Enhancing the Response Rate to Recombinant Uricases in Patients with Gout

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Abstract
Refractory, or uncontrolled, gout is a chronic, progressive, inflammatory arthropathy resulting from continued urate deposition after failed attempts to lower serum uric acid below the therapeutic threshold with oral urate-lowering therapies such as allopurinol and febuxostat. Recombinant uricase is increasingly being used to treat refractory gout; however, the immunogenicity of uricase-based therapies has limited the use of these biologic therapies. Antidrug antibodies against biologic therapies, including uricase and PEGylated uricase, can lead to loss of urate-lowering response, increased risk of infusion reactions, and subsequent treatment failure. However, co-therapy with an immunomodulator can attenuate antidrug antibody development, potentially increasing the likelihood of sustained urate lowering, therapy course completion, and successful treatment outcomes. This review summarizes evidence surrounding the use of immunomodulation as co-therapy with recombinant uricases.

1 Introduction
Uricase, also known as urate oxidase, is an enzyme that catalyzes the degradation of uric acid to 5-hydroxyisourate and allantoin, both of which are readily excreted from the body [1]. Humans and higher primates evolutionarily lost functional uricase [2], resulting in higher circulating levels of urate throughout their lifespans compared with other mammals. The lack of urate degradation, in conjunction with avid renal retention of uric acid [3], makes humans susceptible to hyperuricemia and, subsequently, gout [1].

Gout is a chronic inflammatory arthritis resulting from monosodium urate (MSU) deposition subsequent to elevated serum urate (SU) [4, 5]. When SU levels remain above the solubility limit of 6.8 mg/dL, MSU crystals can precipitate out of solution and begin collecting in joints and extra-articular spaces [4–6]. Refractory, or uncontrolled, gout occurs when first- and second-line treatments aimed at lowering SU are ineffective at the maximum medically appropriate dosage and the signs and symptoms of gout continue to worsen.

Therapeutic uricases are a highly effective treatment for refractory gout and hyperuricemia associated with tumor lysis syndrome. However, because humans no longer express uricase, the biologic enzyme is highly immunogenic, limiting therapeutic efficacy and use [7]. In an effort to increase half-life within the body and reduce immunogenicity, uricases were PEGylated. Pegloticase, a recombinant mammalian uricase conjugated to 10 strands...
of 10-kDa monomethoxy-polyethylene glycol (PEG), is indicated for the treatment of uncontrolled gout that is refractory to oral urate-lowering therapies (ULTs) [8–10]. Pegadricase (previously known as pegsiticase, in development) is a PEGylated uricase derived from *Candida utilis* and similarly designed to hydrolyze urate [11]. Lastly, the naked (non-PEGylated) recombinant *Aspergillus* uricase rasburicase is still in use but is indicated for treating acute hyperuricemia that can occur with tumor lysis syndrome. Rasburicase has been sporadically used to treat severe tophaceous gout [12], but PEGylated enzymes are generally preferred. Properties of pegloticase, pegadricase, and rasburicase are summarized in Table 1.

PEGylating uricase has been moderately successful in mitigating immunogenicity, but PEG is immunogenic itself. In fact, the PEG moiety is the primary target of anti-pegloticase antibodies [10], which increase drug clearance and, subsequently, reduce drug concentrations below therapeutic levels [10]. In phase III clinical trials of pegloticase, only 42% of patients were treatment responders, with loss of response attributed to antidrug antibody development in nearly 60% of nonresponders [9]. Antidrug antibodies limit the efficacy and treatment duration of PEGylated uricase-based therapies while also putting patients at risk for infusion reactions [9, 10]. Approximately one-quarter (26%) of patients administered the US Food and Drug Administration (FDA)–approved regimen of pegloticase experienced infusion reactions in phase III clinical trials [9].

