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Uricases: reflections on recent developments in the management of challenging gout patients

Naomi Schlesinger*, Dan Kaufmann

Division of Rheumatology, Department of Medicine, Spencer Fox Eccles School of Medicine, University of Utah, Salt Lake City, UT 84132, USA

***Correspondence:** Naomi Schlesinger, Division of Rheumatology, Department of Medicine, Spencer Fox Eccles School of Medicine, University of Utah, Salt Lake City, UT 84132, USA. naomi.schlesinger@hsc.utah.edu

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Abstract

Oral urate-lowering therapy (ULT) is key to treating gout. However, many patients receiving oral ULT do not achieve the target serum urate (SU) levels, partly because some patients cannot tolerate or have contraindications to their use, mainly due to comorbidities. This may lead to uncontrolled gout. In species other than humans and some non-human primates, uricase (urate oxidase) converts urate to allantoin, which is more readily excreted by the kidney. Exogenous uricases, considered "enzyme replacement therapy", are a therapeutic option for patients with refractory or uncontrolled gout. Current uricases on the market include pegloticase and rasburicase. Uricase treatment rapidly reduces hyperuricemia and tophaceous deposits and improves the quality of life. This review discusses currently approved uricases on the market and some in development; how best to minimize flares, anti-drug antibody (ADA) formation, infusion reactions, and loss of efficacy, and combination with immunomodulation in patients with gout requiring uricase therapy.

Keywords

Gout, uricase, anti-drug antibodies, infusion reactions, flares

Introduction

Gout is a disease of purine metabolism as well as an autoinflammatory disease, affecting the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and the interleukin-1 (IL-1) pathway. It results from long-standing hyperuricemia [defined as serum urate (SU) levels > 6.8 mg/dL], which leads to monosodium urate (MSU) crystal deposition [1]. Oral urate-lowering therapy (ULT) is key to the treatment of gout. However, many patients receiving oral ULT do not achieve the desired target SU reduction, partly because some patients cannot tolerate or have contraindications to their use, mainly due to comorbidities, such as chronic kidney disease (CKD). This may lead to refractory or uncontrolled gout. These are severe gout patients. These are also patients with a high disease burden, including frequent gout flares (defined as two or more flares annually), widespread tophaceous deposits, and severe pain.

Exogenous uricases, considered enzyme replacement therapy, are a therapeutic option for patients with refractory or uncontrolled gout. Uricase treatment reduces hyperuricemia, leading to rapid resolution of tophi and improved quality of life [2–4].

This review discusses approved and investigational uricases and the clinical challenges associated with their use; loss of efficacy of anti-drug antibodies (ADAs), infusion reactions (IRs), anaphylaxis, and flares.

Uricase in evolution/uricase structure

Urate (also called monosodium urate) is the salt of a uric acid sodium salt. In most mammals, SU levels are highly regulated by the uricase (urate oxidase) enzyme [5]. In species other than humans and some non-human primates, uricase converts urate to allantoin, which is more water-soluble, thus leading to enhanced renal excretion. The uricase gene activity became silenced in a common ancestor of the ape/human lineage, which led to uric acid being the end-product of human purine metabolism [6–8]. Uricases are synthesized primarily in the liver in mammalian species but are also found in the gastrointestinal tract, vascular, and other tissues. Uricase is a tetramer of identical subunits. Each monomer comprises two domains. Integrating the two identical domains produces a folded monomer consisting of an antiparallel β-sheet of eight sequential strands, with helices on the sheet's concave side [9, 10]. The kidney and the gut must eliminate uric acid to maintain urate homeostasis since human tissues have a very limited ability to metabolize uric acid, making humans susceptible to hyperuricemia and gout [11].

Conjugation of polyethylene glycols

Polyethylene glycol (PEG) consists of repeating ethylene glycol units (-CH_2-CH_2-O-) and is synthesized to be highly hydrophilic, possessing a large exclusion volume in aqueous solutions. Enhancing the pharmacological and pharmaceutical properties of proteins through PEG conjugation, known as PEGylation, significantly improves their clinical utility by extending their circulation time, thus increasing their half-life [12]. This process can involve attaching PEG to specific amino-acid residues (e.g., lysine side chains in pegloticase) or targeting unique predetermined sites on the protein. PEGylation also decreases immunogenicity and enhances the solubility and stability of proteins. Consequently, PEGylation enhances both in vitro and in vivo stability, leading to longer circulation times and fewer adverse effects [13]. Due to their foreign nature to the human immune system, exogenous uricases require PEGylation to reduce their immunogenicity, which can also extend their half-life.

