Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

New and emerging therapies for gout

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After nearly 50 years, new drugs are now available or in development for gout. Febuxostat (approved 2009) selectively inhibits xanthine oxidase, preventing uric acid formation and lowering serum urate. Pegloticase (approved 2010) is a recombinant chimeric mammalian uricase that corrects the intrinsic human uricase deficiency. Pegloticase reduces serum urate, and may have particular efficacy against tophi. IL-1β is now understood to be a central actor in acute gouty inflammation. Three IL-1β antagonists – anakinra, rilonacept and canakinumab (all US FDA approved for other uses) – are being evaluated for gout treatment and/or prophylaxis. The renal urate resorbing transporters URAT1 and GLUT9 have been recently characterized as targets of uricosuric drugs; two pipeline drugs, RDEA594 and tranilast, inhibit these transporters and are promising urate-lowering therapies.

Keywords: anakinra • canakinumab • febuxostat • gout • hyperuricemia • pegloticase • RDEA594 • rilonacept • tranilast

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Gout is a disease in which excess accumulation of soluble serum urate (sUA) results in tissue deposition of monosodium urate (MSU) crystals, promoting acute and chronic inflammation and causing soft tissue damage, bone erosion, chronic pain and disability. The current standard of care for gout pharmacologic treatment entails the management of acute attacks with colchicine or anti-inflammatory agents, such as NSAIDs or corticosteroids and, if attacks are recurrent or in the presence of tophi or chronic arthropathy, the initiation of urate-lowering therapy (ULT) with xanthine-oxidase inhibition or uricosuric agents; prophylaxis with daily colchicine or NSAIDs is often utilized to prevent attacks and should be employed when initiating ULT [1]. Until recently, no new treatment for gout had been developed in nearly 50 years, despite the fact that during most of that period gout incidence and prevalence appear to have been rising. However, advances in our understanding of gout, together with a greater appreciation of gout as a public health problem, have accelerated efforts to develop new and better therapies for gout and hyperuricemia. Here we review the most prominent of these new therapies, including agents that have already been approved by the US FDA, and those that are not yet approved but whose state of development is relatively advanced.

Xanthine oxidase inhibition: febuxostat

Uric acid is the end product of purine metabolism in humans, generated by the enzymatic actions of xanthine oxidase (XO, also known as xanthine dehydrogenase) [2]. Inhibition of XO with the purine analogue allopurinol has been the standard of care for ULT in gout patients. However, it is often difficult to achieve successful sUA reduction with this agent. Patient compliance with the drug and adequate physician titration of the agent to reach target sUA levels have historically been suboptimal [3]. While generally well tolerated, side effects such as GI intolerance, abnormal liver function and occasionally a severe hypersensitivity reaction limit the use of allopurinol in some patients. In addition, the safety of the drug in patients with diminished renal function remains controversial.

FUTURE SCIENCE part of fsg

In 2009, the FDA approved febuxostat (Uloric, Takeda Pharmaceuticals), a nonpurine inhibitor of XO, at doses of 40 mg or 80 mg p.o. daily for the treatment of gout in the USA (in Europe marketed as Adenuric®, approved at 80 mg and 120 mg p.o. in 2010) [101], with no dose adjustment for mild-to-moderate renal insufficiency. Although allopurinol and febuxostat inhibit the same enzyme, they do so via different mechanisms. Allopurinol is a purine analogue whose effect on XO depends on the redox state of both the drug and the enzyme. The drug acts as weak competitive inhibitor of the oxidized form of XO, exerting most of its effect upon activation to oxypurinol (by XO, or by the closely related enzyme aldehyde oxidase), which tightly binds and inhibits the reduced form of XO. In contrast, febuxostat inhibits XO activity by high-affinity binding of the drug to the narrow channel leading to the molybdenum-pterin active site (Figure 1) [4]. The agent blocks substrate access to the active site regardless of the redox state of XO [5]. Like allopurinol, febuxostat should not be given with other drugs metabolized by XO, such as azathioprine, 6-mercaptopurine, or theophylline, as it may increase serum levels of these medications.

In Phase III studies, febuxostat demonstrated superiority to allopurinol at doses of 300 mg for sUA reduction. In FACT, 762 patients with gout and hyperuricemia (sUA ≥8 mg/dl) were randomized to receive febuxostat (80 mg or 120 mg) or allopurinol 300 mg once-daily for 52 weeks [6]. The study excluded patients with serum creatinine concentration >1.5 mg/dl or an estimated creatinine clearance (CrCl) <50 ml/min/1.73m^2. Subjects received naproxen or colchicine for prophylaxis against gout flares during the first 8 weeks. The primary end point was sUA <6 mg/dl at the last three monthly measurements, which was achieved by 53% of subjects in the febuxostat 80 mg group, 62% in the febuxostat 120 mg group and 21% in the allopurinol group ($p < 0.001$ for each febuxostat group vs allopurinol). The total number of gout flares (reported separately from adverse events [AEs]) was the same in all groups, but there were more flares during the first 8 weeks in the febuxostat 120 mg group. Treatment-related AEs were similar in frequency across the groups and included abnormal liver-function tests, diarrhea, headaches, joint-related signs and symptoms, and musculoskeletal and connective tissue complaints. More patients in the febuxostat 120 mg group (39%) withdrew from the study compared with the febuxostat 80 mg (34%) and allopurinol group (26%) due to incidence of gout flares and AEs.