Biologic medications often induce the production of antidrug antibodies, particularly in patients with autoimmune conditions (e.g., rheumatoid arthritis, inflammatory bowel disease) [13–19]. For these conditions, disease-modifying antirheumatic drugs (DMARDs) are often the first-line treatment but are continued after a biologic is added to reduce antidrug antibody formation [20]. In the late 1990s, Maini et al. [21] demonstrated that administering oral methotrexate (7.5 mg/week) in combination with the biologic infliximab (1 mg/kg intravenously every 2–4 weeks) improved treatment duration, enhanced disease activity suppression, and increased treatment tolerance in patients with rheumatoid arthritis. Similarly, immunomodulation administered with either pegloticase [22–24] or pegadricase [25–27] increased treatment response rates and has furthered the uncontrolled/refractory gout treatment paradigm. In an open-label trial, pegloticase co-administered with methotrexate reduced production of antidrug antibodies [28] compared with pegloticase monotherapy trials [9], subsequently increasing treatment response rate and decreasing infusion reaction rates [22]. It is important to note that gout is not an autoimmune condition, and DMARDs have no known efficacy in gout treatment. This review summarizes evidence of antidrug antibody attenuation and subsequent clinical benefit of administering an immunomodulating agent with a uricase-based therapy, including improved responder rate and drug survival.

### Table 1 Properties of uricase-based molecules examined in the clinical and research settings

| Uricase molecule | Pegloticase | Pegadricase | Rasburicase |
|------------------|------------|-------------|-------------|
| Molecular weight | 540 kDa    | 304.34 g/mol| 34 kDa      |
| Origin           | Pig-baboon chimeric uricase cDNA amplified in *Escherichia coli* | *Candida utilis* | *Saccharomyces cerevisiae* and *Aspergillus flavus* |
| Disease          | Chronic refractory gout | Chronic refractory gout | Hyperuricemia in acute tumor lysis syndrome |
| Dosing (route of administration) | 8 mg (IV) every 2 weeks | 0.2 or 0.4 mg/kg (IV) monthly | 0.2 mg/kg (IV) daily for up to 5–7 days* |
| Half-life        | 6.4–13.8 days | 3 days | 16–22 h |

*IV intravenously

* Dosing specific to patients with hyperuricemia secondary to tumor lysis syndrome.

2  **Recombinant Uricase In Vivo**

The first parenteral administration of therapeutic uricase in humans was reported in 1957 by London and Hudson [29]. Two patients, one with a long history of gout (male, age 55 years) and another with no history of gout (male, age 63 years), received a preparation of 104 units of uricase administered intravenously in small doses. Temporary reductions in SU were detected in both patients [29]. Although recombinant uricase from a variety of organisms has proven effective in reducing SU in patients with gout, the immunogenicity of uricase itself has limited its therapeutic application by inducing allergic reactions, including anaphylaxis [7, 11, 30]. Protein structure, antigenic epitope exposure, impurities, and contaminants have all been identified as contributing factors
to immunogenicity of therapeutic proteins like uricase [20, 30]. Therefore, uricase is susceptible to proteolysis via immune response to uricase exposure, led by antigen presentation and anti-uricase antibody action (Fig. 1a). As a result, increased drug clearance and decreased serum concentration often precede loss of biologic activity and subsequent treatment inefficacy [20, 31, 32].

3 History of Uricase-Based Monotherapies for Gout

The human body does not produce the uricase enzyme (except for a nonfunctional 10-amino acid fragment of the N-terminus). Thus, our immune system recognizes it as foreign, eliciting the cascade that leads to antidrug antibody production [11].

Rasburicase, a recombinant urate oxidase, is administered intravenously with a daily dose of 0.20 mg/kg for up to 7 days among patients with hyperuricemia secondary to tumor lysis syndrome [33]. The agent was developed for the short-term management of hyperuricemia in pediatric and adult patients with tumor lysis syndrome caused by anticancer therapies for leukemia, lymphoma, and malignant solid tumors [33]. The rasburicase molecule is not PEGylated. Therefore, immunogenicity is directed related to uricase, but what exactly facilitates this immune response is not fully understood [30, 33]. In early-phase clinical trials, rasburicase immunogenicity limited treatment efficacy, with the development of binding and neutralizing anti-uricase antibodies in 61% and 64% of healthy controls, respectively. (N = 28) [30]. Antibody production was rapid, occurring within 1–6 weeks.