However, while free PEG exhibits minimal to no immunogenicity, PEGylation of proteins can induce an immune response, primarily via a T cell-dependent pathway, leading to the production of anti-PEG antibodies (Abs). Anti-PEG Abs are prevalent even among people not exposed to PEGylated drugs, with Ab prevalence ranging from 23% to 72% [14]. This is likely due to daily exposure to PEG-containing products such as cosmetics, toothpaste, shampoos, sunscreens, and processed foods, accounting for the considerable variation in anti-PEG Ab titers [15]. Pegloticase, a PEG-conjugated protein, exhibits this phenomenon, as mentioned below [16, 17]. Factors contributing to Ab formation against PEGylated drugs include the route of drug administration, dosage, pre-existing Abs, the patient's immune status, and genetic factors [18].

Anti-PEG Abs, especially after repeated administration, can diminish the therapeutic efficacy and safety of PEGylated drugs by decreasing subsequent doses' circulation time [19]. These ADAs can neutralize the therapeutic effect of PEGylated drugs and accelerate their clearance from the blood, further reducing their clinical effectiveness [20].

These contrasting effects highlight the complexities and challenges associated with PEGylation, emphasizing the need for continued research to optimize the clinical benefits of PEG-conjugated treatments.

Uricases

It is important to note that all uricases are contraindicated in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency since uricases can trigger life-threatening hemolysis and

methemoglobinemia [21]. G6PD deficiency is an X-linked disorder that affects over 400 million people worldwide of primarily Mediterranean, African, and Asian ancestry [22]. Males of African or Mediterranean ancestry are at higher risk of G6PD deficiency. This is true for all uricases. Hence, the regulatory agencies [The US Food and Drug Administration (FDA) and The European Medicine Agency (EMA)] require (label) screening for G6PD deficiency in all patients before the first uricase infusion.

Uricases approved and in development are discussed below (Table 1).

Table 1. Uricases approved and in development [23–31]

Uricase	Origin	Approval	Indication	Efficacy with immunomodulation	Anaphylaxis	Half-life	IV administration	PEGylated	Ref.
Rasburicase	Recombinant *Aspergillus* uricase	FDA, EMA	Tumor lysis syndrome	NA	6.2%	21 h	0.2 mg/kg daily for up to 5–7 days	No	[23, 24]
Pegloticase	Porcine and baboon uricase	FDA	Uncontrolled gout	83%	3% (active treatment groups)	6–14 days	8 mg every 2 weeks	Yes	[25, 26]
SEL-212	*Candida utilis*	Completed Phase III Submitted to FDA	Uncontrolled gout	High-dose group in 2 Phase III studies 56% and 46%	3.4% (n = 4 anaphylaxis, n = 2 flares)	3 days	0.2 mg/kg monthly	Yes	[27–30]
PRX	Recombinant plant-derived uricase	Phase I	Uncontrolled gout	TBD	TBD	TBD	Dosing TBD	Yes	[31]

NA: not available; TBD: to be determined

Approved uricases

Rasburicase

Rasburicase was approved by the US FDA for children in 2002 and adults in 2009 in tumor lysis syndrome. It is a non-PEGylated recombinant *Aspergillus* uricase. The US FDA and the EMA have approved it for short-term use for pediatric patients and adult cancer patients with tumor lysis syndrome [23, 24]. Rasburicase is administered intravenously for 5 to 7 days. The daily dose is 0.20 mg/kg intravenously in patients with hyperuricemia secondary to tumor lysis syndrome [23, 24]. However, the optimal dosing and duration of therapy for rasburicase have not been established for adults.

Rasburicase has a 21-hour half-life. Six patients in this series (Group 1) received six monthly treatments, and five received one 5-day course (Group 2). Uric acid was suppressed at six months in the monthly treatment group, but there was no appreciable lowering of SU at one or two months in Group 2. Two patients in Group 1 had a decrease in the "tophus area".