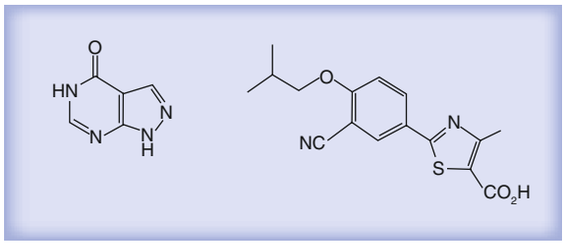

Figure 1. Structure of allopurinol and febuxostat.
(A) Allopurinol, a purine analogue. **(B)** Febuxostat, a nonpurine analogue that binds tightly to XO regardless of the redox state of the enzyme, inhibiting uric acid synthesis.

In APEX, another Phase III study, 1072 gout patients with hyperuricemia (sUA ≥8 mg/dl) were randomized to once-daily febuxostat (80 , 120 or 240 mg), allopurinol (300 or 100 mg in the setting of renal insufficiency), or placebo for 28 weeks [7]. In contrast to FACT, the trial also included 50 patients with moderately impaired renal function (serum creatinine level >1.5 to ≤2.0 mg/dl). The primary end point was the same as that for FACT. A significantly greater proportion of subjects receiving febuxostat 80 mg (48%), febuxostat 120 mg (65%) and febuxostat 240 mg (69%) reached the primary end point than in the allopurinol (22%) or placebo (0%) groups ($p \leq 0.05$). Although the number of subjects with impaired renal function was small, more of them achieved the primary end points as well: 44, 46 and 60% in the febuxostat 80, 120 and 240 mg groups, respectively, versus 0% in the allopurinol and placebo groups.

As in FACT, febuxostat in APEX was well tolerated. However, the APEX trial raised a question about the possibility of increased cardiovascular (CV) events while taking febuxostat. In APEX there were numerically more CV events in the febuxostat group (11 total vs one in placebo and one in the allopurinol group), although this difference was not statistically significant, and all of the patients who had CV events had underlying cardiac disease or risk factors. An open-label extension (OLE) of FACT and APEX, the EXCEL trial, failed to resolve the question of increased CV events while on febuxostat [8]. EXCEL enrolled 1086 subjects and followed them for 40 months. Subjects were allowed to reassign groups if they did not achieve a sUA <6.0 mg/dl, and many more subjects switched from allopurinol to febuxostat than *vice versa*. Although CV adverse event rates did not differ statistically among treatment groups, there were numerically more CV deaths among febuxostat subjects. However, given a tenfold greater exposure to febuxostat than allopurinol in this study, it was difficult to implicate febuxostat as a cause of increased CV events.

The CONFIRMS trial further assessed the safety and efficacy of febuxostat [9]. In CONFIRMS, the largest Phase III trial of febuxostat to date, 2269 patients with gout and hyperuricemia (sUA ≥8 mg/dl) were randomized to febuxostat (40 or 80 mg) or allopurinol (300 or 200 mg in patients with moderate renal impairment)

and followed for 6 months. 65% of participants had mild-to-moderate kidney disease. The primary end point of sUA <6 mg/dl at the final visit was reached in 45.2, 67.1 and 42.1% of patients receiving febuxostat 40 mg, febuxostat 80 mg and allopurinol respectively, indicating that febuxostat 40 mg was noninferior to allopurinol and that febuxostat 80 mg was more effective than allopurinol in lowering sUA ($p < 0.001$). Febuxostat 80 mg was also more effective in lowering urate in renally impaired patients than febuxostat 40 mg or allopurinol, with response rates of 71.6% in the 80 mg group, 49.7% in the 40 mg group and 42.3% in the allopurinol group. Despite the numerically small difference, febuxostat 40 mg also demonstrated a statistically significant benefit over allopurinol. In this trial, all deaths and potentially CV-related AEs were reviewed by a blinded CV end points committee. There were no significant differences in CV end points in febuxostat and allopurinol study groups. These results led the FDA to approve febuxostat, but to require that the package labeling warns to monitor for signs and symptoms of MI and stroke [102]. For its part, the European Medicines Agency does not recommend use of febuxostat in patients with ischemic heart disease or congestive heart failure [103].

Febuxostat induces rapid and sustained urate-lowering, as well as tophus reduction. In an early Phase II, placebo-controlled study in patients with gout and hyperuricemia (sUA ≥8.0 mg/dl), sUA reached a goal of <6.0 mg/dl within 28 days in 56% of patients on feboxostat 40 mg, 76% taking 80 mg and 94% taking 120 mg [10]. Based on these and other data, the labeling recommends starting with 40 mg p.o. daily but increasing to 80 mg p.o. daily if the patient does not reach a sUA <6 mg/dl after 2 weeks [102]. In a 5 year, OLE of this study (FOCUS), subjects were started on febuxostat 80 mg p.o. daily, but physicians were allowed to titrate the dose up or down (although most remained on 80 mg) [11]. 50% of patients discontinued prematurely due to uncertain reasons, AEs or gout flares. Ultimately, 93% (54/58) of patients who completed the study and 83% of all patients enrolled in the study reached the primary end point of sUA <6.0 mg/dl. Gout flares were common initially (47% of all subjects), but trended towards zero by the end of 5 years, and index tophi resolved in 69% (18/26) of subjects with a baseline tophus.

Limited retrospective data also suggest that febuxostat is generally safe to use in patients who have experienced allopurinol toxicity, although such patients should be monitored closely [12]. A retrospective study reported on 13 gout patients with prior severe allopurinol toxicity (including cutaneous, multisystem involvement, renal failure, hepatitis and hematologic abnormalities), who went on to receive febuxostat (started at 40 mg in 12 subjects, 20 mg in one subject, and titrated to reach sUA <6mg/dl). One subject who had a skin reaction to allopurinol developed a cutaneous leukocytoclastic vasculitis with febuxostat; there were no other recurrent AEs, and 10 of the subjects reached their goal sUA for a mean of 10 months of follow-up on doses of febuxostat 20–80 mg daily.

