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

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Summary

Background At present, biological disease-modifying anti-rheumatic drugs (DMARDs) are the only treatment recommended for patients with ankylosing spondylitis who have not responded to first-line treatment with non-steroidal anti-inflammatory drugs (NSAIDs). The TORTUGA trial investigated the efficacy and safety of filgotinib, an oral selective Janus kinase 1 (JAK1) inhibitor, for the treatment of patients with active ankylosing spondylitis.

Methods In this completed, randomised, double-blind, placebo-controlled, phase 2 trial, we enrolled adult patients from 30 sites in seven countries (Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine). Eligible patients had active ankylosing spondylitis and an inadequate response or intolerance to two or more NSAIDs. Patients were randomly assigned (1:1) with an interactive web-based response system to receive filgotinib 200 mg or placebo orally once daily for 12 weeks. Randomisation was stratified by current use of conventional synthetic DMARDs and previous receipt of anti-tumour necrosis factor therapy. The patients, study team, and study sponsor were masked to treatment assignment. The primary endpoint was the change from baseline in ankylosing spondylitis disease activity score (ASDAS) at week 12, which was assessed in the full analysis set (ie, all randomised patients who received at least one dose of study drug). Safety was assessed according to actual treatment received. This trial is registered with ClinicalTrials.gov, number NCT03117270.

Findings Between March 7, 2017, and July 2, 2018, 263 patients were screened and 116 randomly assigned to filgotinib (n=58) or placebo (n=58). 55 (95%) patients in the filgotinib group and 52 (90%) in the placebo group completed the study; three (5%) patients in the filgotinib group and six (10%) in the placebo group discontinued treatment. The mean ASDAS change from baseline to week 12 was –1·47 (SD 1·04) in the filgotinib group and –0·57 (0·82) in the placebo group, with a least squares mean difference between groups of –0·85 (95% CI –1·17 to –0·53; p<0·0001). Treatment-emergent adverse events were reported in 18 patients in each group, the most common being nasopharyngitis (in two patients in the filgotinib group and in four patients in the placebo group). Treatment-emergent adverse events led to permanent treatment discontinuation in two patients (a case of grade 3 pneumonia in the filgotinib group and of high creatine kinase in the placebo group). No deaths were reported during the study.

Interpretation Filgotinib is efficacious and safe for the treatment of patients with active ankylosing spondylitis who have not responded to first-line pharmacological therapy with NSAIDs. Further investigation of filgotinib for ankylosing spondylitis is warranted.

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Introduction

Ankylosing spondylitis is a chronic, immune-mediated disease that is characterised by inflammation of the sacroiliac joints and spine and a young age of onset (20–40 years).[1] Some patients also experience signs and symptoms in their peripheral joints (eg, synovitis, enthesitis, and dactylitis), as well as extra-articular manifestations, including anterior uveitis, psoriasis, and inflammatory bowel disease.[1,2] Ankylosing spondylitis has a worldwide prevalence of about 0·5% and is more common in men than in women.[1,3] The disease can be progressive and associated with chronic pain and functional impairment, leading to substantial loss of quality of life and work productivity.[4–6] Ankylosing spondylitis (also known as radiographic axial spondyloarthritis), together with non-radiographic axial spondyloarthritis, comprise the entire spectrum of axial spondyloarthritis.[1]

The primary aim of therapy for patients with ankylosing spondylitis is to maximise physical function and long-term health-related quality of life.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) are the recommended

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Research in context

Evidence before this study

We searched PubMed without language restrictions for articles published between Jan 1, 2000, and Aug 30, 2018, that contained the term "ankylosing spondylitis" in the title. Of 4849 articles retrieved, 376 described clinical trials in adults and reported on the safety and efficacy of several potential therapies for ankylosing spondylitis. These included biological disease-modifying anti-rheumatic drugs (DMARDs) that target tumour necrosis factor (TNF; adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), interleukin (IL)-17 (secukinumab), IL-12 and IL-23 (ustekinumab), IL-23 only (risankizumab), IL-6 (sarilumab and tocilizumab), and T-cell activation (abatacept), and targeted synthetic DMARDs, such as a phosphodiesterase type-4 inhibitor (apremilast) and a Janus kinase (JAK)1/3 inhibitor (tofacitinib). To date, the only DMARDs to be approved for ankylosing spondylitis have been anti-TNF agents and secukinumab. Several drugs, including abatacept, apremilast, risankizumab, ustekinumab, tocilizumab, and sarilumab, have not shown efficacy in patients with ankylosing spondylitis compared with placebo. Moreover, currently approved biological DMARDs require injection, which can be inconvenient, and patients with ankylosing spondylitis can experience a lack or loss of response to existing therapies. Therefore, new oral treatments with different modes of action and acceptable routes of administration are needed.