Rasburicase is not PEGylated. Thus, immunogenicity is directly related to the uricase. Ab formation has been reported to occur within 1 to 6 weeks [32]. In discussing rasburicase immunogenicity, it should be indicated that IRs are uncommon with a first course of treatment for the prevention of tumor lysis syndrome, but with second courses, there is a measurable incidence: None of the 97 patients who were reviewed experienced anaphylaxis during the first rasburicase course; however, six patients (6.2%) experienced anaphylaxis during a subsequent rasburicase treatment course (P = 0.03) [32]. Repeated administrations in gout patients are problematic.

Rasburicase has been used off-label in patients with tophaceous gout who are refractory to, have adverse events (AEs), or are contraindicated for treatment with allopurinol [33] and other oral ULTs in Europe. Its high immunogenicity and short half-life limit its use for gout. Some Europeans have been informally giving rasburicase with methotrexate monthly but have not published results (personal communication).

Pegloticase

Pegloticase was approved by the US FDA in 2010 for treating chronic gout in adults who do not respond to conventional therapy [34]. The EMA granted approval for chronic gout treatment in 2013, but the

manufacturer later withdrew its marketing authorization in the EU for commercial reasons in 2016 [25, 26]. Pegloticase is a chimera of porcine and baboon liver uricases conjugated to a 10 kDa PEG moiety [4, 19]. The recommended dosage for treating uncontrolled gout is 8 mg/mL, administered intravenously every two weeks.

The 2020 American College of Rheumatology (ACR) Guidelines recommend pegloticase for patients with uncontrolled gout, defined by the failure of oral ULT and other interventions to meet SU targets, recurrent gout flares (at least 2 per year), or the presence of persistent subcutaneous tophi [35]. Similarly, the 2016 European Alliance of Associations for Rheumatology (EULAR) guidelines suggest pegloticase for patients suffering from tophaceous gout with poor quality of life who cannot achieve SU targets [36].

Pegloticase is a very potent ULT that profoundly lowers SU levels. Significant reduction in tender and swollen joint counts and pain, improvements in both patients' global assessment and quality of life, and resolution of tophi within months, not years (45% at six months, mean time to complete resolution 9.9 months) were observed with pegloticase treatment [4]. In the pivotal pegloticase trials, only 42% of patients had a complete response defined as SU levels lower than 6 mg/dL ≥ 80% of the time in months 3 and 6 vs 0% for placebo ($P < 0.001$) [4].

Polyethylene glycol immunogenicity—anti drug antibodies when using pegloticase

The immunogenicity associated with pegloticase is directed against the PEG moiety [16]. In contrast, Abs to uricase was infrequent. The ADAs lead to reduced efficacy, increased risk for IRs, and decreased treatment duration of PEGylated uricase [4, 37].

During the pivotal trials of pegloticase, anti-pegloticase, and anti-PEG Abs were observed following prolonged exposure to pegloticase. In its Phase III randomized controlled trials (RCTs), ADAs were detected in 89% of patients at least once during the 6-month study period. Among the patients receiving pegloticase, 41% (69 out of 169) developed high titer anti-pegloticase Abs (> 1:2,430), and 40% (67 out of 169) developed anti-PEG Abs [38]. Anti-pegloticase Abs typically emerged within 2–3 months of treatment, resulting in a failure to achieve sustained SU lowering, reduced efficacy, and an increased risk of IRs [38]. Up to 50% of patients had anti-PEG Abs even without prior exposure to pegloticase [17].

Age may influence Ab formation. 61% of patients who were 70 or older were pegloticase responders; 50% of patients ≥ 60 years old were responders, and 30% of patients < 60 years old were responders ($P = 0.015$) [37].

For patients undergoing uricase therapy, it is crucial to discontinue oral urate-lowering therapies and monitor SU levels as a biomarker for developing anti-drug Abs.

