Rilonacet for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial

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Abstract

Objective. To evaluate the efficacy and safety of IL-1 inhibitor rilonacept (IL-1 Trap) for gout flare (GF) prevention during initiation of uric acid-lowering therapy (ULT) with allopurinol in a multiregional phase 3 clinical trial.

Methods. Hyperuricaemic adults (n=248) from South Africa, Germany and Asia with gout and two or more GFs within the past year were initiated on allopurinol and randomized 1:1:1 to once-weekly s.c. treatment with placebo (PBO), rilonacept 80 mg (R80) or rilonacept 160 mg (R160) for 16 weeks. The primary endpoint was the number of GFs per patient through week 16.

Results. The population was predominantly male and racially diverse (white, 53.2%; Asian, 33.1%; black, 13.7%). Across treatments, most patients completed the study (87.8-92.9%). At 16 weeks the mean number of GFs per patient was reduced by 71.3% with R80 (0.35) and by 72.6% with R160 (0.34) relative to PBO (1.23; both P < 0.0001). The proportion of patients without GFs was higher with R80 (74.4%) and R160 (79.5%) than with PBO (43.9%; both P < 0.0001), and the proportions of patients on rilonacept with multiple GFs were significantly lower (P < 0.001). Overall, the incidence of adverse events (AEs) was similar between PBO (61.0%) and rilonacept (65.1%). Injection site reactions, generally mild, were the most frequent AE with rilonacept (1.2% PBO, 12.2% R80 and 17.9% R160); none of these injection site reactions led to withdrawal. There were no study drug-related serious AEs or deaths.

Conclusion. Rilonacept significantly reduced the occurrence of GFs associated with initiation of ULT, with >70% of patients having no flares, and demonstrated an acceptable safety and tolerability profile.


Key words: crystal arthropathies, clinical trials and methods, cytokines and inflammatory mediators, inflammation, biologic therapies.

Introduction

When serum uric acid concentrations exceed the limit of solubility [approximately 405 µmol/l (6.8 mg/dl)] [1, 2], monosodium urate (MSU) crystals may deposit in joints and soft tissues. These crystals can initiate an inflammatory response that manifests as gouty arthritis, which is clinically characterized by recurrent painful flares in one or more joints.

Long-term gout management relies on strategies that include lifestyle changes and pharmacological agents...
such as uric acid-lowering therapies (ULTs), which are targeted towards reducing and maintaining serum uric acid concentrations at subsaturating levels to reverse crystal deposition [3–6]. Currently available ULTs include allopurinol, probenecid and the recently approved febuxostat and pegloticase (in the USA only).

However, initiation of long-term ULT may itself initially promote flares, possibly as a result of crystal remodeling during their dissolution [7]. It has been suggested that flares occurring during initiation of ULT may substantially contribute to low adherence with ULT, resulting in poorer outcomes [8–10]. Non-adherence to therapy has been reported in up to 50% of patients within 3 months of initiation [8, 9], and 50–75% of patients become non-adherent during the first year [11, 12]. Treatment with NSAIDs or colchicine for several months has been recommended to prevent gout flares (GFs) during ULT initiation despite the fact that few controlled studies have demonstrated their efficacy for this use [3, 4, 6]. Furthermore, a recent study suggested that as many as 90% of gout patients may have at least one contraindication to NSAIDs, and ~40% have a strong contraindication to colchicine [13]. Consequently there is an unmet need for effective, well-tolerated flare prevention therapies.

IL-1 has been determined to be a major inflammatory factor in gout [14, 15]. Its role in flares was confirmed by case reports and early phase trials of the IL-1 inhibitors anakinra and canakinumab [16–20], and by an early phase trial that demonstrated that IL-1 inhibition with rilonacept reduced GFs associated with ULT initiation [21]. These studies suggested that IL-1 inhibition represents a mechanism-based approach to reducing GFs as part of an overall management strategy.

Rilonacept is a soluble decoy receptor fusion protein that binds IL-1α and IL-1β, thus preventing their activation of cell surface receptors. Rilonacept was generated using Trap Technology and is known as IL-1 Trap [22]. In the USA and European Union, rilonacept has been approved for the treatment of cryopyrin-associated periodic syndromes [23], a group of rare diseases that share with gout an underlying NLRP3 inflammasome-mediated excess production of IL-1β. The half-life of rilonacept (~8.6 days) allows for convenient weekly s.c. dosing and avoids prolonged exposure after cessation of treatment [23].