Few hypersensitivity reactions to rasburicase have been reported at the first infusion, but the incidence of infusion reactions progressively increases with subsequent doses. No events of anaphylaxis were reported during the first course of therapy according to a retrospective chart review, but 6.2% of patients experienced anaphylaxis during subsequent treatment (N = 97) [30]. Further, a compassionate use trial included 173 children and 72 adults with malignancies who were treated daily with rasburicase for 1–7 days. Fifteen subsequent courses were administered to 12 patients, resulting in two possible hypersensitivity reactions [34]. Another study that included 131 adults with leukemia- or lymphoma-associated hyperuricemia reported antidrug antibody formation in 14% of patients who received daily rasburicase for 5–7 days. Patients who developed antidrug antibodies had received 0.15 mg/kg (n = 2) or 0.20 mg/kg (n = 15) of rasburicase daily [35]. Off-label use of rasburicase has been reported in patients with tophaceous gout refractory to or contraindicated for treatment with allopurinol [12]. Of the ten patients who received daily or monthly rasburicase infusions, two experienced allergic reactions (bronchospasm or cutaneous eruption) that led to therapy discontinuation [12]. Additionally, 80% of patients experienced one or more adverse event, most commonly acute gout flare [12].

Pegloticase is a PEGylated recombinant uricase, administered as biweekly infusions (8 mg), and is indicated to treat chronic or uncontrolled gout that is refractory to first- and second-line oral ULTs [8]. The pegloticase molecule consists of uricase covalently conjugated to 10 strands of 10-kDa monomethoxy-PEG [8, 10]. Pegloticase has a half-life between 6.4 and 13.8 days, remaining in circulation between infusions to continuously catalyze the conversion of urate to allantoin [9, 37]. In phase III, randomized, placebo-controlled trials of pegloticase as monotherapy, 42% of patients treated biweekly with pegloticase were treatment responders, defined as those who had SU levels < 6.0 mg/dL for ≥ 80% of the time during months 3 and 6 of treatment [9]. In these early registration trials, pegloticase was associated with the development of high-titer binding antidrug antibodies [8], which largely targeted the PEG moiety [10]. Surprisingly, 89% of patients receiving pegloticase had detectable anti-pegloticase antibodies that, at high titers, were associated with an increase in pegloticase clearance, loss of treatment response, and increased risk for infusion reactions [9, 38].

Another PEGylated uricase, pegadricase, was developed to treat chronic refractory gout. The pegadricase molecule is characterized by the covalent attachment of 20-kDa PEG to the primary amines of uricase [11, 39]. Preclinical trials of pegadricase demonstrated a reduction in SU levels to < 6 mg/dL after a single treatment in uricase-deficient hyperuricemic mice. However, continued pegadricase administration failed to maintain initial SU reductions, and evidence of immunogenicity was observed [11, 39]. Early phase trials of pegadricase monotherapy (0.4-mg/kg infusions every 28 days) showed similar levels of immunogenicity as those seen with pegloticase monotherapy [25, 26]. Comparable results were observed in phase II trials in which patients treated with pegadricase developed high-titer antidrug antibodies by day 14 of treatment; by day 30, SU levels had returned to baseline in the majority of patients [25].

4 Use of Uricase-Based Therapies With Immunomodulation

Severe gout is generally managed by rheumatologists, who routinely administer immunomodulators to attenuate antidrug antibodies along with the use of biologics for other diseases, including rheumatoid arthritis [16], inflammatory bowel disease [14, 18, 19], Crohn’s disease [13], and spondyloarthritis [15, 17]. This approach has been applied to
the treatment of chronic refractory gout by rheumatologists through the coadministration of uricase and immunomodulation. Published reports have demonstrated that uricase with concomitant immunomodulation has improved response rates in patients with uncontrolled gout as summarized in Table 2.

### 4.1 Pegloticase and Immunomodulation

Coadministering an immunomodulating agent with pegloticase should theoretically attenuate antidrug antibody development in much the same way as it does for biologics used to treat rheumatoid arthritis. Methotrexate may increase T-cell sensitivity to apoptosis, disrupting the pathway to immunogenicity. Methotrexate may increase T-cell sensitivity to apoptosis, ultimately disrupting PEGylated uricase antigen presentation and B-cell antibody production against PEGylated uricase. This would subsequently diminish neutralization of PEGylated uricase activity (Fig. 1c) [40].