Studies are underway to further characterize febuxostat. For example, a Phase II trial is examining the effect of febuxostat on renal function in gout patients with moderate-to-severe renal impairment (NCT01082640) [104]. In this study, patients will be followed for change in serum creatinine while on different doses of febuxostat. To explore CV risks with febuxostat use, a Phase III trial (the CARES trial) evaluating CV safety of febuxostat and allopurinol in gout patients with CV comorbidities is actively recruiting patients (NCT01101035) [105]. This will also be the first trial in which febuxostat is compared with allopurinol at doses up to 600 mg p.o. daily.

In summary, clinical trials to date have demonstrated effectiveness of febuxostat for lowering sUA, and at a dose of 80 mg, febuxostat appears to be more effective than allopurinol 300 mg daily. Studies also indicate that febuxostat is more effective than allopurinol in patients with reduced GFR, and is safe in patients with mild or moderate kidney disease. However, it should be noted that although allopurinol in practice is commonly prescribed as 100–300 mg daily, it is approved by the FDA for up to 800 mg. The studies reviewed here have only compared febuxostat to fixed doses of allopurinol, which were not titrated to what might be its optimal dose. Indeed, a 2010 European position paper posits that, in light of the current data and considering cost, febuxostat should be reserved for patients who have failed or have contraindications to allopurinol and uricosuric therapy [13].

Uricase replacement: pegloticase & pegsitacase

Unlike most mammals, humans lack a functional gene for uricase, the enzyme that converts uric acid to allantoin. Since uric acid is less soluble than allantoin, uricase deficiency and the resultant rise in sUA levels render humans more susceptible to crystal precipitation and gout [14]. Evolutionary biologists have identified specific mutations that resulted in this loss of enzymatic activity during primate evolution, suggesting that loss of uricase may at one time have conveyed an evolutionary advantage [15]. Biologists have variously speculated that increased sUA levels helped maintain blood pressure during eras of low dietary sodium availability, provided antioxidant activity, or provided benefits for neuronal development [16]. Uricase replacement has been a theoretical option since the 1970s, when nonrecombinant

urate oxidase extracted from *Aspergillus flavus* was studied in patients with hyperuricemia in the setting of malignancy, and in gout patients taking azathioprine and thus not eligible to receive allopurinol simultaneously [17]. However, this preparation was highly immunogenic, and commonly induced acute hypersensitivity reactions including bronchospasm and hypoxemia.

A recombinant *Aspergillus* uricase, rasburicase, was developed with hopes of reducing immunogenicity [17]. Rasburicase is effective for both preventing and treating tumor lysis syndrome [18–20]. Although rasburicase may be better tolerated than its extracted predecessor, it remains immunogenic and treatment of tumor lysis with rasburicase is generally limited to only a few doses to minimize hypersensitivity. Rasburicase was also explored to treat gout, with case reports of its use in severe tophaceous gout [21,22]. However, an exploratory study of 10 patients with chronic tophaceous gout found 80% developed gout flares and 20% developed infusion reactions to the medication [23]. It has not been pursued further as a treatment for chronic gout.

Further attempts to reduce uricase immunogenicity have led to the development of a pegylated form, pegloticase (Krystexxa®, Savient Pharmaceuticals) [24]. Pegloticase is a recombinant chimeric mammalian (porcine and baboon) uricase generated in a modified *E. coli* strain, covalently conjugated to several monomethoxypoly (ethylene glycol) strands [25,106]. Phase I studies explored both subcutaneous and intravenous delivery; the intravenous form was less immunogenic, and thus became the approved route [25,26]. After an initial setback in 2009 when the FDA declined pegloticase approval due to manufacturing issues, the drug was approved in 2010 for the treatment of chronic gout in adult patients refractory to conventional therapy, at a dose of 8 mg iv. every 2 weeks [107]. A similar agent, Uricase PEG 20 (Pegsitacase, EnzymeRx, a subsidiary of 3SBio) is in Phase I development for intramuscular administration for gout treatment (NCT01038947) [108,109]. Importantly, owing to its potential to generate an oxidant load, pegloticase is contraindicated in patients who are G6PD deficient.

Two Phase III studies (GOUT 1 and GOUT 2) led to FDA approval of pegloticase [27,28]. In the aggregate data from those two studies, 212 patients with treatment-failure gout were randomized to receive placebo (43 patients), pegloticase 8 mg iv. every 2 weeks (85 patients) or every 4 weeks (84 patients) for 6 months, with all patients also receiving prophylaxis against acute gouty arthritis. Treatment failure gout was defined as ≥3 flares in the previous 18 months, ≥1 tophus or gouty arthropathy; sUA ≥8 mg/dl; and either prior failure of the maximum medically appropriate dose of allopurinol or contraindication to allopurinol. The primary outcome was sustained reduction of the sUA to less than 6 mg/dl. This outcome was achieved in 0, 42 and 35% of the groups respectively. In addition, 40% of the patients in the every 2 weeks dosing group had complete resolution of at least one tophus by 6 months, compared with 7% in the placebo group.

In data from an OLE trial after the initial GOUT 1 and 2 trials (sometimes referred to as GOUT 3), further benefits were noted regarding tophus reduction in patients receiving pegloticase for up to 30 months [29]. There were 308 tophi documented at the outset of the initial trials, with complete resolution of 58% of these by the end of the OLE. For many patients, their first complete tophus resolution occurred in the OLE. In addition to lowering sUA and tophus size, pegloticase use has been associated with improvement in health-related quality of life. Of the 212 treated patients in the original Phase III trials, 157 completed the SF-36 and HAQ-DI at baseline and weeks 13, 19 and 25. When compared with placebo, patients treated with pegloticase every 2 weeks had significantly less disability and pain, and improved SF-36 Physical Component Summary Scores [28,30].

