and no events of AHS [Stamp et al. 2011].

Febuxostat

Febuxostat is a nonpurine-specific XOI that is primarily metabolized in the liver. It is currently approved in the US at doses of 40–80 mg/day and up to 120 mg/day in Europe. In a 52-week phase III trial that compared febuxostat 80 and 120 mg to allopurinol 300 mg in 762 patients with estimated glomerular filtration rate (eGFR) > 50 ml/min, 53%, 62%, and 21%, respectively, achieved a SU of 6 mg/dl [Becker et al. 2005a]. Another large phase III trial compared febuxostat 80, 120, and 240 mg to fixed doses of allopurinol, 300 and 100 mg based on renal function, in patients with normal and impaired renal function [Schumacher et al. 2008]. Among patients with normal kidney function, the primary end point of SU less than 6 mg/dl was achieved in 48%, 65% and 69% of the 80, 120 and 240 mg of febuxostat compared to only 22% in the allopurinol arm. Results were similar in the groups with renal impairment. An important observation for all studies comparing febuxostat with allopurinol, and claiming a higher potency for febuxostat, is that allopurinol comparator doses are fixed and not titrated as recommended in most practice guidelines. This places allopurinol at a relative disadvantage, and should call for a word of caution about simplistic statements of comparative efficacy.

Diarrhea, nausea and elevation of liver enzymes are the most common side effects reported for febuxostat [Becker et al. 2005a, 2005b; Schumacher et al. 2008]. Also, increased gout flare rates have been reported with higher febuxostat doses when compared to allopurinol [Becker et al. 2005]. This was, nevertheless, expected as rapid and pronounced reductions in SU are known to commonly induce flares. A nonstatistically significant increase in the frequency of cardiovascular events in the febuxostat arms of a subsequent clinical trial was noted. This is of unclear clinical relevance and is currently carefully followed in postmarketing analyses [Becker et al. 2010; White et al. 2012]. It would be
expected that any cardioprotective effect of allopurinol mediated by reduction in oxidative stress should also be observed with febuxostat [De Abajo et al. 2015; Grimaldi-Bensouda et al. 2015; MacIsaac et al. 2016] Although an adverse cardiovascular profile for febuxostat is far from confirmed, the clinical concern for this has led to the development of a comparative cardiovascular outcomes trial [MacDonald et al. 2014].

Cost remains the biggest limitation in febuxostat use; a reason why cost-analysis studies describe it as a second option after allopurinol has shown to be ineffective, not tolerated or contraindicated [Beard et al. 2014; Jutkowitz et al. 2014].

**Uricosurics**

Uricosurics are the second class of ULT currently available, which act by increasing renal urate excretion (see Figure 1). This is mediated by selective inhibition of organic anion transporters (OATs) present in the proximal tubular cells (see Figure 2). All uricosurics carry with them the increased risk of precipitation of urate stones; a reason why under-elevated urinary urate is a contraindication to the use of these agents [Khanna et al. 2012]. Benzbromarone and probenecid are the two main agents available in this class. Sulfinpyrazone, although still available in few countries, has been very restricted in its use for gout and therefore will not be discussed.

**Probenecid**

Probenecid acts by inhibiting URAT 1 and GLUT 9 transporters (see Figure 2), and is the prototypical uricosuric drug. In a small case series of 30 patients on probenecid monotherapy and 27 patients on probenecid and allopurinol, 33% and 37% reached a target SU of 6 mg/dl, respectively [Pui et al. 2013]. Another trial of probenecid at a dose of 1000 mg twice a day added to allopurinol 300 mg daily resulted in 65% of patients reaching a target SU of 5 mg/dl [Reinders et al. 2007]. Probenecid is still reserved as an option for those who cannot tolerate allopurinol or cannot reach target SU on monotherapy with xanthine-oxidase inhibitors.