Berhanu et al. [41] were the first to report pegloticase treatment in the presence of immunomodulation. In this single case report, azathioprine (50 mg/day) was initiated 2 weeks prior to the first pegloticase infusion. The patient
underwent 98 weeks of pegloticase therapy, with two transient increases in SU coinciding with azathioprine noncompliance. The next case was published by Freyne [42] and involved a patient who completed a successful 38-week treatment course of pegloticase. The patient had received a heart transplant 14 years earlier and was chronically immunosuppressed with mycophenolate mofetil (3000 mg/day) and cyclosporin (100 mg/day). Bessen et al. [43, 44] then published two reports that included eight patients who received pegloticase in the presence of immunomodulation (methotrexate \(n = 6\), methotrexate then azathioprine \(n = 1\), cyclosporin \(n = 1\)). All were considered pegloticase responders.

The first methodical examination of pegloticase with immunomodulation involved coadministration of pegloticase with methotrexate, a DMARD commonly used by rheumatologists, in an attempt to increase duration of therapy and increase the proportion of patients achieving therapeutic benefit [45]. Presentation of that case series by Botson and Peterson [45] in late 2018, along with a later case series by Albert et al. [46], has led to a progressive increase in the use of immunomodulators with pegloticase in the United States [47]. Both independent case series showed increased treatment response rates with concomitant immunomodulation compared with pegloticase monotherapy (80–100% [45, 46] vs 42% [9]). Because the uncontrolled gout population is often complicated by multiple cardiometabolic and renal comorbidities [4], and methotrexate use is limited by kidney dysfunction, Masri et al. [48] retrospectively examined leflunomide with pegloticase. Treatment response rates were similar to those observed with methotrexate, with four of six patients (67%) considered treatment responders.

Given the strong case evidence supporting immunomodulator use with pegloticase, a small open-label trial (MIRROR OL) examining oral methotrexate (15 mg/week) as co-therapy to pegloticase was performed. In that study, 11 of 14 patients (79%) who received one or more pegloticase infusion met the 6-month treatment response criteria (SU < 6 mg/dL for ≥ 80% of month 6) [22]. All patients received methotrexate for 4 weeks prior to and during pegloticase therapy. Pharmacokinetic data and antidrug antibody titers showed higher pegloticase peak and trough concentrations and attenuated antidrug antibody levels, respectively, compared with the pegloticase monotherapy phase III trials [28]. Another small open-label trial examined treatment response rate of pegloticase plus azathioprine (1.25 mg/kg/day for 7 days, then 2.5 mg/kg/day) co-therapy. Six of ten patients (60%) who completed therapy met treatment response criteria at 24 weeks. Of the four nonresponders, two lost urate-lowering efficacy, one experienced an infusion reaction during the first pegloticase infusion, and one had subjective intolerance to azathioprine and discontinued therapy [49]. All patients began azathioprine 2 weeks prior to the first pegloticase infusion. Pharmacokinetic and antidrug antibody data were not reported.

Two randomized controlled trials performing head-to-head comparisons of pegloticase in the presence and absence of immunomodulation have been completed. The RECIPE trial examined whether the addition of mycophenolate mofetil (1000 mg/day for 14 weeks beginning 2 weeks prior to the first pegloticase infusion) could effectively and safely reduce immunogenicity, as reflected in an increased treatment response rate [24]. The treatment response rate was 86% at week 12 (SU < 6 mg/dL at week 12, \(n = 22\)) in the mycophenolate mofetil arm vs 40% (\(n = 10\)) in the placebo arm (primary endpoint) [24]. The proportion of patients who maintained clinical response (SU ≤ 6 mg/dL) at week 24 after discontinuing mycophenolate mofetil at week 12 was 30% (vs. 68% at week 12, secondary endpoint) [24]. This finding prompted the investigators to consider the need for ongoing immunomodulation during the entire course of pegloticase therapy [24]. Pharmacokinetic and antidrug

| Underlying cause of hyperuricemia | Pegloticase [8, 9, 22, 23] | Pegadricase [11, 25–27, 39] | Rasburicase [12, 30, 33, 34] |
|-----------------------------------|---------------------------|-----------------------------|-----------------------------|
| FDA approval status               | Uncontrolled gout         | Uncontrolled gout           | Tumor lysis syndrome        |
| Efficacy, \(n/N\) (%)             | Approved with indication  | Phase II (NCT03905512)      | Approved with indication    |
| Monotherapy                       | 36/85 (42%)               | N/A                         | 80/92 (87%)                 |
| With immunomodulation             | 68/82 (83%)\(^a\)        | 115/143 (81%)               | N/A                         |
| Patients with antidrug antibodies, \(n/N\) (%) |                               |                             |                             |
| Monotherapy                       | 134/150 (89%)             | 5/5 (100%)                  | 17–18/28 (61–64%)\(^b\)    |
| With immunomodulation             | 2/14 (14%)                | N/A                         | N/A                         |