Consistent with the effects of other ULTs, gout flares (reported as AEs in much of the pegloticase literature) were common in the Phase III studies of pegloticase, especially during the first 3 months of treatment: in the every 2 weeks group, 74% of patients flared in months 1–3 and 41% in months 4–6; in the every 4 weeks group, 81% flared in months 1–3 and 57% in months 4–6; whereas in the placebo group, 51% flared in months 1–3 and 67% in months 4–6 [27,28,106]. Infusion reactions were also common, despite premedication with steroids and antihistamines prior to drug infusion (every 2 weeks group 26%, every 4 weeks group 41%, placebo group 5%). Thus, and despite its clear advantages over rasburicase, pegloticase continues to display significant immunogenicity. Infusion reactions were severe in a significant number of patients, with anaphylaxis in 0% in the placebo group, 6.5% of the every 2 weeks group and 4.8% of the every 4 weeks group [106]. As a result, the FDA mandated a black-box warning on the package insert regarding the risk of anaphylaxis and infusion reactions, and pegloticase should only be administered with premedication, and in settings where providers are prepared to deal with hypersensitivity reactions.

Overall, 19% of patients receiving pegloticase withdrew due to AEs, versus 9% in the placebo group [28]. Congestive heart failure was a notable adverse event in the trials, occurring in three patients treated with pegloticase. The mechanism by which pegloticase may cause worsening heart failure is not known (one hypothesis being the fluid load of the infusion with steroid

pretreatment), and the manufacturer recommends caution when using the agent in this patient population [106]. Also of note were two CV deaths and one nonfatal MI among pegloticase-treated patients, all in patients with four or more CV risk factors at baseline [28]. This suggests that CV risk optimization prior to therapy would be prudent.

Both infusion reactions and a relatively high rate of pegloticase treatment failure over time appear to relate to the immunogenicity of the molecule. In the GOUT 1 and 2 trials, 153 patients who received pegloticase (out of 169 in the treatment group) had samples analyzed at 3 and 6 months for antibodies against the pegloticase protein (anti-PGL) as well as the polyethylene glycol adducts [27,31]. High-titer anti-PGL antibodies occurred in 60% (51/85) of nonresponders but only in 1% (1/68) of responders ($p < 0.001$). Antibody formation also correlated with infusion reactions, with infusion reactions occurring in 53% (16/30) of subjects with high-anti-PGL titers in the every 2 weeks group versus 6% among those with low or undetectable titers. Additional data suggest that most infusion reactions could be avoided if the drug is discontinued when a loss of response of sUA occurs [28,32]. Physicians prescribing pegloticase should therefore monitor their patients' sUA levels prior to infusion, and consider discontinuing treatment if urate levels increase to ≥6 mg/dl (particularly if this occurs on two consecutive measurements) [106].

Despite these complexities, pegloticase clearly works well for some patients who might otherwise remain burdened by refractory gout. In data presented at the European League Against Rheumatism meeting in 2011, results from a long-term open-label extension study suggest that patients who maintain a persistent response to pegloticase can use it safely for over 2.5 years [33]. 19 persistent responders continued pegloticase therapy 8 mg every 2 weeks. Of these, 84% continued to have normalized sUA for >2 years. By week 50, 90% of subjects in the trial had a complete or partial tophus resolution, and 78% of all tophi had complete resolution. This effect was sustained at weeks 78 and 102. Three infusion reactions occurred out of 810 infusions, and none were severe enough to be characterized as anaphylaxis.

Overall, pegloticase is an exciting new advance for treatment-failure gout. It represents an important alternative for patients who cannot tolerate or have failed other urate-lowering agents, and may be particularly useful for patients with tophi. Pegloticase immunogenicity suggests that its use probably ought to be restricted to physicians with expertise in its administration. In the future, intramuscular formulations for uricase replacement may become available.

IL-1β blockade: anakinra, rilonacept & canakinumab

The centrality of interleukin-1β as a driver of MSU crystal-induced inflammation has only recently been appreciated. In a gout attack, MSU crystals are phagocytosed by macrophages via mechanisms that also result in activation of the NALP3 (cryopyrin) inflammasome [34]. Phagocytosis and inflammasome activation may occur via engagement of the Toll-like receptors (TLR)2 and TLR4, followed by activation of the TLR adaptor protein MyD88 or may proceed through other mechanisms such as direct membrane interaction, NADPH oxidase activation or potassium fluxes; these mechanisms are not *a priori* mutually exclusive [35–38]. The NALP3 inflammasome is a multimolecular platform whose functional enzyme, caspase 1, converts pro-IL-1β to IL-1β [39], resulting in secretion of active IL-1β. Soluble IL-1β can then act on its originating or neighboring phagocytes to stimulate production of both additional IL-1β and other inflammatory mediators including TNF-α, IL-6 and IL-8 [40–42]. Complement activation and IL-1β-independent mechanisms may also fuel these inflammatory processes [43–46]. The result is intense phagocyte activation and further stimulation of inflammatory cascades. IL-1β also acts locally on endothelial and synovial cells to promote inflammation [47]. IL-1β receptors are comprised of two subunits, IL-1β receptor type 1 (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) [48]. IL-1β must engage both subunits to trigger cell signaling.

For patients who have failed or do not tolerate standard therapies for acute gout, gout prophylaxis or chronic active gouty arthritis, IL-1β antagonism has emerged as a potential therapeutic option [49,50]. Anakinra, rilonacept and canakinumab are three IL-1β antagonists with different mechanisms of action that work toward the same end point of IL-1β blockade (Figure 2) [47]. These agents were initially developed not for gout, but for either cryopyrin-associated periodic fever syndrome (CAPS; in which mutations of NALP3 are associated with inappropriate IL-1β release) or rheumatoid arthritis, conditions for which they have demonstrated efficacy [51–53].