Although the efficacy of uricosurics is believed to be impaired with decreasing glomerular filtration rate (GFR), a recent study showed no difference in the percentage of patients achieving target SU when comparing patients with GFR below or above 50 ml/min/1.73m² [Pui et al. 2013]. Probenecid also has multiple significant drug interactions with commonly used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), beta-lactams, and heparin, which limit its use.
Benzbromarone is a potent uricosuric that acts via inhibition of URAT 1 and GLUT 9 transporters. Benzbromarone was shown to be more potent than probenecid when used as an add-on to 300 daily mg of allopurinol, with 92% of participants reaching a target SU of 5 mg/dl [Reinders et al. 2007]. Two different studies that compared benzbromarone to allopurinol showed higher potency of benzbromarone compared to the standard dose (300 mg) of allopurinol, but almost equal effectiveness after up-titration of allopurinol [Perez-Ruiz et al. 1998; Reinders et al. 2009]. A systematic review of available evidence concluded that there is no difference in urate-lowering potency between benzbromarone and allopurinol. The same review concluded that benzbromarone is more potent than probenecid at achieving SU goals [Kydd et al. 2014].

Efficacy in benzbromarone has been seen even in patients with an estimated GFR of 20 ml/min [Lee et al. 2008]. Despite its high efficacy, benzbromarone was withdrawn from the market in several countries due to postmarketing reports of abnormal liver function and deaths from hepatic failure. This risk was especially high in patients taking high doses of 300 mg daily [Hautekeete et al. 1995]. Interestingly, the systematic review by Kydd and colleagues concluded that when compared with probenecid, benzbromarone resulted in fewer withdrawals due to adverse events (AE) and fewer incidence of AE [Kydd et al. 2014].

Uricases (pegloticase)
Uricase, the enzyme responsible for the breaking down of urate to the more water-soluble allantoin (see Figure 1) was somehow lost during the evolution of man [Orowan, 1955]. This vital step in the final product of purine metabolism became a viable therapeutic target with the development of recombinant uricases.

Pegloticase, a porcine recombinant polyethylene-glucol conjugated uricase was FDA approved in 2014, is currently indicated for gout, refractory to conventional ULT or patients with severe disease burden (e.g. deforming tophaceous gout) [Khanna et al. 2012]. However, this indication was not supported by the United Kingdom’s National Institute for Health and Care Excellence (NICE) based on its high cost and adverse reactions [NIOHCA, 2013].

Two phase III trials compared two different pegloticase infusions strategies (8 mg intravenously every 2 and 4 weeks) with placebo for a primary outcome of achieving a SU of less than 6 mg/dl for at least 80% of the time between months 3 and 6 [Sundy et al. 2011]. Based on combined results from both trials, 42% and 35% of responders were observed in the every 2 weeks and every 4 weeks groups, respectively. Another analysis that evaluated the same regimens in their response on tophi reduction, reported that the proportion of patients who, after 6 months had complete resolution of at least one tophus without the development of new tophi or enlargement of another tophus, was 45%, 26% and 8% in the every 2 weeks, every 4 weeks, and placebo groups, respectively [Baraf et al. 2013]. Due to its rapid urate-reduction effect, use of pegloticase can cause a significant amount of acute flares even with the concomitant use of prophylactic therapy [Sundy et al. 2011].

Infusion reactions (IRs), which mainly consist of chest discomfort, flushing, and dyspnea have been reported in 20–40% of patients and occur more commonly with less frequent infusions [Baraf et al. 2014]. IRs occur most commonly in patients who developed high-titer antipegloticase antibodies, with formation of these occurring in approximately 40% of patients. The titer of these antibodies correlates with loss of the urate-lowering effect, with up to 91% and 71% of patients (in the every 2 and 4 weeks dosing, respectively) losing efficacy in the achievement of goal SU before the development of an IR [Lipsky et al. 2014]. However, a study that included organ transplant recipients on immunosuppressive agents such as tacrolimus, mycophenolate mofetil, cyclosporine A, or azathioprine showed a decreased risk for the formation of antipegloticase antibodies and this has generated interest for further research about a potential role of immunosuppression to prevent the formation of antipegloticase antibodies [Hershfield et al. 2014]. Current research is also ongoing due to some postmarketing concerns about higher frequency on cardiovascular events in patients receiving pegloticase [Gentry et al. 2014].

New therapies in development
Despite available therapies, gout is inadequately managed. This fact, in addition to emerging evidence of the possible role of hyperuricemia and gout in cardiovascular and metabolic comorbidities have led to the development of newer agents.
Most of them, including lesinurad which has been recently approved by the US FDA, are uricosuric agents developed based on the increasing knowledge of renal urate transporters (see Figure 1 and 2). Here we will discuss some of the new drugs currently under study, including phase I and II trials (see Table 1).