A phase 3 trial from North America provided additional support for the efficacy and safety of rilonacept for prevention of GFs associated with ULT initiation [24]. The purpose of the current study was to confirm and expand upon these data in a multiregional clinical setting.

Methods

Study design and population

This randomized, double-blind, placebo-controlled, phase 3 study was performed at study sites in Germany, India, Indonesia, Republic of South Africa and Taiwan. The study received approval from all local ethics committees or institutional review boards as appropriate and was performed in accordance with the current revision of the Declaration of Helsinki; all patients provided written informed consent prior to participation.

For inclusion, patients had to be 18–79 years old with a documented presence of either at least 6 of the 13 criteria of the ARA (1977 ARA preliminary criteria) for the classification of acute arthritis of primary gout [25] or MSU crystals in joint fluid. A serum uric acid concentration ≥445 μmol/l (7.5 mg/dl) and a self-reported history of two or more GFs within the past year were also required.

Key exclusion criteria included, but were not limited to, an acute GF within 2 weeks prior to screening; use of glucocorticoids or colchicine within 4 weeks prior to screening; use of NSAIDs within 2 weeks prior to screening; use of allopurinol, probenecid or sulphinpyrazone within 3 months prior to screening and history of allergy to allopurinol or inadequate urate-lowering response to allopurinol.

Randomization and interventions

Patients were randomly allocated using an interactive voice recognition system 1:1:1 to parallel treatment with placebo, rilonacept 80 mg or rilonacept 160 mg, with all treatments administered s.c. once weekly for 16 weeks. The sponsor, investigators and patients were blinded to treatment allocation up to the time of the analysis.

Loading doses of placebo, rilonacept 160 mg (in the 80 mg group) and rilonacept 320 mg (in the 160 mg group) were administered on treatment day 1, followed by 15 weekly doses. Patients were also initiated on allopurinol 300 mg daily starting on day 1. Allopurinol was titrated every 2 weeks, as needed, up to a maximum daily dose of 800 mg, to achieve serum urate <357 μmol/l (6 mg/dl). For all patients, the initial daily allopurinol dose and titration increment were adjusted based on baseline creatinine clearance estimated using the Cockroft-Gault equation [26]. Although anti-inflammatory agents such as colchicine and NSAIDs were not allowed for flare prevention, acute GFs were treated at the investigators’ discretion for up to 10 days with an NSAID and/or oral glucocorticoid; while study treatments were continued. A safety follow-up was performed 5 weeks after the last injection of study drug; patients continued allopurinol therapy during follow-up.

Outcomes

The presence or absence of a flare was reported by patients in a daily diary using a telephone interactive voice response system. On all flare days, the flare characteristics were queried, including assessment of flare joint pain using a 0–10 numerical rating scale (0 = no pain, 10 = severe pain) with a recall period of 24 hours, swelling, tenderness, redness, rapidity of pain onset, range of motion, warmth and other GF symptoms.

The primary efficacy endpoint was the mean number of GFs per patient through week 16. Except as noted elsewhere, for analysis purposes the GF definition incorporated several of the features being evaluated by OMERACT (Outcome Measures in Rheumatology) [27]
and required that all of the following three criteria be met: the presence of patient-reported acute articular pain typical of a gout attack that is deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic; the presence of at least two of the following three signs/symptoms: joint swelling, tenderness and redness; and the presence of at least one of the following clinical variables: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior GF.

Secondary efficacy endpoints, assessed from day 1 to week 16, included the proportion of patients with one or more GFs and with two or more GFs, the mean number of GF days per patient and the mean number of days per patient with a pain score ≥5 (daily diary). An additional secondary endpoint was the number of GFs using a definition from a prior phase 2 study with rilonacept: patient-reported articular pain typical of a gout attack that is deemed to require treatment with an anti-inflammatory agent. Pre-specified exploratory endpoints included evaluations of onset of action of rilonacept for GF prevention.

On-treatment study visits occurred at baseline and at weeks 2, 4, 8, 12 and 16, at which times patients were assessed by physical examination, clinical laboratory values, serum urate levels and review of the flare diary and adverse events (AEs). Safety and tolerability were evaluated up to and including the safety follow-up at week 20. Safety analysis was based on the incidence of AEs, physical examinations at study visits including vital signs, electrocardiogram and clinical laboratory assessments including haematology and liver enzyme values.

