Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial

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Summary

Background The Janus kinase 1 (JAK1) pathway has been implicated in the pathogenesis of psoriatic arthritis. We aimed to investigate the efficacy and safety of filgotinib, a selective JAK1 inhibitor, for the treatment of psoriatic arthritis.

Methods The EQUATOR trial was a randomised, double-blind, placebo-controlled phase 2 trial that enrolled adults from 25 sites in seven countries (Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine). Patients (aged ≥18 years) had active moderate-to-severe psoriatic arthritis (defined as at least five swollen joints and at least five tender joints) fulfilling Classification for psoriatic arthritis (CASPAR) criteria, active or a documented history of plaque psoriasis, and an insufficient response or intolerance to at least one conventional synthetic disease-modifying anti-rheumatic drug (csDMARD). Patients continued to take csDMARDs during the study if they had received this treatment for at least 12 weeks before screening and were on a stable dose for at least 4 weeks before baseline. Using an interactive web-based system, we randomly allocated patients (1:1) to filgotinib 200 mg or placebo orally once daily for 16 weeks (stratified by current use of csDMARDs and previous use of anti-tumour necrosis factor). Patients, study team, and sponsor were masked to treatment assignment. The primary endpoint was proportion of patients achieving 20% improvement in American College of Rheumatology response criteria (ACR20) at week 16 in the full analysis set (patients who received at least one dose of study drug), which was compared between groups with the Cochran-Mantel-Haenszel test and non-responder imputation method. This trial is registered with ClincalTrials.gov, number NCT03101670.

Findings Between March 9, and Sept 27, 2017, 191 patients were screened and 131 were randomly allocated to treatment (65 to filgotinib and 66 to placebo). 60 (92%) patients in the filgotinib group and 64 (97%) patients in the placebo group completed the study; five patients (8%) in the filgotinib group and two patients (3%) in the placebo group discontinued treatment. 52 (80%) of 65 patients in the filgotinib group and 22 (33%) of 66 in the placebo group achieved ACR20 at week 16 (treatment difference 47% [95% CI 30·2–59·6], p<0·0001). 37 (57%) patients who received filgotinib and 39 (59%) patients who received placebo had at least one treatment-emergent adverse event. Six participants had an event that was grade 3 or worse. The most common events were nasopharyngitis and headache, occurring at similar proportions in each group. One serious treatment-emergent adverse event was reported in each group (pneumonia and hip fracture after a fall), one of which (pneumonia) was fatal in the filgotinib group.

Interpretation Filgotinib is efficacious for the treatment of active psoriatic arthritis, and no new safety signals were identified.

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Introduction

Psoriatic arthritis is a chronic, inflammatory musculoskeletal disease that affects an estimated 30% of patients with psoriasis.[1,2] It is a heterogeneous disorder characterised by skin and nail disease, musculoskeletal manifestations (such as peripheral arthritis, axial disease, enthesitis, and dactylitis), and other extra-articular manifestations that can involve the bowel, eyes, or cardiovascular system.[1,3] In addition to joint pain, psoriatic arthritis can cause irreversible structural damage and disability,[4] leading to impaired daily functioning and reduced quality of life, with progressive worsening over time.[5] The economic burden of psoriatic arthritis is substantial, with the use of biological therapy being an important driver of direct[6] and indirect[7] costs.

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Research in context

Evidence before this study

We searched PubMed for English language articles published between Jan 1, 2000, and Aug 7, 2018, with "psoriatic arthritis" in the title. Of the 3990 articles found, 206 described clinical trials in adults. Among these were a number of potential treatments for psoriatic arthritis, including biological disease-modifying anti-rheumatic drugs (DMARDs)—such as anti-tumour necrosis factor (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), T-cell activation blockers (abatacept, alefacept), anti-interleukin (IL)-12 and IL-23 (ustekinumab), anti-IL-17 (brodalumab, ixekizumab, secukinumab), anti-IL-6 (clazakizumab), and anti-CD11a (efalizumab)—and targeted synthetic DMARDs, such as phosphodiesterase type-4 inhibitor (apremilast) and Janus kinase (JAK)1/3 inhibitor (tofacitinib). Treatment of psoriatic arthritis is complicated by the heterogeneous nature of the disorder, which is characterised by skin and nail disease, musculoskeletal manifestations (eg, peripheral arthritis, axial disease, enthesitis, and dactylitis) and other extra-articular manifestations that can involve the bowel, eyes, or cardiovascular system. The range of different targets investigated for psoriatic arthritis, and given that only a minority of patients achieve desired thresholds of response (such as minimal disease activity), suggests that there is a need for an effective treatment that addresses the multiple aspects of this disease.