**Uricosurics**

**Lesinurad (RDEA594).** Lesinurad is a URAT1 and OAT4 inhibitor, which increases proximal renal tubule urate excretion. RDEA806, which is the prodrug for lesinurad, is a nonnucleoside reverse transcriptase inhibitor in trials for HIV treatment that was found to have significant hypouricemic properties. An initial phase II trial of 208 patients with gout with SU over 6 mg/dl and a creatinine clearance (CrCl) over 60 ml/min despite allopurinol, were randomized to combination therapy by adding 200, 400 and 600 mg of lesinurad daily or placebo [Perez-Ruiz et al. 2010]. After 28 days, 79%, 74%, and 63% of patients achieved SU reduction below 6 mg/dl in to 600, 400 and 200 mg lesinurad groups compared to only 25% in the placebo group. This study was followed by a phase IIb extension that enrolled 126 patients to assess the ongoing efficacy of the combination strategy with a 44-week follow up [Perez-Ruiz et al. 2011] Approximately 78% of the patients receiving lesinurad maintained SU levels below 6 mg/dl by week 44, compared to only 56% of patients in the placebo group. Allopurinol was adequately titrated in this follow-up study. Even more, 59% of the patients in the lesinurad group achieved a SU of less than 5 mg/dl. No significant differences in AEs were noted between groups in any of the two studies.

With promising results in the phase II trials, recent phase III trials have been done showing the efficacy and safety of lesinurad. The CLEAR-1 study was 12 month randomized, double-blind trial that compared lesinurad, 200 or 400 mg daily, in combination with allopurinol to allopurinol with placebo [Saag et al. 2015b]. This study included 603 patients who were inadequate responders, meaning not reaching SU less than 6 mg/dl, already on adequate allopurinol dosing. SU less than 6 mg/dl at 6 months, which was the study’s main outcome, was reached in 59.2% and 54.2% in the lesinurad 400 and 200 mg, respectively, compared to only 27.9% in the placebo group. Goal SU of less than 5 mg/dl was also achieved in twice as many patients in the lesinurad 200 mg group compared to placebo, and up to four times as much in the lesinurad 400 mg. The main AEs observed were elevations of serum creatinine (SCr) readings two times above the baseline level. However, all patients in the lesinurad 200 mg group presented resolution of the increased SCr by the end of the study without need to discontinue medication, as well as 85% of patients in the higher dose group. Other AEs were not significantly different between the groups. Similar results were observed from the international CLEAR-2 study [Bardin et al. 2015]. A recent combined analysis of both CLEAR-1 and CLEAR-2 studies, that pooled 1208 patients and divided them into groups based on estimated CrCl (<60, <90 or ⩾90 ml/min) [Saag et al. 2015a].

Efficacy, measured as a proportion of patients achieving SU goal of less than 6 mg/dl was consistently greater (p < 0.05) across all groups compared to placebo. No significant difference in incident of AEs was noted between different groups. Elevation in SCr occurred more frequently among the lesinurad groups, particularly in the 400 mg groups, however most of these patients presented resolution in SCr levels by the end of the study. The LIGHT study, which evaluated lesinurad 400 mg as monotherapy as an option for patients intolerant or with contraindications to XOIs, showed a significant reduction in SU compared to placebo [Tausche et al. 2015]. However, only 29.9% achieved SU below 6 mg/dl, and effectiveness was not as encouraging as those observed in the combination trials. In this trial, there was a higher frequency of SCr elevations in individuals receiving lesinurad (8.4%) and almost half of them did not present resolution of SCr elevation by the end of the trial. A final study that focused on patients with chronic tophaceous gout, the CRYSTAL study, evaluated the combination of lesinurad and febuxostat with SU goals of 5 and 6 mg/dl [Dalbeth et al. 2015]. At 6 months, approximately 76% of patients on the lesinurad 400 mg group achieved the goal SU of less than 5 mg/dl. A higher proportion of patients achieving SU goal of 5 mg/dl was also seen in patients in the lesinurad 200 mg group, and this was clearly observed amongst all different SU goal levels. Improvement in the resolution of one or more tophus and decrease in tophus area was reported in the lesinurad 200 and 400 mg groups compared to placebo. The safety profile was overall consistent with previous studies, with more individuals with elevations in SCr being observed.
in the lesinurad 400 mg group and most of the individuals returning to baseline SCr by the study’s final visit. The importance of maintained SU lowering by ULT was clearly shown by a pooled analysis of the CLEAR-1, CLEAR-2 and CRYSTAL studies, where a lower SU goal was clearly correlated with improvement in tophi burden (measure by total tophus area) and incidence of gout flares requiring therapy [Terkeltaub et al. 2015]. The safety of lesinurad in patients with CKD and other comorbidities is still unknown. The drug has been recently approved by the US FDA for the management, in association with a XOI, of hyperuricemia in gout [FDA, 2015]. The European Medicines Agency has also recently approved the 200 mg dose of lesinurad for the management of hyperuricemia in chronic gout [EMA, 2015].