Added value of this study

To our knowledge, this is the first randomised, placebo-controlled, phase 2 study to show the efficacy of a selective JAK1 inhibitor in patients with ankylosing spondylitis, supporting use of selective JAK1 inhibition as a viable new treatment option for these patients. Filgotinib significantly reduced the ankylosing spondylitis disease activity score after 12 weeks compared with placebo in patients with active ankylosing spondylitis. We also assessed the safety and tolerability of filgotinib and its effect on several secondary endpoints, including signs and symptoms of ankylosing spondylitis, physical function, spinal mobility, peripheral arthritis, enthesitis, spinal and sacroiliac joint inflammation (assessed with MRI), fatigue, and quality-of-life measures. We showed that filgotinib was well tolerated over 12 weeks of treatment. The safety profile was consistent with findings from trials of filgotinib in patients with other conditions, including rheumatoid arthritis, Crohn's disease, and psoriatic arthritis.

Implications of all the available evidence

Selective inhibition of JAK1 by filgotinib is effective in treating active ankylosing spondylitis and can be considered for use in patients who have had an inadequate response to first-line pharmacological therapy with non-steroidal anti-inflammatory drugs. The findings of our study might ultimately lead to an increase in the number of treatment options with alternative mechanisms of action available for patients with ankylosing spondylitis. Confirmation of these findings in larger phase 3 trials with longer-term follow-up is needed. Such studies are also necessary to establish the long-term safety profile of selective JAK1 inhibition by filgotinib in patients with active ankylosing spondylitis.

first-line pharmacological therapy for patients with ankylosing spondylitis.[7] In patients with persistently high disease activity who have had an inadequate response to conventional therapy, the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) is recommended.[7] Current practice is to start with anti-tumour necrosis factor (TNF) therapy; secukinumab, an inhibitor of interleukin (IL)-17, is the only approved bDMARD for ankylosing spondylitis that has an alternative mechanism of action.[7]

The advent of anti-TNF drugs, and more recently of IL-17 inhibitors, represents an important step forwards in the treatment of ankylosing spondylitis. However, a lack or loss of response to existing therapies remains problematic for some patients, especially given the limited availability of drugs with different modes of action.[8] Therapies with alternative mechanisms of action, such as inhibitors of IL-6 or IL-23 pathways, have not shown efficacy.[9,10] Therefore, additional targeted drugs that can effectively improve ankylosing spondylitis outcomes with an acceptable safety profile are needed.

The IL-23/IL-17 immune axis has been implicated in the pathogenesis of ankylosing spondylitis.[11] Several cytokines, including those involved in the IL-23/IL-17 axis, signal through the Janus kinase (JAK) family of tyrosine kinases.[8] Intracellular inhibition of the JAK pathway, therefore, offers the potential to reduce the proinflammatory signalling implicated in the pathogenesis of ankylosing spondylitis.[12,13] Tofacitinib, a JAK inhibitor that preferentially inhibits signalling via JAK3 and JAK1, has shown efficacy in the treatment of patients with active ankylosing spondylitis, including favourable MRI changes; a phase 3 clinical trial of tofacitinib in patients with ankylosing spondylitis is currently recruiting (NCT03502616).[14] Filgotinib is an oral, selective JAK1 inhibitor currently under investigation for the treatment of several inflammatory diseases. Clinical studies have shown the therapeutic potential and acceptable safety profile of filgotinib in rheumatoid arthritis,[15–17] Crohn's disease,[18] and psoriatic arthritis.[19] Several global phase 3 trials of filgotinib are ongoing or have recently been completed, including in patients with rheumatoid arthritis (NCT02873936, NCT02889796, NCT02886728, and NCT03025308), Crohn's disease (NCT02914561 and NCT02914600), or ulcerative colitis (NCT02914522 and NCT02914535). We aimed to investigate the efficacy and safety of filgotinib compared with

placebo for the treatment of patients with ankylosing spondylitis.