Added value of this study

To our knowledge, the EQUATOR trial is the first double-blind, placebo-controlled phase 2 study investigating the efficacy and safety of a selective JAK1 inhibitor in psoriatic arthritis. In addition to the primary endpoint (20% improvement in American College of Rheumatology [ACR] response criteria [ACR20]), we investigated various secondary and exploratory endpoints, including those that assess peripheral arthritis, psoriasis, enthesitis, dactylitis, and overall psoriatic arthritis disease activity, and multiple patient-reported outcomes, such as physical functioning, pain, and fatigue. These data provide a detailed picture of the effect of filgotinib on several domains of psoriatic arthritis. The results show that selective inhibition of JAK1 by filgotinib is effective in treating signs and symptoms of active psoriatic arthritis across various disease manifestations. In addition, filgotinib has a favourable safety profile over 16 weeks of treatment, which is consistent with findings from trials of other rheumatologic conditions.

Implications of all the available evidence

The results of this study support the development of filgotinib for the treatment of psoriatic arthritis in patients with an inadequate response to conventional synthetic DMARDs. Larger, global phase 3 trials in psoriatic arthritis are needed to confirm these findings and to extend observations over a longer period of time. Additionally, the safety of selective JAK1 inhibition should be explored further to determine whether the theoretical advantage of increased selectivity translates into a better safety profile in clinical practice.

There are several therapeutic options available to patients with psoriatic arthritis, which target disease pathogenesis, relieve inflammation, improve health-related quality of life, or prevent long-term structural damage.[8,9] Such options include non-steroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate and leflunomide.[8] Many patients have an inadequate response to NSAIDs or csDMARDs, or both. There is now an increasing number of drugs available to treat patients with psoriatic arthritis, including necrosis factor (TNF) agents, other classes of biological disease-modifying DMARDs (bDMARDs), such as those targeting interleukin (IL)-17, IL-12 and IL-23, and orally administered targeted synthetic DMARDs (tsDMARDs), such as apremilast and tofacitinib.[8,9] Patient-specific disease characteristics, such as the presence of psoriasis and other comorbidities and patient preference for oral versus injectable treatments, might affect clinical decision making among these drugs.[10] Despite the increased number of therapeutic options for psoriatic arthritis, the absence or loss of response to existing therapies, and issues with safety and tolerability, can lead to discontinuation of treatment.[11] Therefore, there is still a need for conveniently administered agents with novel and targeted mechanisms of action and an acceptable safety profile that can effectively improve psoriatic arthritis outcomes.

Many cytokines contribute to the inflammation of skin and joints in those with psoriatic arthritis. The Janus kinase (JAK) family of tyrosine kinases (JAK1, JAK2, JAK3, and TYK2 in humans) are key signalling proteins that are vital for downstream intracellular transduction of cytokine-mediated signals.[12] Tofacitinib is a tsDMARD that inhibits JAK1 and JAK3 (and JAK2 to a lesser degree).[13] Tofacitinib has shown efficacy in patients with psoriatic arthritis who have an inadequate response to csDMARDs or anti-TNF therapy.[14,15] Drugs that block or reduce the activity of TNF and other cytokines in the IL-23 and IL-17 pathways have also shown efficacy in psoriatic arthritis.[16] JAK inhibitors can directly or indirectly block the activity of these cytokines. Reduction of the proinflammatory activity of multiple cytokines simultaneously by JAK inhibition is an attractive mechanism for the treatment of psoriatic arthritis.

Filgotinib is an oral JAK inhibitor that is different from previously characterised tsDMARDs because it is selective for JAK1 over other JAK family members.[17] Preclinical characterisation of filgotinib showed that it prevents

JAK1-mediated T helper cell 1 and 2 differentiation (driven by interferon γ and IL-4, respectively) and, to a lesser extent, T helper cell 17 differentiation (driven by transforming growth factor β, IL-23, IL-6, and IL-1β). Filgotinib reduced concentrations of inflammatory cytokines and chemokines in mouse and rat models of collagen-induced arthritis, and signs and symptoms of psoriatic arthritis in a mouse model.[17,18] In the phase 2b DARWIN1 and DARWIN2 trials, which included over 800 patients with rheumatoid arthritis treated for 24 weeks, filgotinib improved the signs and symptoms of active rheumatoid arthritis with significant responses at week 1.[19,20] Both trials met their primary endpoint of a significant improvement in American College of Rheumatology (ACR) 20 response rates at week 12 in patients treated with filgotinib (versus placebo) when given as monotherapy or in combination with methotrexate.[19,20] Treatment with filgotinib was also associated with rapid and sustained improvements in patient-reported outcomes up to week 24 compared with placebo.[21] Based on the strength of the phase 2 data in rheumatoid arthritis (and positive data in phase 2 studies in Crohn's disease[22] and active ankylosing spondylitis[23]), global phase 3 trials have started in patients with rheumatoid arthritis (NCT02873936, NCT02889796, NCT02886728, NCT03025308), Crohn's disease (NCT02914561, NCT02914600), and ulcerative colitis (NCT02914522, NCT02914535).