\(^a\) Pooled response rate for immunomodulation with methotrexate, mycophenolate mofetil, leflunomide, azathioprine, and cyclosporin

\(^b\) Rates of binding and neutralizing antibodies examined in healthy controls, respectively

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antibody findings were not reported. The only other randomized controlled trial directly comparing pegloticase plus oral methotrexate (15 mg/week) with pegloticase plus placebo (MIRROR RCT; NCT03994731) recently completed. In this study, patients underwent a 2-week methotrexate tolerance test followed by 2:1 randomization into either the pegloticase plus methotrexate arm or the pegloticase plus placebo arm. Methotrexate or placebo was then administered for 4 weeks prior to and during the 52-week pegloticase treatment period. The primary endpoint was the proportion of patients who were treatment responders, defined as SU < 6 mg/dL during ≥ 80% of month 6. The trial did meet its primary endpoint [50], but results have not yet been reported.

Kidney transplant recipients have an increased prevalence of gout compared with nontransplant patients due to lower renal urate excretion and hyperuricemic effects of some immunosuppressants, particularly cyclosporin [51]. Thus, it is particularly important to effectively manage hyperuricemia and gout in kidney transplant recipients. Interim results from a phase IV study (PROTECT; NCT04087720) assessed pegloticase response in kidney transplant recipients with uncontrolled gout, all of whom were maintained on a stable post-transplant immunosuppressive regimen [52–54]. At the time of analysis, of the 15 patients who had completed therapy, ten had sustained SU reduction, three discontinued treatment (two for COVID-19; one withdrew consent), and two had loss of treatment response and discontinued therapy [53].

In summary, the literature strongly supports the use of immunomodulation co-therapy with pegloticase. This is emphasized in a systematic literature review published in 2021 that summarized and examined pegloticase with immunomodulation efficacy rates in published case reports, case series, and clinical trials [23]. The overall treatment response rate across all published cases and trials was 83% [23], a notable increase from the established 42% response rate observed in the phase III pegloticase clinical trials [9].

4.2 Pegloticase and Rapamycin

Rapamycin, administered in synthetic vaccine poly (lactic-co-glycolic acid) nanoparticles (SVP-rapamycin), has been shown to attenuate antidrug antibody formation [39, 55]. Co-administration of the rapamycin-nanoparticle complex (ImmTOR™) with free PEGylated uricase antigen (e.g., pegloticase) facilitates the induction of tolerogenic dendritic cells followed by antigen-specific regulatory T cells, leading to an immunosuppressive response (Fig. 1b) [39, 55]. Further, this tolerogenic dendritic cell control inhibits B cells and T cells from producing antidrug antibodies against pegloticase via prevention of interleukin-2 production [39, 56]. Considering this mechanism of action, ImmTOR™ must be administered with free antigen to mediate immunogenicity and prevent antidrug antibody formation [25].

Preclinical studies of pegloticase administered with and without SVP-rapamycin were performed in uricase-deficient mice and nonhuman primates [39]. Following monthly pegloticase dosing (mice: 100 μg, primate: 4 mg/kg), animals who received SVP-rapamycin (mice: 50 μg, primate: 3 mg/kg) plus pegloticase had lower antidrug antibody titers, higher levels of uricase activity, and lower SU levels than animals who had only received pegloticase [39]. Further, mean SU was maintained < 6 mg/dL after approximately 6 weeks of therapy only in the SVP-rapamycin group [39].