Anakinra (Kineret®, Swedish Orphan Biovitrum) is a recombinant IL-1β receptor antagonist (IL-1ra) that binds and blocks IL-1R1, thus preventing IL-1β from initiating signal transduction (Figure 2) [110]. Anakinra has a half-life of 4–6 h and is dosed at 100 mg sc. daily; it is approved by the FDA for use in rheumatoid arthritis. In initial studies in RA patients, there were more serious infections with anakinra compared with placebo (2 vs 1%) [110]. In subsequent trials looking at IL-1β inhibition in gout, chronic or active infection has therefore been a standard exclusion criteria.

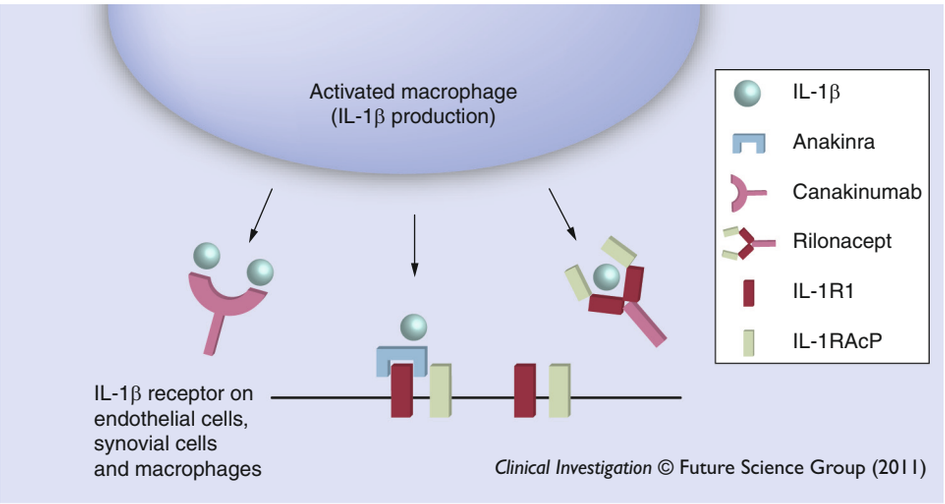

Figure 2. Sites of IL-1β antagonism by anakinra, canakinumab and rilonacept during a gout flare. Anakinra binds to and blocks IL-1R1. Canakinumab binds to soluble IL-1β and prevents it from reaching its target. Rilonacept acts as a soluble receptor to neutralize soluble IL-1β. See text for details.
IL-1R1: IL-1β receptor type 1; IL-1RAcP: IL-1 receptor accessory protein.

A 2007 pilot study investigated the use of anakinra in patients with acute gout with promising results. So *et al.* conducted an open label, proof-of-concept trial in 10 patients having either an acute gout flare or chronic tophaceous gout with recurrent flares on initiation of urate-lowering therapy [54]. Subjects either could not tolerate or had failed standard anti-inflammatory therapies. However, only one patient had failed steroids. Subjects received 100 mg anakinra sc. daily for 3 days. In all subjects, self-reported gout severity was significantly reduced within 48 h after the first injection. By day 3, patients reported a mean reduction in pain of 79%, and on physical examination 90% of affected joints showed complete resolution.

Results were only slightly less compelling in a case series of 10 patients receiving anakinra for acute gout flare [55]. All of these patients had previously received oral or intravenous steroids with inadequate response at the time of the index flare, and nine were unable to receive NSAIDs due to renal disease. Patients received a mean of 3.2 anakinra injections, and outcomes were categorized as good, partial, or no response. Six subjects had a good response, although nearly all re-flared within 1 month; three had a partial response; one had no response. The authors speculated that the lower response rate they observed (relative to the study by So *et al.* described above) might have been related to the refractory nature of the enrollees' gout. Two subjects continued anakinra use on a long-term basis (3 and 19 months, respectively) and had minimal or no recurrence of gouty attacks.

Rilonacept (Arcalyst®, Regeneron pharmaceuticals; also known as IL-1 Trap) is a dimeric fusion protein comprised of the extracellular domains of the human IL-1R1 and IL-1RAcP fused to the Fc portion of IgG1 (Figure 2) [111]. In contrast to anakinra, which blocks the IL-1 receptor, rilonacept targets IL-1β itself, binding IL-1β and preventing its ability to engage its receptors. Rilonacept has a half-life of 34–57 h and is approved for CAPS, with a 320 mg loading dose followed by 160 mg sc. weekly. Rilonacept has recently been investigated for treatment of chronic active gouty arthritis, treatment of acute flares, and prophylaxis against flares during initiation of ULT.

In a single-blind, nonrandomized proof-of-concept trial, rilonacept reduced pain in patients with treatment-resistant chronic active gouty arthritis (one or more continuously inflamed joints for the 4 weeks prior to screening) [56]. Ten subjects were enrolled. After 6 weeks, six patients self-reported a ≥50% improvement in pain ($p \leq 0.001$), and five had ≥75% improvement ($p \leq 0.01$). One patient withdrew due to an injection site reaction.

In a Phase III study of rilonacept for acute gout, the SURGE trial, 255 patients with acute gout were randomized to receive subcutaneous placebo on day 1 plus indomethacin for 3 days, subcutaneous rilonacept 320 mg on day 1 plus indomethacin for 3 days, or subcutaneous rilonacept 320 mg on day 1 plus p.o. placebo for 3 days, and assessed for pain reduction at 72 h [57]. All groups experienced a reduction in pain. For the rilonacept-only and indomethacin-only groups, mean pain reduction ± SD was -0.69 ± 0.97 and -1.40 ± 0.96 respectively (5-point Likert scale); these two values were not assessed as to whether there was a statistically significant difference between the two treatments. No significant difference in pain reduction was observed between the indomethacin-only and rilonacept plus indomethacin groups.