Statistical analysis
All analyses were performed on the full analysis set, defined as all randomized patients who received any of the evaluated study medications. SAS version 9 (SAS Institute, Cary, NC, USA) was used for all analyses. The safety set included all patients who received any study medication, and the safety analysis was based on the treatment received.

To control for type I error, step-down sequential testing was used for the primary endpoint by comparing rilonacept 80 mg versus placebo only if the comparison of rilonacept 160 mg versus placebo was statistically significant. A two-sided Wilcoxon rank sum test was used for primary endpoint comparison. For secondary endpoints, continuous variables were analysed with a Wilcoxon rank sum test, and variables that were proportions were analysed using Fisher’s exact test. All tests were two-sided; a P-value < 0.05 was considered to demonstrate statistical significance. The rate ratios (for GFs per patient) and risk ratios (for occurrence of one or more and two or more GFs) were calculated as the treatment values divided by the placebo values, with the reciprocals indicating risk reduction. These ratios and their 95% CIs were estimated using generalized linear models, the former with a log-linked Poisson model and the latter with a log-linked binomial model. Rate reductions were calculated as 1 minus the rate ratio, and risk reductions were calculated as 1 minus the risk ratio. The time to first flare was analysed using Kaplan–Meier survival function curves.

Results
A total of 248 patients were randomized to placebo (n = 82), rilonacept 80 mg (n = 82) and rilonacept 160 mg (n = 84) (Fig. 1), with the majority of patients (75%) from South Africa. Twenty-six patients (10.5%) withdrew from the study before week 16, 10 each (12.2%) in the placebo and rilonacept 80 mg groups and 6 (7.1%) in the rilonacept 160 mg group. There were no withdrawals due to lack of efficacy, and only three patients withdrew due to AEs, all in the rilonacept 80 mg group. Two hundred and forty patients attended the 2-week visit, 236 patients attended the 4-week visit, 230 patients attended the 8-week visit, 225 patients attended the 12-week visit and 222 patients attended the 16-week visit.

Demographic and clinical characteristics were similar among the treatment groups (Table 1). The population was predominantly male (93.1%) with a mean (s.d.) age of 51.1 (12.1) years and was racially mixed; approximately half was white (53.2%), one-third Asian (33.1%) and the rest black (13.7%). The mean (s.d.) BMI was 30.8 (5.9) kg/m², and 50.8% of the study population was obese (BMI ≥ 30 kg/m²).

The mean daily dose of allopurinol from day 1 through week 16 was similar among the treatment groups (supplementary Table S1, available at Rheumatology Online). The cumulative number of flares was 101 with placebo, rilonacept 80 mg and rilonacept 160 mg, respectively.

Primary endpoint
At the end of the double-blind treatment period (week 16), the cumulative number of flares was 101 with placebo, 29 with rilonacept 80 mg and 28 with rilonacept 160 mg (Fig. 2). The rilonacept 160 mg group was characterized by significantly fewer GFs per patient (0.34, 95% CI 0.15, 0.52) relative to placebo (1.23, 95% CI 0.89, 1.58; P < 0.0001), a 72.6% rate reduction (95% CI 58.4, 82.0). Sequential testing of the 80 mg dose showed significantly fewer GFs per patient (0.35, 95% CI 0.21, 0.50; P < 0.0001), a 71.3% rate reduction (95% CI 56.6, 81.0) (Fig. 2). In a pre-specified exploratory analysis that evaluated flare occurrence at early time points, significant separation from placebo in the number of GFs per patient was observed as early as 1 week after initiating treatment with rilonacept 160 mg, mean (s.d.) of 0.10 (0.3) and 0.22 (0.42) for R160 and placebo, respectively (P < 0.05). For R80, separation was observed at 2 weeks; 0.18 (0.45) and
These differences were maintained over the treatment period (Fig. 2).

**Secondary endpoints**

The proportions of patients who reported one or more GFs by week 16 were significantly lower in both rilonacept groups relative to placebo ($P < 0.001$) (Fig. 3). Similarly, when patients were grouped by those reporting two or more GFs, rilonacept resulted in significantly lower proportions of patients ($P < 0.001$). While approximately one-third (32.9%; 27 of 82) of patients in the placebo group reported multiple GFs, only 8.5% (7 of 82) and 6.0% (5 of 84) of patients treated with rilonacept 80 and 160 mg, respectively, had multiple flares (both $P < 0.001$) (Fig. 3). The risk ratio for having one or more GFs during the 16-week treatment period was 0.457 (95% CI 0.301,
For rilonacept 80 mg and 160 mg, representing risk reductions of 54.3% (95% CI 30.8, 69.9) and 63.5% (95% CI 41.9, 77.1), respectively. Similarly, risk reductions for having two or more GFs were 74.1% (95% CI 43.8, 88.0) and 81.7% (95% CI 54.8, 92.6) for rilonacept 80 and 160 mg, respectively.