An early phase I clinical trial examining efficacy and safety of pegloticase plus rapamycin co-therapy was performed in patients with uncontrolled symptomatic gout (mean baseline SU: 7.14 ± 1.3 mg/dL) and included antidrug antibody analyses [26]. Patients received a single dose of SVP-rapamycin alone (0.03–0.5 mg/kg), pegloticase alone (0.4 mg/kg), or encapsulated pegloticase plus rapamycin (SEL-212; SVP-rapamycin: 0.03–0.3 mg/kg, pegloticase: 0.4 mg/kg). SVP-rapamycin alone had no effect on SU levels. The pegloticase monotherapy group had a rapid reduction in SU, which remained below baseline levels in only 20% of patients. In contrast, patients treated with SEL-212 demonstrated a rapid, dose-dependent reduction in SU levels with a corresponding inhibition of antiuricase antibody development. The loss of response in the pegloticase monotherapy arm was attributed to high antidrug antibody titers (> 1000) [26]. In the subsequent phase II efficacy and safety study of SEL-212 (N = 143), an 81% response rate at week 12 was seen among patients receiving 0.125 mg/kg or 0.15 mg/kg of ImmTOR™ with 0.2 mg/kg or 0.4 mg/kg of pegloticase after three monthly doses [27]. Earlier response rates associated with pegloticase monotherapy were much lower, indicating that the addition of rapamycin to attenuate immunogenicity helped facilitate the increase in treatment efficacy [26, 39].

4.3 Rasburicase

To the best of our knowledge, rasburicase has not been examined in the presence of immunomodulation. The therapy is used to treat acute hyperuricemia associated with hematologic malignancies and is generally used on a short-term basis. That said, antidrug antibodies have been shown to inhibit rasburicase activity [57].

5 Discussion

Rheumatologists routinely manage autoimmune and inflammatory diseases with infused biologic therapies. Therefore, managing uncontrolled gout primarily resides with them.
Patients with uncontrolled gout have poorer overall health [58–60] and quality of life [58] than patients with controlled gout [58–60], and unlike rheumatoid arthritis, which has several biologic therapies [61], uncontrolled gout that is refractory to oral ULT has only one FDA-approved treatment, pegloticase [8]. Efforts are underway to develop other treatment options, including an oral uricase (NCT04987294); however, at this time, loss of therapeutic response to pegloticase leaves no other available medical therapies for patients with uncontrolled gout.

Rheumatologists often prescribe DMARDs with biologic therapies to both enhance treatment response rates and increase duration of therapy [61]. However, careful consideration must be taken when adding any medication for patients with uncontrolled gout, who often have several cardiometabolic and/or renal comorbidities [9, 62]. Because uricase-based therapies are often the last line of therapy for patients with uncontrolled gout, treatment success is critical. There is strong evidence supporting the use of immunomodulation with PEGylated uricases, whether coadministered or co-formulated, showing a marked increase in the proportion of patients who have sustained urate lowering and successful treatment outcomes [22–27]. In the case of pegloticase, methotrexate has been most studied, but leflunomide, azathioprine, and mycophenolate mofetil may also be candidates for co-therapy to attenuate antidrug antibody production [22–24]. Given the complexity of this patient population, a variety of therapy options is helpful and necessary for tailoring therapy to each patient’s needs. For example, methotrexate is contraindicated in patients who have alcoholism or liver disease and must be used with caution in those with renal dysfunction [63]. For co-formulated systems such as SEL-212 (pegadricase plus SVP-rapamycin), immunomodulation is limited to rapamycin, which may not be optimal for all patients with uncontrolled gout [25, 55]. Because the human immune system naturally weakens with age [64], pegloticase appears to be less immunogenic in older patients [10]. Pegloticase phase III clinical trials showed that 61% of patients older than 70 years of age and 50% older than 60 years of age were treatment responders. In contrast, only 30% of patients under the age of 60 years were treatment responders [10]. The evidence of antidrug antibody attenuation and subsequent clinical benefits of administering an immunomodulating agent with a uricase-based therapy continue to be topics of intense research and exploration.

6 Conclusion

Uricase-based therapies are effective at lowering SU in patients with uncontrolled gout that is refractory to oral ULT. PEGylated uricases have a longer half-life than the naked enzyme when they are not neutralized by antidrug antibodies. Therefore, mediating the immunogenicity of these biologics is essential for successfully managing uncontrolled gout over the long-term. The literature suggests that a variety of immunomodulators can be used as co-therapy to attenuate antidrug antibody development, subsequently maintaining bioavailability and increasing treatment response rates. Given that patients with uncontrolled gout have limited treatment options, maximizing therapeutic success through the use of uricase-based biologics and concomitant immunomodulation is of the utmost importance.

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Declarations

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Code availability Not applicable.

Ethics approval This review did not involve the collection or analysis of new data and only examined data already published in the literature.

Consent to participate Not applicable.

Consent for publication This review only contains aggregate findings from published studies and does not contain individual patient data.

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