**Arhalofenate (MBX-102).** Arhalofenate is a long-acting dual action medication whose main uricosuric effect comes from the selective inhibition of URAT1 and OAT4 [Choi et al. 2012]. It is also a peroxisome proliferator-activated receptor-γ modulator, and through this mechanism, is capable of reducing IL-1β levels with a potential added benefit of reducing gout flares.

While being initially intended as a type 2 diabetes mellitus drug, an analysis of four global double-blinded phase II randomized controlled trials (RCTs) including 955 patients analyzed the effect of different doses of arhalofenate on SU [Saha et al. 2011]. Statistically significant dose-dependent reductions from baseline SU were observed in 13%, 22%, and 29% of the patients receiving arhalofenate 200, 400, and 600 mg daily respectively. When analyzing patients whose baseline SU was above 6 mg/dl, 48%, 78%, and 83% of patients receiving 200, 400, and 600 mg of arhalofenate achieved a SU below 6 mg/dl compared to only 25% in the placebo group. The safety profile was overall good, with significant reductions in fasting glucose, hemoglobin A1c and triglycerides were seen in all treatment arms.

A phase II study evaluated a sequential combination strategy using arhalofenate and febuxostat [CymaBay Therapeutics, 2015a, 2015b]. One arm used 600 daily mg of arhalofenate for 2 weeks, followed by sequential weekly coadministration of febuxostat at 80 mg and 40 mg daily, with 2 final weeks of febuxostat as monotherapy at 40 mg daily. A second analogous arm used an arhalofenate dose of 800 daily mg with a final febuxostat monotherapy phase of 80 mg daily. The combination therapy showed a significant effectiveness in the reduction of SU, with the highest dose combination (arhalofenate 800 mg and febuxostat 80 mg) showing 100%, 93% and 79% of patients reaching a SU of less than 6, 5 and 4 mg/dl, respectively. Treatment was well tolerated, with no serious AEs reported. No patients presented any significant elevations in SCr and only one patient presented an elevation in liver transaminases. Another phase II trial was designed not only for evaluation of arhalofenate’s urate lowering effect, but also to evaluate its ability to prevent flares. This 12-week RCT used arhalofenate, in 600 or 800 mg daily doses, when compared to placebo, allopurinol 300 mg daily, and allopurinol 300 mg daily in combination with colchicine 0.6 mg daily [Steinberg et al. 2015]. Participants receiving the arhalofenate 800 mg dose presented a flare rate reduction of 46% and 41% when compared to allopurinol monotherapy and placebo, respectively. These flare rate reductions, although statistically significant, were not as effective as the ones achieved by the allopurinol and colchicine combination arm. By the end of the study, the mean percentage change in SU was 12% and 16% in the arhalofenate 600 and 800 mg when compared to placebo and did not result in a statistically significant number of participants reaching a target SU of less than 6 mg/dl. The only serious AE reported was nephrolithiasis in a patient in the allopurinol group, and no significant differences regarding the need for management of AE was noticed between the different groups. Again, no changes in SCr where noticed among the patients receiving arhalofenate.