This phase 2 trial aimed to evaluate the efficacy of filgotinib on the signs and symptoms of active moderate-to-severe psoriatic arthritis in patients with an inadequate response or intolerance to csDMARDs. We also studied other features of psoriatic arthritis and additional signs and symptoms of peripheral arthritis, psoriasis, enthesitis, dactylitis, safety and tolerability, physical functioning, fatigue, and pain.

Methods

Study design and patients

In this double-blind, randomised, placebo-controlled, phase 2 study, patients were recruited at 25 sites in Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine (appendix p 2).

Eligible patients were 18 years or older, met classification criteria for psoriatic arthritis (CASPAR),[24] and had a diagnosis of psoriatic arthritis for at least 12 weeks before screening. Patients had active moderate-to-severe disease defined as at least five swollen joints (from a 66 swollen joint count) and at least five tender joints (from a 68 tender joint count), active or a documented history of plaque psoriasis, and an insufficient response or intolerance to at least one csDMARD. Patients continued to take csDMARDs during the study if they had received this treatment for at least 12 weeks before screening and were on a stable dose for at least 4 weeks before baseline.

Patients who had received treatment with more than one anti-TNF agent, or any alkylating agent, JAK inhibitor, or other investigational or approved biologic immune-modulator at any time, were excluded. Other key exclusion criteria were receipt of intramuscular or intravenous corticosteroids or intra-articular injection within 4 weeks before screening, receipt of oral steroids (>10 mg/day prednisone or equivalent), receipt of oral steroids (≤10 mg/day prednisone or equivalent) at a dose that was not stable for at least 4 weeks before baseline, or very poor functional status or inability to perform self-care. Full eligibility criteria are listed in the appendix (p 3).

The study conformed to Good Clinical Practice guidelines and Declaration of Helsinki Principles. The protocol was reviewed and approved by the central or individual independent ethics committees in each participating country. All patients provided written informed consent before participation. An external data monitoring committee reviewed progress throughout the study and did interim safety data reviews. A cardiovascular event adjudication committee reviewed and adjudicated major adverse cardiovascular events, including all fatalities. The study protocol and protocol amendments are included in the appendix (p 21, pp 8–11).

Randomisation and masking

Patients were enrolled by investigators and randomly assigned (1:1), by use of a computerised interactive web response system, to receive either filgotinib 200 mg

See Online for appendix

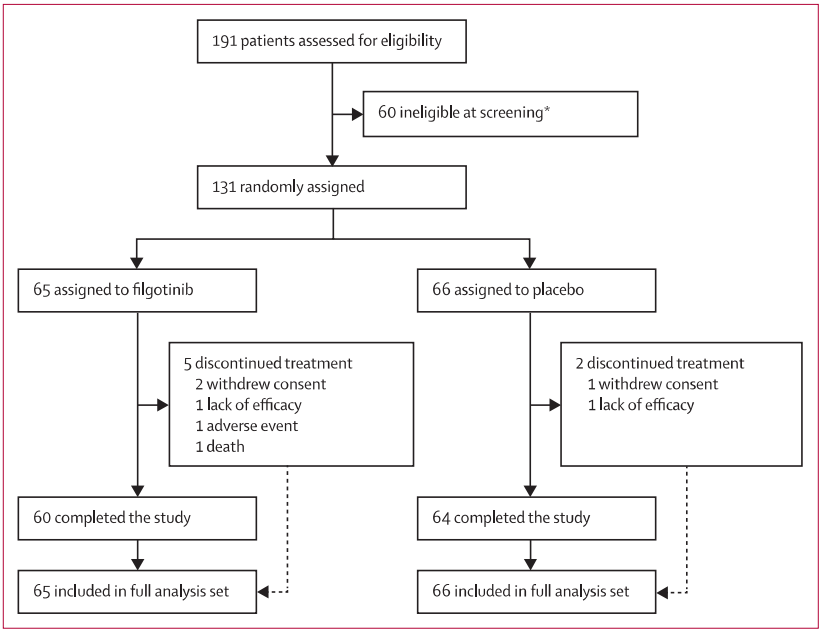

Figure 1: **Trial profile**

*Participants could be ineligible for more than one reason, the most common reasons being positive serology for HIV-1 or HIV-2, hepatitis B virus, or hepatitis C virus, or any history of infectious hepatitis from any cause (except hepatitis A; n=23); having laboratory values that were out of range (n=18); having untreated or inadequately treated latent tuberculosis infection (n=9); not having an insufficient response or intolerance to at least one conventional synthetic disease-modifying anti-rheumatic drug (n=3); and having unconfirmed active psoriatic arthritis (defined as five or more swollen joints and five or more tender joints; n=3).