Rilonacept has been studied for prophylaxis against flares during initiation of ULT with allopurinol in two mirror-image Phase III randomized double-blind placebo controlled trials, PRE-SURGE I and PRE-SURGE II, with a total of 489 subjects [58,112]. In these trials, patients were randomized to receive either rilonacept (160 mg loading dose followed by 80 mg weekly, or 320 mg loading dose followed by 160 mg weekly) or placebo sc. for 16 weeks. The primary end points was

number of gout flares/patient. Results were similar in both studies. In PRE-SURGE I, the placebo group had 1.06 flares/patient versus 0.29 in the 80 mg-weekly group and 0.21 in the 160 mg weekly group (73 and 80% reduction, respectively). Injection site reactions were more common in the treatment groups (19.8% in the 160 mg weekly group and 8.8% in the 80 mg weekly group vs 1.3% in the placebo group). Other AEs were similar in frequency across the groups and included respiratory tract infections, musculoskeletal pain and headache; no serious infections occurred in any group.

In RE-SURGE, a Phase III safety trial, 1315 gout patients either initiating or taking ULT were randomized to either subcutaneous rilonacept (320 mg loading dose followed by 160 mg weekly) or placebo for 16 weeks [112]; results were similar to those in the smaller PRE-SURGE trials. It is worth noting that rilonacept has not yet been compared with standard prophylactic therapies for gout prophylaxis, and the Phase III data has only been presented in abstract and press-release form.

Cankinumab (Ilaris®, Novartis) is also being studied for both gout flare treatment and prophylaxis. Canakinumab is a fully humanized anti-IL-1β monocloncal antibody that selectively binds and blocks the activity of IL-1β **(Figure 2)** [113]. Canakinumab has a half-life of 21–28 days and is dosed once every 8 weeks for CAPS, for which it is currently FDA approved.

In a Phase II dose-finding study, 200 subjects who were refractory to, or unable to take colchicine or an NSAID, were randomized to receive a single subcutaneous injection of canakinumab (10, 25, 50, 90 or 150 mg) or triamcinolone 40 mg (TA) i.m., as treatment of an acute gout flare. Changes in pain score were assessed both initially and up to 8 weeks [59]. At all doses, canakinumab was associated with greater pain reduction than TA. Time to 50% reduction in pain was a median of 1 day in the canakinumab 150 mg group versus 2 days in the triamcinolone group ($p < 0.001$). Time to recurrent flare was also delayed in the canakinumab groups; by 8 weeks, 3.7% of canakinumab 150 mg patients had had a flare versus 45% of TA patients. Overall, canakinumab was well tolerated. In a study of quality of life measures among these subjects, those receiving canakinumab 150 mg experienced improvement in SF-36 scores measuring mental and physical well being that surpassed those of the TA group [59,60]. For example, physical functioning at 7 days increased from 41.5 to 80 (39 points) in the canakinumab 150 mg group, but from 38.4 to 61.5 (23.3 points) in the TA group. On the other hand, functional disability scores were equally improved in both treatment arms at 7 days.

Larger, Phase III studies, β-RELIEVED I (NCT01080131) and an extension study β-RELIEVED II (NCT01194921), are underway comparing canakinumab 150 mg to triamcinolone 40 mg for the treatment of acute gout flare, when NSAIDs and/or colchicine have been ineffective or are contraindicated [114,115].

Canakinumab is also under investigation for gout prophylaxis during initiation of allopurinol therapy. In a Phase II trial, canakinumab at a range of doses (one-time doses of 25, 50, 100, 200, 300 mg or an every 4 week dosing regimen for a total of 150 mg) was compared with colchicine 0.5 mg p.o. daily for flare prevention in patients starting ULT [61]. 432 patients were randomized and followed for 16 weeks. The percentage of patients with flares was lower for all canakinumab groups (25 mg, 27.3%; 50 mg, 16.7%; 100 mg, 14.8%; 200 mg, 18.5%; 300 mg, 15.1%; every 4 weeks 16.7%) compared with the colchicine group (44.4%). AEs were similar across the groups.

In summary, the possibility of IL-1β blockade offers new prospects for treatment of acute and chronic gouty arthritis and to prevent flares during ULT. The anti-IL-1β agents under study are not yet FDA-approved for treatment of gout, but all show promise and are potentially available for off-label use. Patients who are likely candidates for IL-1β therapy are those for whom standard therapies fail or for whom co-morbidities limit standard therapies. High cost, variable half-lives, and the side effects of biologic therapy will all need to be considered in deciding whether and when to use these agents.

URAT1 inhibition: RDEA594 & tranilast

SUA is determined by the balance between urate production by the liver and other tissues, dietary intake and urate excretion by the kidneys and the intestine. The GI tract is responsible for excretion of 30% of urate produced daily while renal excretion accounts for the remaining 70%. The majority of patients with gout underexcrete urate, requiring higher serum concentrations in order to achieve urate balance by the kidneys [62]. Therefore, renal underexcretion (the etiology of which is likely to be both genetic and environmental) contributes significantly to elevated sUA levels, and correcting urate underexcretion is a logical target for urate-lowering therapy in gout.