**Tranilast.** Tranilast, which was initially developed as medication for asthma and other allergic conditions in Japan, was shown to reduce SU levels in healthy volunteers. This is achieved through inhibition of GLUT9 and URAT1 transporters and promotion of renal excretion of urate [Mandal et al. 2010]. Two phase II clinical trials evaluated the effect of tranilast, one by using a single dose of tranilast with doses ranging from 100 to 900 mg, and the second study using total daily doses of 300, 600 or 900 mg daily during 7 days [Sundy and Kitt, 2010]. The first study reported mean SU decrease of 0.17 and 0.24 mg/dl at 4 and 24 hours, respectively. In the second study, mean SU reductions of 1.1, 3.2 and 3.3 mg/dl were reported in the tranilast 300, 600 and 900 mg groups, respectively. Besides its urate lowering effect, tranilast has also been reported...
to reduce inflammation induced by monosodium urate (MSU) crystals in vivo, by suppressing leucocyte infiltration and plasma extravasation in a similar magnitude to colchicine and indomethacin [Serafini and Emerling, 2010]. This would represent an added benefit to ULT therapy offered with the possibility of flare prevention. A phase II clinical trial using tranilast in combination with allopurinol was carried out, however no results have been published yet.

Levotofisopam. Levotofisopam is the S-enantiomer of a 2,3-benzodiazepine, tofisopam, which is approved in several countries outside the US for the management of anxiety. Two phase I trials showed a reduction of SU levels in healthy individuals, and although the mechanism is not known precisely, it is thought to be through enhancement of urate excretion. In a phase II trial with 13 patients with hyperuricemia with gout, one day of levotofisopam 500 mg daily followed by TID doses and one final single dose on day 7 showed a mean absolute SU reduction of 3.9 mg/dl (range 2.3–5.3) [Noveck et al. 2012]. All patients achieved the SU goal below 6 mg/dl, with a mean treated SU of 4.1 mg/dl. No serious AEs were reported, with 23% of patients experiencing a gout flare. Further investigations on levotofisopam are pending.

Verinurad (RDEA3170). RDEA3170 is a URAT1 inhibitor that has shown to be three times more potent than benz bromarone and 100 times more potent that probenecid in vitro studies [Ahn et al. 2013]. At the moment, no further studies or results have been reported regarding the development of this agent.

XOIs

Topiroxostat. Topiroxostat (FYX-501) is a selective XOI that acts by structure and mechanism-based inhibition (competitive versus noncompetitive enzymatic inhibition), combining allopurinol and febuxostat’s XOI mechanisms, respectively. This medication is currently approved in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA) in doses from 20 to 80 mg twice daily [PMDA, 2013]. The half-life for topiroxostat is 20 h, and even after the dissociation of the topiroxostat–XO complex, the enzyme does not recover complete activity. A Japanese phase III study showed that the percentage decrease in SU obtained by topiroxostat 120 mg/day was comparable to allopurinol 200 mg/day, with 72.4% of patients achieving the goal SU of less than 6 mg/dl. AEs were similar overall when compared with allopurinol and placebo, except for elevation of transaminases.

Regarding indication of patients with baseline renal impairment, a 22-week RCT randomized patients with a baseline eGFR between 30–60 ml/min/1.72m² to topiroxostat 160 mg daily or placebo and evaluated the SU reduction [Hosoya et al. 2014]. Percent decrease in SU in patients in the treatment group and placebo were 45.38% and 0.08%, respectively, with 90% of patients receiving topiroxostat achieving a SU less than 6 mg/dl. There were no significant changes in renal function between groups, with the added effect of a decrease in the urinary albumin-to-creatinine ratio. Increases in liver enzymes were reported, but these were not considered statistically significant and no serious AEs were reported.

Ulodesine. Ulodesine (BCX4208) is a novel and unique agent in its class which acts by inhibiting purine nucleoside phosphorylase (PNP), an enzyme which is one step before XO in the production of urate (see Figure 1). Ulodesine administration has shown a dose-dependent effect on the reduction of xanthine and hypoxanthine [Bantia et al. 2013]. Urate production is inhibited in this way, therefore representing an exciting agent for the management of hyperuricemia in gout. An initial randomized placebo-controlled trial compared oral doses of 40, 80, 120 mg daily in 60 gout patients with a baseline SU over 8 mg/dl [Fitz-Patrick et al. 2010]. SU was reduced by 2.7, 3.3 and 4.4 mg/dl in the 40, 80 and 120 mg groups, respectively. No placebo-treated subjects achieved the SU goal of less than 6 mg/dl, compared to 33%, 36% and 31% of the subjects receiving the 40, 80 and 120 mg daily doses by
the end of 3 weeks. A higher proportion of patients in each respective dose achieved the goal SU at least once during the whole 3 week period. All lymphocyte subsets were decreased by 30–70% with all ulodesine doses, however none of the subjects had to stop treatment due to lymphocyte reduction. No other significant AEs were reported.