By week 16, placebo-treated patients had reported a mean of 11.2 flare days per patient (95% CI 6.6, 15.8), whereas 4.3 flare days per patient (95% CI 0.5, 8.1) were reported with rilonacept 80 mg and 1.9 flare days per patient (95% CI 0.6, 3.1) with rilonacept 160 mg. The fewer flare days per patient at both rilonacept doses were significant relative to placebo (P < 0.0001), representing reductions of 61.5% and 83.4% for the 80 and 160 mg doses, respectively.

Treatment with rilonacept also resulted in significantly fewer days per patient with a pain severity score ≥ 5 relative to placebo. For the 80 mg dose, this reduction was from 4.3 days (95% CI 2.6, 6.0) with placebo to 1.7 days (95% CI 0, 3.5; P < 0.0001), and for rilonacept 160 mg, the reduction was to 0.9 days (95% CI 0.3, 1.5; P < 0.0001).

When GF was defined as patient-reported articular pain typical of a gout attack that requires treatment with an anti-inflammatory agent, the observed trends were similar to the primary analysis; the number of flares per patient...
during the 16-week treatment period was 1.51 (95% CI 1.10, 1.92) for placebo, 0.62 (95% CI 0.33, 0.91) for rilonacept 80 mg and 0.48 (95% CI 0.27, 0.70) for rilonacept 160 mg. These values were significantly lower with rilonacept (both \( P < 0.0001 \)) and represent reductions of 58.9% and 68.1% for the 80 and 160 mg doses, respectively.

The estimated median time to first GF in the placebo group was 34 days (supplementary Fig. 1, available at Rheumatology Online), significantly earlier than for either of the rilonacept groups (\( P < 0.0001 \)), for which the median time could not be estimated since <50% of rilonacept patients treated reported a GF.

### Safety and tolerability

The overall incidence of AEs was similar among treatment groups (Table 2). AEs were generally of mild to moderate severity. Serious AEs occurred with a similar frequency across treatment groups, and none was considered by the investigator to be related to study medication. No deaths occurred during the study. There were three discontinuations due to AEs, all in the rilonacept 80 mg group: one was for gastric cancer (not related to treatment), and the other two, gout exacerbation and neutropenia, were considered related to study medication.

The most frequently reported AEs were injection site reactions and upper respiratory tract infections (Table 2). Injection site reactions occurred with a substantially higher frequency in rilonacept-treated patients and accounted for much of the increase in treatment-related AEs. In contrast, there was no clear rilonacept-associated increase in infections. There were two reports of serious infection in patients receiving rilonacept 80 mg (one appendicitis and one pyelonephritis), neither of which was deemed by the investigator to be related to study treatment. No tuberculosis or other opportunistic infections were reported, and the overall rate of infections was similar among treatment groups. Similar proportions of patients developed anti-rilonacept antibodies (ADA) in the rilonacept 80 mg (24%) and 160 mg (29%) groups. When analysing treatment-emergent AEs by ADA status, AEs were balanced within each treatment group, with the possible exception of injection site reactions with rilonacept 80 mg. Injection site reactions occurred in a small number of patients in this treatment group, although the proportion was higher in ADA-positive patients (25%) than in ADA-negative patients (8.1%). However, in the rilonacept 160 mg group, injection site reactions were balanced in ADA-positive patients (16.7%) and ADA-negative patients (8.3%).

### Discussion

There remains a need for adequate flare prevention during the initiation of ULT, since gout patients are characterized by substantial comorbidities that may limit or contraindicate the use of NSAIDs and colchicine [13], the currently recommended treatments. Furthermore, up to almost half of the patients using NSAIDs and colchicine may nevertheless experience flare, including multiple flares [28–30]. The results of this phase 3 study support the potential benefits of the IL-1 inhibitor rilonacept in preventing GFS during ULT initiation. These results are consistent with and confirm those of a previous phase 3 trial [24] and the original proof-of-principle study [31], both of which demonstrated significant reductions in GFS when once-weekly s.c. administration of rilonacept was initiated concomitantly with allopurinol.