Renal urate handling is a complex combination of reabsorption of filtered urate load and tubular urate secretion [63]. Two important urate transporters, which have been recently characterized and play important roles in urate reabsorption by the proximal tubule, are URAT1 and GLUT9 [64,65]. The renal urate-anion exchanger URAT1 (coded by gene *SLC22A12*) is located in the luminal membrane of the proximal tubule, where it transports urate from the tubular lumen to the cytosol in exchange for Cl^- or organic anions. By contrast, GLUT9 (coded by gene *SLC2A9*) is a sugar transport facilitator family protein that acts as a voltage-driven

urate transporter [66]. It is expressed in the basolateral membrane of the proximal tubule and is responsible for efflux of urate from the intracellular space to the circulation [67]. Together, these two proteins promote the movement of urate from the proximal tubule into the renal interstitium (Figure 3). After many years of use, it is now known that the traditional uricosuric agents probenecid, benzbromarone and sulfinpyrazone inhibit these two transporters, thus blocking urate reabsorption and promoting urate excretion [64,65].

While effective in some patients, toxicities, inconvenience and limited efficacy – particularly in the setting of decreased glomerular filtration – have limited the use of these older agents [68]. Probenecid is the oldest uricosuric agent available, having been first introduced in 1951 [69]. Probenecid has limited efficacy in patients with a CrCl <50 ml/min, is relatively contraindicated in patients with a history of nephrolithiasis, and may require b.i.d. or more frequent dosing [116]. The drug is overall well tolerated but major side effects include precipitation of acute gouty arthritis (like other urate-lowering therapies), gastrointestinal intolerance and uric acid stone formation (although for patients with uric acid stones, urine alkalinization with potassium citrate may permit safe probenecid administration) [70]. Probenecid also alters plasma concentrations of drugs such as penicillins, cephalosporins, salicylates, acetaminophen and indomethacin, a result of its ability to inhibit other renal organic anion transporters such as OAT1 and OAT3 (Figure 3) [71]. Benzbromarone, a uricosuric that has been shown to be more potent than allopurinol 300 mg and probenecid 2 g/day [72–74], was introduced in the 1970s but was withdrawn in 2003 due to reports of serious liver damage (it is still available in some parts of Europe, for use in cases of allopurinol intolerance) [75,76]. Sulfinpyrazone is another uricosuric agent that is available only in limited markets. Like probenecid, these agents increase the risk of uric acid kidney stones, particularly since gout patients often have a low urine pH that puts them at increased risk for stone formation [77].

Newer uricosuric agents targeting URAT1 and GLUT9 are under development. One such 'pipeline' drug, currently being evaluated in clinical trials is RDEA594 (Lesinurad, Ardea Biosciences). RDEA594 is an active metabolite of RDEA806, a novel non-nucleoside reverse transcriptase inhibitor, which was serendipitously found to have a uricosuric effect [78]. As an oral, once-daily inhibitor of URAT1-mediated urate transport by the proximal tubule, RDEA594 increases urinary urate excretion. Unlike probenecid, RDEA594 *in vitro* does not inhibit other renal organic anion transporters and thus does not seem to have significant drug interactions [79]. Moreover, RDEA594 has been studied in subjects with impaired renal function, including patients with mild (estimated CrCl 50–80 ml/min), moderate (CrCl 30–50 ml/min), and severe impairment (CrCl <30 ml/min). While the agent did not show efficacy in patients with severe impairment, it significantly increased urate excretion not only in subjects with normal renal function, but also in those with mild or moderate kidney disease [80].

In a Phase II, placebo-controlled trial, 123 gout patients (sUA ≥8 mg/dl and estimated CrCl ≥60 ml/min) were randomized to receive either placebo or RDEA594 200, 400 or 600mg p.o. daily, and followed for sUA level [81]. The proportions of patients achieving sUA <6mg/dl at 4 weeks on 600, 400, 200 mg and placebo were 60, 42, 13 and 0%, respectively. There were no serious AEs.

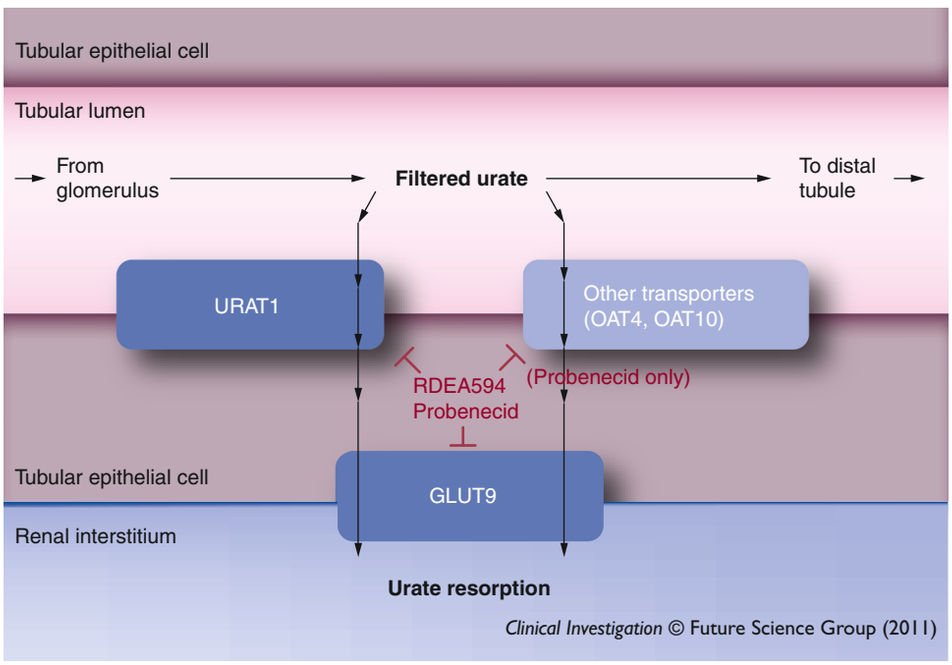

Figure 3. URAT1 and GLUT9 as targets of urate-lowering therapy. Soluble urate is filtered through the glomerulus (left). Within the tubule, urate may be resorbed by multiple anion transporters including URAT1 and others on the luminal surface and GLUT9 at the basilar surface, promoting hyperuricemia. Both RDEA595 and probenecid inhibit URAT1 and GLUT9, promoting urate excretion. Probenecid also inhibits other transporters, possibly contributing to its proclivity for drug–drug interactions.