An initial 12-week RCT comparing four different doses of ulodesine (5, 10, 20 and 40 mg/day) with allopurinol 300 mg/day to allopurinol monotherapy showed a significantly greater proportion of patients achieving the SU goal, with a safe profile and adequate tolerance to the combination [Becker et al. 2013]. The 24-week extension which included 160 patients from the original study showed that by the end of trial, 40%, 50%, 46% and 55% of the patients receiving the 5, 10, 20 and 40 mg/day of ulodesine, respectively, achieved a goal SU less than 6 mg/dl [Hollister et al. 2013]. This compared to only 25% of patient in the allopurinol-placebo group. AE frequency and severity, including infectious AEs, were similar among ulodesine groups and placebo. Protocol-specified withdrawals due to CD4+ less than 350 cells/ml occurred in 4 and 11 patients in the ulodesine 20 and 40 mg/day groups, respectively. All subjects were tested for response to Tetanus Toxoid and Pneumococcal Polysaccharide Vaccine, showing no significant difference in response between the ulodesine-treated and placebo subjects. Although initial concerns of inhibition of PNP was raised, due to absence of PNP in immunodeficiency and autoimmune disorders, evidence so far seems encouraging. Ulodesine has also shown a well tolerated drug-interaction profile, which is an important factor in the management of gout patients who usually have a high comorbidity-burden [Bantia et al. 2013].

**Conclusion**

Despite its high prevalence and a significant impact in productivity and quality of life associated with its inadequate management, gout has mirrored other orphan diseases when considering the paucity of therapeutic options. This, associated with socio-economical and educational barriers described in the management of gout, has led to a suboptimal patient care and poor health outcomes.

Treatment failure is sometimes related to poor tolerance and side effects to available therapeutic options, even including serious AEs such as AHS. Although febuxostat has emerged as an option, wide availability is still limited because of cost and health insurance coverage considerations. Availability of newer drugs, especially the emerging uricosurics such as lesinurad, will allow for the introduction into clinical practice of combination regimens that have shown promising results in several studies. The high efficacy seen in these combination studies could also represent an alternative for management of tophaceous gout when pegloticase use is limited by IRs, high cost, or the formation of neutralizing antipegloticase antibodies. In addition, the development of novel therapeutic classes targeting dual and complementary targets for gout is encouraging.

Combined action as XOI/URAT1 inhibitors and ULT/IL-1β antagonists hold a promise for a more comprehensive and simplistic approach to gout therapy in the future.