Infusion reactions

IRs are defined as occurring during or within 2 h after the end of an infusion. In the pivotal Phase III trials, IRs were observed in 26% of patients receiving pegloticase every two weeks, compared to 5% in the placebo group [4], with 3% of IRs happening during the first infusion. In 88% of these cases, a loss of urate-lowering efficacy was noted prior to the patient's first IR [37]. This led to the recommendation to discontinue pegloticase if SU levels rose above 6 mg/dL before the next infusion. IRs were the second most common AE following gout flares, with symptoms including chest discomfort, flushing, and dyspnea. Some IRs met the FDA's criteria for anaphylaxis. Managing IR symptoms involved strategies such as slowing the infusion rate, pausing and resuming the infusion at a slower pace, and administering antihistamines, fluids, steroids, and analgesics.

The pivotal pegloticase trials did not include stopping rules. Reviewing the pivotal trial data, it became clear that SU is a biomarker for predicting IRs. Once the drug is started, pre-infusion SU can be used as a surrogate for the presence of anti-pegloticase Abs [39]. Hence, one must monitor the SU levels before each infusion and stop pegloticase treatment when the SU levels are > 6 mg/dL before two consecutive infusions.

Immunomodulation

The major limitation of pegloticase is immunogenicity [38, 39]. Although pegloticase effectively lowered SU, in the pivotal trials, only 42% of patients maintained an SU lower than 6.0 mg/dL at six months of therapy, likely due to the development of ADAs. Concomitant immunomodulation administered with pegloticase significantly improves the durability and efficacy of the response, as well as safety. Administering immunomodulation with disease-modifying antirheumatic drugs (DMARDs), including methotrexate, azathioprine, leflunomide, and mycophenolate mofetil (MMF), leads to reduced ADA production, decreased IRs and increased treatment response [39–44].

The MIRROR (Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving Pegloticase) study was a randomized, double-blind, placebo-controlled trial focused on patients with uncontrolled gout. The primary measure of success was the percentage of patients maintaining SU levels under 6 mg/dL for at least 80% of the time during the sixth month. The study's findings indicated a 71% response rate in the group treated with pegloticase and methotrexate, compared to 38.5% in the pegloticase and placebo group [48]. Moreover, patients who received pegloticase with methotrexate experienced a significant reduction in IRs, with only 4% (4 of 96) having IRs vs 31% (15 of 49) in the placebo group [48].

The RECIPE (Reducing Immunogenicity to Pegloticase) trial assigned patients with uncontrolled gout to either MMF (1 gram twice daily, n = 22) or placebo (n = 10) with a 2-week run-in period before starting biweekly pegloticase [41]. After 12 weeks, MMF was discontinued. The primary endpoint of having SU at or below 6 mg/dL at 12 weeks was achieved by 86% (19 of 22) of patients in the MMF group, compared to 40% (4 of 10) in the placebo group. At 24 weeks, 68% of those in the MMF group-maintained SU-lowering, whereas only 30% of those in the placebo group did. Notably, no IRs were reported in the MMF group, while 30% occurred in the placebo group [41].

In the TRIPLE (Tolerization Reduces Intolerance to Pegloticase and Prolongs the Urate Lowering Effect) study, participants were treated with azathioprine (starting at 1.25 mg/kg daily for one week, increasing to 2.5 mg/kg daily) and maintenance of daily 2.5 mg/kg with pegloticase infusion (n = 12). Interim analysis showed that six patients completed the treatment, while two continued this treatment after the study, all maintaining SU levels below 6 mg/dL. Of the four patients not included in this analysis, two lost urate-lowering efficacy, one experienced an IR, and one was intolerant to azathioprine [44].

Following the MIRROR trial results, the US FDA expanded the pegloticase label to endorse co-treatment with methotrexate for patients with uncontrolled gout. Combining pegloticase with immunomodulators like methotrexate is gaining popularity due to its increased efficacy and reduced ADA formation [42, 45]. Most patients respond positively to this co-treatment, showing improved outcomes while on immunomodulation therapy [17].

Uricases in late-stage development

SEL-212

SEL-212 has completed 2 Phase III studies. SEL-212 is a two-component intravenous treatment delivered by sequential infusions of nanoparticles containing sirolimus (SEL-110), previously referred to as SVP (synthetic vaccine particles)-rapamycin or ImmTOR®, immediately followed by the recombinant uricase enzyme pegadricase (SEL-037). Pegadricase is a PEGylated uricase derived from *Candida utilis* [46, 47].