The urate-lowering effect of RDEA594 in combination with XO inhibitors has also been under investigation. In combined data from two Phase I trials evaluating the effect of RDEA594 with concurrent febuxostat or allopurinol, 100% of patients receiving either combination treatment achieved target sUA level of below 6 mg/dl versus 67, 56 and 20% of patients receiving only febuxostat 40, 80 or allopurinol 300 mg, respectively [82,83]. In a Phase II trial, 208 gout patients with persistent hyperuricemia (here defined as sUA >6.0 mg/dl) despite allopurinol use were randomized to placebo or RDEA594 (200, 400 or 600 mg p.o. daily), while continuing allopurinol (stable dose of 200–600 mg daily) [84]. Baseline median sUA in these subjects ranged from 6.3–7.1 mg/dl across the three treatment groups. At 4 weeks, sUA decreased by 16, 22 and 30% in the 200, 400 and 600 mg groups, respectively; sUA increased by 3% in the placebo group. The RDEA594 400 mg group had the highest proportion of patients (23%) with gout flares requiring treatment. There were no serious AEs, but two combination group subjects dropped out, one with urticaria and the other with an elevated serum lipase level (it was unclear if this was related to the study drug).

RDEA594 seems to have several advantages over probenecid, although more data are needed. It has more specificity for URAT1 with less potential for drug interactions. Its uricosuric effect also seems to be maintained over a greater range of renal function, although this aspect of efficacy requires further investigation. It remains to be seen whether, in larger studies, RDEA594 will be found to cause kidney stones, a theoretical concern. Although there have been no reported cases of kidney stones with RDEA594, it seems logical that its uricosuric effect in gout patients would increase risk for uric acid stones (as probenecid does), unless the drug also raises urine pH to reduce the risk of uric acid precipitation. This potential effect has not yet been demonstrated or studied to our knowledge. Further evaluation with a larger patient population will be needed before RDEA594 will deserve consideration for use outside of clinical trials.

Another novel urate-lowering agent, NU1618 (Nuon Therapeutics Inc.), combines tranilast and allopurinol for the treatment of gout. Tranilast is an anti-inflammatory and immunmodulatory drug that is marketed in Japan and South Korea for treatment of asthma and atopic dermatitis. It was recently found to lower sUA by inhibiting both the URAT1 and GLUT9 urate transporters [85]. In a Phase II trial with 20 subjects with gout and hyperuricemia (mean baseline sUA 8.1 mg/dl), subjects receiving tranilast and allopurinol had a significantly greater reduction in sUA than tranilast or allopurinol alone. No serious AEs were reported and the combination was well tolerated [86].

While it is too early to speculate, targeted URAT1 inhibition may offer gout patients more efficient oral urate-lowering than XO inhibition monotherapy, or may serve as an alternative if XO inhibitors are not tolerated. It may be even more useful to inhibit URAT1 in combination with XO inhibitors, since combination approaches appear to offer greater efficacy than the use of either class of agent alone.

Future perspective

Our rapidly expanding knowledge of the biology of hyperuricemia and gout, together with a growing insight into the limitations of currently available gout therapies, has led to a plethora of new gout therapies either already available or in active clinical development. Drug mechanism, efficacy and side effect profile, along with physician experience, will dictate how these new agents will best be used, and the extent to which they will supplant older treatments.

Febuxostat offers an important alternative for oral ULT to those who fail or do not tolerate allopurinol. For now, allopurinol remains the first-line agent for urate reduction. However, given the ease of once daily dosing of febuxostat, minimal titration required for efficacy, and the drug's safety in renal disease, one can imagine physicians moving to febuxostat more readily in the future. Pegloticase currently has a smaller niche, approved only for treatment failure gout, but offers patients with refractory gout and tophi a new avenue for treatment. Different formulations (i.e., intramuscular) may become available in the future, making the drug more convenient. IL-1β antagonism appears to show efficacy both in acute gout and prophylaxis. Due to the expense of biologic therapy and risks of injection site reactions and other toxicities, these agents are not likely to replace the current standard of care, although if approved they may offer refractory patients much needed relief from gouty flares. Targeted URAT1 inhibition with RDEA594 or other agents may expand the options for oral sUA reduction in the future. The future may also hold further investigation into combination therapy with IL-1β antagonists and uricase agents, or other potent urate-lowering drugs, to allow for rapid urate reduction with fewer gout flares.

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Executive summary

- New medications are changing the landscape for gout therapies.
- Febuxostat is a nonpurine inhibitor of xanthine oxidase, approved in the US in 2009 for gout at a dose of 40 mg or 80 mg p.o. daily.
  - Febuxostat requires no dose adjustment for mild-to-moderate kidney disease (GFR >30).
  - There is no clear link between febuxostat and increased cardiovascular risk, but patients should be monitored for signs or symptoms of cardiovascular events.
- Pegloticase is a pegylated uricase, approved for treatment failure gout in 2010 at a dose of 8 mg iv. every 2 weeks.
  - Pegloticase holds promise for patients who have failed oral urate-lowering therapy and have a high tophus burden.
  - Infusion reactions and anaphylaxis are a concern.
- IL-1β is now understood to be a central actor in the inflammation of acute gout.
  - Anti IL-1β agents anakinra, rilonacept and canakinumab are under investigation for both acute gout and flare prevention with promising results.
- URAT1 and GLUT9, urate transporters in the proximal tubule, play important roles in urate reabsorption.
  - RDEA594 and tranilast, which block URAT1 and increase urinary urate excretion, are under investigation for gout treatment.

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