In the current study, efficacy of rilonacept for GF prevention was observed as early as 1 week after initiating treatment. Over the 16-week treatment period the number of GFS per patient was 71.3% and 72.6% lower with once-weekly doses of rilonacept 80 mg and 160 mg, respectively, relative to placebo. These values are consistent with the rate reductions of 73.0% and 80.0% that were observed at these doses in a similarly designed
North American phase 3 trial that used the same flare definition [24]. Importantly, only 20–25% of patients treated with rilonacept reported flares, compared with more than half (56%) of placebo patients, and among these patients only 8.5% and 6.0% of patients in the R80 mg and R160 mg groups, respectively, had multiple flares relative to 32.9% with placebo (both \( P < 0.001 \)).

A dose–response relationship between 80 mg and 160 mg was not evident for the primary efficacy endpoint, but secondary efficacy endpoints based on the proportion of patients with flares or the number of flare days slightly favored the higher dose.

Both doses of rilonacept were generally well tolerated, with an incidence of overall AEs that was similar among the treatment groups. No treatment-related serious AEs were reported, and only two of the withdrawals due to AEs were considered by the investigator to be related to study treatment: one case of neutropenia and one case of gout exacerbation, both in the rilonacept 80 mg treatment group. Consistent with the previous study [24], injection site reactions, generally mild and not leading to withdrawals, were the most common treatment-related event (12.2% and 17.9% in the R80 mg and R160 mg groups, respectively) and accounted for much of the increase in treatment-related AEs in the rilonacept groups relative to placebo. Although 25–30% of patients developed generally low–titre ADA, overall there was no clear association of ADA with safety or efficacy.

The primary definition of GF that was used included items from recommendations in a recent consensus statement [27] and was enhanced by incorporation of patient-reported clinical characteristics that have been suggested to increase specificity [32]. When the flare definition used in a prior phase 2 study was applied, the significance of the results was comparable with those of the main analysis, suggesting robustness of rilonacept efficacy for flare prevention. However, risk reduction was lower than in the main analysis, supporting the proposition of greater specificity of the primary definition.

Although there has been concern that biologic agents such as rilonacept that target pro-inflammatory cytokines have the potential to interfere with response to infection [33], the proportions of patients reporting an infection were similar among treatment groups, and there were no reports of tuberculosis or other opportunistic infections. Nevertheless, maintaining an index of suspicion for infection in a patient treated with rilonacept would seem appropriate.

As the most widely used ULT in clinical practice [11], allopurinol was used to standardize ULT in this study. Across treatment groups, similar doses of allopurinol resulted in similar reductions in uric acid levels, indicating that rilonacept did not appear to alter the ability of allopurinol to reduce uric acid. While it could be argued that its sole use as a ULT represents a limitation of the study, since the increased risk of flares during the initiation of ULT appears to be related to reducing uric acid levels rather than the mechanism of action of the ULT [e.g. decreasing uric acid production (allopurinol and febuxostat)] vs increasing renal excretion of uric acid (probenecid)], the ability of rilonacept to decrease flare risk is not likely to be altered with the use of other ULTs. Another perceived limitation is that the starting dose of allopurinol, 300 mg daily (in patients with normal renal function), may potentially increase the risk of flares relative to a lower starting dose. However, since a 300 mg dose is commonly initiated in clinical practice, this study potentially provides a better real-world assessment of rilonacept for flare prevention than if a lower allopurinol dose had been initiated.

A strength of this study is the global scope and heterogeneity of the population. The relative consistency of these results with those of the North American phase 3 study in a more homogeneous population [24] demonstrates robustness and suggests that the efficacy and safety profiles are likely generalizable to the clinical setting.

In conclusion, this international phase 3 trial confirms and extends previous data supporting the efficacy and tolerability of IL-1 inhibition with rilonacept for GF prevention in patients initiating ULT. Efficacy was robust, whether calculated based on the number of flares per patient or the proportion of patients with flares. This ability to reduce the risk of flares may contribute to better disease control by increasing long-term adherence to ULT and suggests that rilonacept is likely to be of clinical benefit for some patients when incorporated into an appropriate gout management strategy.

**Rheumatology key messages**

- IL-1 inhibition represents a mechanism-based approach to reducing GFs as part of gout disease management.
- Rilonacept significantly reduced the occurrence of GFs associated with initiation of urate-lowering therapy.
- Rilonacept for GF prevention demonstrated an acceptable safety and tolerability profile.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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