Much of the renewed interest in hyperuricemia and gout arises from emerging evidence about the impact of hyperuricemia in cardiovascular and metabolic conditions. Although still inconclusive, the potential benefits of ULT in early hypertension or CKD outcomes could be easier to implement in practice with new generation drugs having safer side effect profiles [Feig et al. 2008; Kanji et al. 2015]. Some of these drugs such as arhalofenate and topiroxostat have shown promising improvements in metabolic disease markers such as hemoglobin A1c reductions, improvement in lipid profiles, and reductions in microalbuminuria. More specific pathways targeted by this new generation of
<table>
<thead>
<tr>
<th>Code name</th>
<th>Generic name</th>
<th>Clinical trial phase</th>
<th>Trial</th>
<th>Duration of study</th>
<th>Dose [mg/d] Monotherapy / combination</th>
<th>Outcomes [SU goal less than 6 mg/dl]</th>
<th>Approval status</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uricosurics</strong></td>
<td></td>
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<tr>
<td>RDEA594</td>
<td>Lesinurad</td>
<td>III</td>
<td>CLEAR-1</td>
<td>12 months</td>
<td>200 or 400 + allopurinol versus allopurinol</td>
<td>54.2% and 59.2%, respectively, versus 27.9%</td>
<td>EMA approved; FDA approved.</td>
<td>[Saag et al. 2015b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CLEAR-2</td>
<td>12 months</td>
<td>200 or 400 + allopurinol versus allopurinol</td>
<td>55.4% and 66.5%, respectively, versus 23.3%</td>
<td></td>
<td>[Bardin et al. 2015]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LIGHT</td>
<td>6 months</td>
<td>400 versus placebo</td>
<td>29.9% versus 1.9%</td>
<td></td>
<td>[Tausche et al. 2015]</td>
</tr>
<tr>
<td>RDEA3170</td>
<td>Verinurad</td>
<td>II</td>
<td></td>
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<tr>
<td>MBX-102</td>
<td>Arhalofenate</td>
<td>II</td>
<td>Up to 24 weeks</td>
<td></td>
<td>200, 400, 600 versus placebo</td>
<td>49%, 78%, 83%, respectively, versus placebo</td>
<td></td>
<td>[Saha et al. 2011]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 weeks</td>
<td>600 or 800 with febuxostat 40 or 80m versus febuxostat 40 or 80</td>
<td>800 + febuxostat 40 or 80 = 100%</td>
<td></td>
<td>[CymaBay Therapeutics, 2015a, 2015b]</td>
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<td></td>
<td></td>
<td>600 + febuxostat 80 = 94%</td>
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<td></td>
<td></td>
<td></td>
<td>600 + febuxostat 40 = 79%</td>
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<td></td>
<td></td>
<td>Febuxostat 80 = 93%</td>
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<tr>
<td>Tranilast</td>
<td></td>
<td>II</td>
<td>1 week</td>
<td>300, 600, 900</td>
<td>1.1, 3.2 and 3.3 (in mg/dl), respectively*</td>
<td>Not approved</td>
<td></td>
<td>[Sundy et al. 2010]</td>
</tr>
<tr>
<td>Levotofisopam</td>
<td></td>
<td>II</td>
<td>1 week</td>
<td>500, followed by 1500</td>
<td>100%</td>
<td>Not approved</td>
<td></td>
<td>[Noveck et al. 2012]</td>
</tr>
<tr>
<td>Topiroxostat</td>
<td></td>
<td>II</td>
<td>22 week</td>
<td>160 versus placebo</td>
<td>90%</td>
<td>Approved by PMDA</td>
<td></td>
<td>[Hosoya et al. 2014]</td>
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<td><strong>PNP inhibitors</strong></td>
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<tr>
<td>BCX4208</td>
<td>Ulodesine</td>
<td>II</td>
<td>3 weeks</td>
<td>40, 80, 120 versus placebo</td>
<td>33%, 36%, 31%, respectively, versus none</td>
<td>Approved by PMDA</td>
<td></td>
<td>[Fitz-Patrick et al. 2010]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II</td>
<td>24 weeks</td>
<td>5, 10, 20, 40 with allopurinol versus allopurinol</td>
<td>40%, 50%, 46% and 55%, respectively, versus 25%</td>
<td></td>
<td>[Hollister et al. 2013]</td>
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<tr>
<td><strong>Dual inhibitor</strong></td>
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<tr>
<td>RLBN1001</td>
<td></td>
<td>II</td>
<td>Unknown</td>
<td></td>
<td></td>
<td>No results</td>
<td></td>
<td></td>
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<tr>
<td>KUX-1151</td>
<td></td>
<td>I</td>
<td>Unknown</td>
<td></td>
<td></td>
<td>No results</td>
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</tr>
</tbody>
</table>

*mean SU reduction.

EMA, European Medicines Agency; FDA, Food and Drug Administration; PMDA, Pharmaceutical and Medical Devices Agency (Japan); PNP, purine nucleotide phosphorylase; SU, serum urate; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor.
drugs would also represent better drug-interaction profiles, which has been an important limiting factor in the management of gout patients with high comorbidity burden.

The approval of febuxostat, pegloticase, and the more recent availability of lesinurad, start filling a decades-long gap in the management of gout. Encouraging results in the upcoming trials could lead to further development of new therapeutic agents. Hopefully, this will translate into improvements in clinical outcomes, quality of life, productivity, and even cardiometabolic profiles in patients with gout.

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**Conflict of interest statement**

The authors declare that there is no conflict of interest.

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