In a Phase II trial, "Compare the Efficacy of SEL-212 to pegloticase in Gout Patients Refractory to Conventional Therapy (COMPARE)", researchers compared SEL-212 and pegloticase for treating patients with uncontrolled gout [27] (Tables 2 and 3). The study included two groups: one received intravenous SEL-212 [ImmTOR (0.15 mg/kg) and pegadricase (0.2 mg/kg)] monthly, and the other intravenous pegloticase 8 mg bi-weekly for six months. The main aim was to assess the proportion of participants maintaining SU levels under 6 mg/dL for at least 80% during the third and sixth months. Pegadricase did not meet the primary endpoint of statistical superiority SU < 6 mg/dL for at least 80% of the time during

months 3 and 6 combined: 53% pegadricase vs 46% pegloticase (P = 0.181) [27]. Although pegadricase didn't achieve the primary goal of reducing SU levels < 6 mg/dL for a minimum of 80% of the time, it did show a notable decrease in mean SU levels compared to pegloticase during months 3 and 6 combined (P = 0.003). Gout flares were similar between the two groups. Regarding AEs, participants in the pegadricase group experienced a higher incidence of gout flares (60.2% vs 50.6%), infections (25.3% vs 18.4%), and infusion-related reactions (15.7% vs 11.5%) compared to the pegloticase group. Stomatitis, a known side effect of rapamycin, was reported in 9.6% of participants in the SEL-212 group and none in the pegloticase group [27].

Table 2. Comparison between pegloticase and pegadricase Phase II: COMPARE trial [27]

	Pegloticase (n = 87)	**Pegadricase (n = 83)**
Origin	Porcine and baboon Uricase	*Candida Utilis*
Treatment regimen	8 mg every 2 weeks IV	0.2 mg/kg pegadricase, 0.15 mg/kg ImmTOR monthly IV
Immunomodulation	Methotrexate 15 mg PO weekly	Rapamycin
Efficacy	Pegadricase did not meet the primary endpoint of statistical superiority SU (serum urate) < 6 mg/dL for at least 80% of the time during months 3 and 6 combined: 59% pegadricase vs 46% pegloticase, P = 0.181	
	Decrease in mean SU levels compared to pegloticase (P = 0.0033)	
AEs n (%)	34 (39.1%)	45 (54.2%)
Gout flare	20 (23.0%)	27 (32.5%)
infusion-related reaction	10 (11.5%)	13 (15.7%)
Headache	0	4 (4.8%)
Hypertriglyceridemia	2 (2.3%)	3 (3.6%)
Aphthous ulcer	0	2 (2.4%)
Pegylation	yes	yes
Half-life (days)	6–14	3

Table 3. SEL-212 Phase II COMPARE trial [27] and Phase III-DISSOLVE 1 & 2 trials [29, 30]

	COMPARE	**DISSOLVE 1**	**DISSOLVE 2**
Treatment groups	SEL-212 [ImmTOR (0.15 mg/kg) and pegadricase (0.2 mg/kg)] monthly vs pegloticase 8 mg bi-weekly for six months	SEL-110 (high dose: 0.15 mg/kg and low dose: 0.1 mg/kg) +SEL-035 (0.2 mg/kg) vs placebo	SEL-110 (high and low doses) +SEL-035 vs placebo
Population studied	n = 170 (n = 83 for SEL-212, n = 87 for pegloticase)	n = 112 Uncontrolled gout refractory to conventional treatment (US)	n = 153 Uncontrolled gout refractory to conventional treatment (Global)
	Patients with uncontrolled gout		
Efficacy	Pegadricase did not meet the primary endpoint of statistical superiority SU (serum urate) < 6 mg/dL for at least 80% of the time during months 3 and 6 combined: 59% pegadricase vs 46% pegloticase, P = 0.181	Studies met the primary efficacy endpoint of achieving and maintaining a SU < 6 mg/dL for ≥ 80% of the time during the sixth treatment period. High-dose group: 56% and 46% of pts responded to treatment; Low-dose group: 48% and 40% of pts responded to treatment	
	Decrease in mean SU levels compared to pegloticase (P = 0.0033)		
AEs n (%)	45 (54.2%)	Pooled AEs: 3.4% and 4.5% infusion reactions to high and low doses, respectively.	
		Serious AEs: 3.4% (n = 4 anaphylaxis, n = 2 gout flares)	
Gout flare	27 (32.5%)	NA	
Infusion-related reaction	13 (15.7%)	NA	
Headache	4 (4.8%)	NA	
Hypertriglyceridemia	3 (3.6%)	NA	
Aphthous ulcer	2 (2.4%)	NA	