Methods

Study design and patients

In this double-blind, randomised, placebo-controlled, phase 2 study, we recruited patients with ankylosing spondylitis at 30 sites in Belgium, Bulgaria, Czech Republic, Estonia, Poland, Spain, and Ukraine (appendix p 2). Eligible patients were aged 18 years and older with a diagnosis of ankylosing spondylitis that fulfilled the modified New York classification criteria (with sacroiliitis confirmed by radiography within 12 months of screening; appendix p 3).[20] Patients had to have active ankylosing spondylitis, defined as a Bath ankylosing spondylitis disease activity index (BASDAI) of 4 or higher and spinal pain scored as 4 or more at screening and baseline; a high-sensitivity C-reactive protein (CRP) concentration of 3·0 mg/L or higher at screening; and an inadequate response to two or more NSAIDs given at the therapeutic dose range for 4 weeks or more. Permitted conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) during the study (which must have been taken for at least 12 weeks before screening, with a stable dose for at least 4 weeks before baseline) were methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Use of one NSAID or a cyclooxygenase-2 inhibitor was permitted provided that the drug was used at a stable dose for at least 2 weeks before baseline. Previous use of one TNF inhibitor was allowed (capped at 30% of enrolled patients), with a minimum washout period before screening of 4 weeks (for etanercept), 8 weeks (for adalimumab, certolizumab pegol, and golimumab), or 12 weeks (for infliximab). Patients who were receiving high-potency opioid analgesics (methadone, hydromorphone, morphine, or oxycodone) at the time of the study or had received previous treatment with more than one TNF inhibitor, any alkylating agent, JAK inhibitors, or other investigational or approved biological drug at any time were excluded from the study. Full eligibility criteria are listed in the appendix (pp 4–6).

The study protocol was reviewed and approved by the central or individual independent ethics committee in each participating country. The study conformed to Good Clinical Practice guidelines and Declaration of Helsinki Principles. All patients provided written informed consent. An external data monitoring committee reviewed study progress and conducted interim reviews of safety data. A separate cardiovascular event adjudication committee reviewed major adverse cardiovascular events, as well as all deaths. The study protocol and protocol amendments are in the appendix (pp 7–10, 23–138).

Randomisation and masking

Patients were randomly assigned (1:1) with a computerised interactive web-response system, to receive filgotinib 200 mg or matching placebo once a day for 12 weeks. Randomisation was stratified by current use of csDMARDs and previous receipt of TNF inhibitor therapy. Drug kits were identified by a unique number. At baseline and weeks 4 and 8, the site staff contacted the interactive web-response system for the appropriate kit number to dispense; the kit contained the relevant study drugs for the next 4 weeks. Filgotinib and placebo were presented as visually identical, orally administered tablets. The patients, site staff, investigators, study team, and sponsor were masked to treatment assignment.

Procedures

Screening was done within 4 weeks before randomisation. Eligible patients were assessed at baseline (day 1), at weeks 1, 2, 4, 8, and 12, and at a follow-up visit at week 16 (or 4 weeks after the last dose of study drug). Patients were instructed to take their study drugs at the same time each day. Study assessments and their timings are summarised in the appendix (p 11).

See Online for appendix

Outcomes

The primary endpoint was change from baseline to week 12 in the ankylosing spondylitis disease activity score (ASDAS). ASDAS is a composite score of five domains: total back pain; patient's global assessment of disease activity; peripheral joint pain, joint swelling, or both; duration of morning stiffness; and CRP concentration. The components were scored on a scale of 0 (none) to 10 (very severe) by the patient, except for CRP concentration, which was assessed at a central laboratory. The composite score was calculated centrally by the sponsor. Investigators, study staff, and sponsors were unaware of post-baseline CRP concentrations.

Secondary endpoints included change over time in the ASDAS and in the proportion of patients achieving Assessment of SpondyloArthritis international Society response criteria (ASAS20, ASAS40, ASAS5/6, and ASAS partial remission; full definitions in appendix p 12). As secondary endpoints, we also assessed change over time in 44 tender joint counts and 44 swollen joint counts (assessed only in patients with one or more affected joints at baseline); the proportion of patients with clinically important improvement (decrease of ASDAS from baseline ≥1·1), major improvement (decrease of ASDAS from baseline ≥2·0), or inactive disease (ASDAS <1·3); individual components of the ASAS response criteria and the ASDAS; the BASDAI, including analysis of the individual items; the Bath ankylosing spondylitis functional index (BASFI); the Bath ankylosing spondylitis metrology index (BASMI); the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI score (assessment of 23 spinal discovertebral units) of the spine and of the sacroiliac joints; and scores on the Short-Form Health Survey (SF-36) and the Ankylosing Spondylitis Quality of Life questionnaire (ASQoL). Further information about the assessments of the secondary endpoints is provided in the appendix (p 12).