NA: not available; pts: patients

The Phase III DISSOLVE trials which studied SEL-212 in patients with gout refractory to conventional therapy have been completed (Table 3). There were two active treatment arms of sequential infusions of SEL-110 and SEL-037 every 28 days and a placebo. There were two SEL-110 doses—0.15 (high-dose)

mg/kg and 0.1 (low-dose) mg/kg. Patients in both active treatment arms received 0.2 mg/kg of SEL-037. The primary endpoint was the percentage of participants who achieved and maintained SU < 6 mg/dL for ≥ 80% of the sixth 28-day treatment period in the active treatment groups vs placebo. The topline results were recently reported [28]. Response rates in the treatment groups were significantly ($P \leq 0.0015$) greater than placebo. The high dose response rate was 56% in DISSOLVE I and 8% in DISSOLVE II. For patients ≥ 50 years old, the high dose response rate was 65% and 48% in DISSOLVE I and II, respectively. A few IRs were observed after SEL-212 administration. Infusion-related reactions (≤ 1 h) were reported in 3 (3.4%) in the high-dose group, 4 (4.5%) in the low-dose group, and 0 (0.0%) in the placebo arms [29]. Of the initial 265 participants who participated in the primary phase of the study, 143 individuals (54%) completed the 6-month extension period. The primary reasons for participants discontinuing the study were adherence to the stopping rule. Other reasons for study discontinuation included voluntary withdrawal (approximately 10% in each treatment group) and AEs (reported at rates of 13.8%, 6.8%, and 2.2% in the high-dose, low-dose, and placebo cohorts, respectively). By the 12-month mark, when the data from both trials were amalgamated, around 50% of patients in the high-dose group and 43% in the low-dose group were still undergoing treatment and demonstrating positive responses, as evidenced by an intention-to-treat analysis. Both dosages were significantly superior compared to the 8% response rate observed in the placebo group ($P < 0.0001$).

Within the subset of participants presenting with tophi at the study's outset, which accounted for roughly half of the total study population, response rates at the 12-month mark remained low. 41% and 43% exhibited responses in the high-dose and low-dose SEL-212 groups, respectively. Those from the placebo group with baseline tophi exhibited a response rate of 9%.

Uricases in early-stage development

PRX-115

PRX-115 is a recombinant pegylated uricase enzyme expressed in plant cells. The use of plant cell cultures for therapeutic recombinant protein production is becoming increasingly popular [49]. Protalix's ProCellEx® platform utilizes plant cell cultures as an alternative to conventional mammalian cell-based production methods. The plant-derived uricase may offer advantages such as reduced immunogenicity and an extended half-life [31]. A Phase I clinical trial, involving a double-blind, placebo-controlled, single dose-escalation study in individuals with elevated SU levels, is currently underway to assess the safety, pharmacokinetics, pharmacodynamics, reduction of SU levels below 6.0 mg/dL, and immunogenic response to PRX-115.

Minimizing flares with anti-inflammatory prophylaxis

The exact mechanism by which ULT can trigger gout flares has yet to be well understood. Flares may occur due to preexisting MSU crystals' chemical or physical changes when ULT induces rapid SU lowering [50]. In patients who experience fast and dramatic SU lowering, such as that seen with uricase treatment, a high incidence of flares has been observed. Thus, it is unsurprising that flares were the most commonly reported AEs due to pegloticase infusions. Up to 80% of patients on pegloticase treatment had flares during the first three months of therapy, despite flare prophylaxis initiated one week before the first infusion and continued throughout the study [4, 50]. The pilot study for rasburicase showed a similarly high incidence of flares [25].

While gout flares observed during pegloticase therapy are documented as AEs, they actually signify evidence of the drug's effectiveness. Individuals undergoing pegloticase treatment are more prone to experiencing gout flares because of the rapid reduction in SU levels [4, 51]. As a result, the frequent occurrence of gout flares during pegloticase treatment highlights the importance of implementing prophylactic measures to prevent flares in patients receiving pegloticase.

The choice of anti-inflammatory drugs for prophylaxis is limited to low-dose colchicine (0.5, 0.6 or 1.0 mg daily) and non-steroidal anti-inflammatory drugs (NSAIDs). Colchicine is the only FDA-approved drug for anti-inflammatory prophylaxis. However, it is often contraindicated, non-efficacious, or intolerable

in patients with gout [52]. NSAIDs, too, are not recommended due to possible AEs, especially in patients with comorbidities. In the pivotal pegloticase trials during months 1–3, gout flares were higher for pegloticase-treated patients than in the placebo group [4]. However, with continued treatment during months 4–6, a significant reduction in flares was observed, as was the case in the SEL-212 studies.

The drug choice for anti-inflammatory prophylaxis depends on the patient's comorbidities. In patients with CKD 3–5 and patients with heart disease, NSAID use is not advised. In CKD 3–5, the dosage of colchicine may be limited. Pegloticase infusions are preceded by methylprednisolone to prevent IRs and it has been suggested that methylprednisolone may have some prophylactic effect on flare prevention.

IL-1 is a key cytokine in gouty inflammation [53]. Although IL-1 inhibition is a logical target for preventing gout flares IL-1 inhibitors have not been approved by the EMA or FDA for flare prophylaxis. Instead, canakinumab, a neutralizing monoclonal Ab, is approved to treat flares [49]. While one should note that a single subcutaneous injection of canakinumab 150 mg used to treat severe flares also demonstrates a long-lasting effect over three months when compared to an intramuscular injection of 40 mg triamcinolone acetonide; this apparent flare prophylactic effect is off-label [54]. It has been shown that a single dose of canakinumab 150 mg subcutaneously resolves flares within 48 h and prevents new gout flares in patients initiating pegloticase + methotrexate [55].

Conclusions

Humans lack a functional uricase. Exogenous uricases, or "uricase enzyme replacement therapy", mimic the uricases found in other species. Uricases are increasingly used to treat uncontrolled gout. However, they are immunogenic, leading to ADA formation. Formation of ADAs against the uricase enzyme and/or the PEG moiety leads to IRs and decreased efficacy. Innovative approaches are needed to develop therapeutic pegylated uricases with improved properties such as soluble expression, neutral pH solubility, and high expression in *E. coli* as well as low potential for immunogenicity [11]. Coadministration of methotrexate with pegloticase and rapamycin-containing nanoparticles with pegadricase suppresses ADA production leading to improved long-term uricase efficacy.

Current uricases on the market include pegloticase and rasburicase. Pegloticase is indicated for uncontrolled gout, whereas rasburicase is approved to prevent tumor lysis syndrome. The EMA has recommended uricase-based treatments in its gout treatment guidelines, but despite widespread interest in new developments in this therapeutic area, there is no option in Europe for such treatment; it is currently available only in the US.

Which is better pegloticase or SEL-212? This is unclear. Pegadricase did not exhibit a statistical superiority in reducing SU < 6 mg/dL for at least 80% of the time during months 3 and 6 when compared with pegloticase (53% pegadricase vs 46% pegloticase, $P = 0.181$) [28, 29]. The main limitations of pegloticase are gout flares and IRs following ADA formation. Using pegloticase and pegadricase in combination with immunomodulation decreases ADA formation and improves SU-lowering and treatment outcomes. Uricases in development will likely be studied with immunomodulation, leading to enhanced urate-lowering efficacy and increased use in refractory and uncontrolled gout patients.

Abbreviations

Abs: antibodies

ADA: anti-drug antibody

AEs: adverse events

EMA: European Medicine Agency

FDA: US Food and Drug Administration

G6PD: glucose-6-phosphate dehydrogenase

IL-1: interleukin-1

IRs: infusion reactions

MMF: mycophenolate mofetil

NSAIDs: non-steroidal anti-inflammatory drugs

PEG: polyethylene glycol

SU: serum urate

ULT: oral urate-lowering therapy

Declarations

Author contributions

NS and DK: Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Naomi Schlesinger who is the Associate Editor of Exploration of Musculoskeletal Diseases had no involvement in the decision-making or the review process of this manuscript.

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