Original Article

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Efficacy and safety of filgotinib versus tocilizumab in active rheumatoid arthritis: A randomized, open-label, multicenter study with clinical and musculoskeletal ultrasound evaluation (TRANSFORM study)

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SUMMARY: Janus kinase (JAK) and interleukin-6 (IL-6) inhibitors are therapeutic options for patients with rheumatoid arthritis (RA) with inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); however, no randomized controlled trial has compared their efficacy and safety. Since both act through the JAK–signal transducer and activator of transcription pathway, a comparative evaluation is warranted. We conducted a prospective, randomized, open-label trial at 55 centers in Japan, randomizing patients with active RA despite csDMARD therapy in a 1:1 ratio to receive 200 mg/day filgotinib or subcutaneous tocilizumab as monotherapy; the primary endpoint was American College of Rheumatology (ACR) 50 at week 12, and secondary endpoints included clinical disease activity indices, musculoskeletal ultrasonography scores, patient-reported outcomes, and serum biomarkers through 52 weeks. Twenty-six patients were enrolled (13 per group) before study termination due to insufficient recruitment, and descriptive analyses were performed. At week 12, ACR50 was achieved in 38.5% (5/13) patients in the filgotinib group and 46.2% (6/13) in the tocilizumab group (risk difference: −7.69%; 95% confidence interval: −42.26 to 28.8). Both groups showed early and sustained improvements in disease activity from week 2. The improvement in patient global assessment scores was greater with filgotinib at week 2 but the difference diminished thereafter, and serum IL-6 level decreased with filgotinib but increased with tocilizumab. Four serious adverse events occurred with filgotinib, including infections and cardiac events. Because this study was underpowered and the analysis was descriptive, larger studies are needed to confirm these findings and define optimal use. (The study was registered in the Japan Registry of Clinical Trials (*https://jrct.niph.go.jp*) as jRCTs071200107 and in ClinicalTrials.gov as NCT05090410.)

Keywords: rheumatoid arthritis, filgotinib, JAK inhibitor, tocilizumab, musculoskeletal ultrasound, biomarker

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting the synovial joints (*1*). Uncontrolled disease activity in RA may lead to joint destruction and deformities, impairing the quality of life. Therefore, controlling the disease activity using a treat-to-target strategy is required to prevent joint destruction (*2*).

The standard initial treatment in patients with active RA is conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate (MTX); however, a considerable proportion of patients are refractory to treatment with csDMARDs. The choice of DMARDs in the second phase of treatment is crucial for patients with inadequate or intolerant csDMARDs (*3,4*). Biological DMARDs (bDMARDs), primarily used in the second phase after an inadequate response to csDMARDs, provide better clinical outcomes, including clinical remission in patients with RA. Recently, janus kinase (JAK) inhibitors have emerged as the second choice of treatment for patients with RA with an inadequate response or intolerance to csDMARDs (*3,4*).

Proinflammatory cytokines — overproduced and overexpressed — such as interleukin-6 (IL-6), bind to their receptors to activate the JAK-signal transducer and activator of transcription (STAT) signaling pathways, which are implicated in the pathogenesis of RA (*5*). JAK inhibitors effectively suppress disease activity by inhibiting the JAK-STAT signaling pathways.

Filgotinib is a preferential JAK1 inhibitor developed by Gilead (Foster City, CA, USA). In previous studies, approximately 50% of patients with RA receiving filgotinib achieved clinical remission after an inadequate response to csDMARDs (*6,7*). In addition, the effects of JAK inhibitors, including those of filgotinib, are non-inferior or superior to those of tumor necrosis factor (TNF) inhibitors in patients with active RA and an inadequate response to MTX (*7-10*); however, currently, no head-to-head comparison between JAK and IL-6 inhibitors has been performed. IL-6 inhibitors indirectly suppress the JAK-STAT pathway by inhibiting IL-6 signaling. IL-6 plays a key role in activating JAK1-dependent pathways (*5*). Among the currently available JAK inhibitors, filgotinib exhibits a relatively high selectivity for JAK1. Therefore, a comparative evaluation of the efficacy and safety profiles of filgotinib and IL-6 inhibitors is warranted.

Clinical remission can be achieved in a substantial proportion of patients with RA through the introduction of JAK inhibitors or bDMARDs. However, even in patients who achieve clinical remission, musculoskeletal ultrasonography (MSUS) may reveal residual synovitis, an important finding that predicts subsequent joint damage and clinical relapse (*11-14*). MSUS is widely used for evaluating disease activity in RA as a noninvasive, objective, relatively inexpensive, and repeatable imaging modality (*15,16*). Incorporating MSUS alongside clinical disease activity indices provides a more comprehensive assessment of treatment response at the joint level.

This study aimed to evaluate the non-inferiority of filgotinib monotherapy over IL-6 inhibitor monotherapy in patients with RA with an inadequate response to csDMARDs. In addition, we evaluated changes in disease activity using both MSUS and clinical disease activity indices to achieve a more precise assessment in this population. We also performed a comprehensive analysis of serum biomarkers, including a wide range of cytokines and chemokines. However, this study was terminated prematurely because patient enrollment did not progress sufficiently to achieve the target sample size. Given that the planned sample size was not reached, the prespecified non-inferiority analysis was not performed; instead, we limited the analyses to descriptive statistics and estimation-focused analyses.

2. Materials and Methods

2.1. Study design

This prospective, randomized, open-label, two-arm, and interventional clinical trial was conducted at 55 centers across Japan (Supplementary Table S1, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). The study was registered in the Japan Registry of Clinical Trials (*https://jrct.niph.go.jp*) as jRCTs071200107 and in ClinicalTrials.gov as NCT05090410. It was approved by the certified review board of Nagasaki University (reference number, CRB20-026). Written informed consent was provided by patients before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki (*17*), Clinical Trials Act (since February 2019), Act on the Protection of Personal Information and related regulatory notifications, and approved study protocol.

2.2. Changes from the previously published protocol

The study protocol has been previously published (*18*). This study was initiated on March 3, 2021. However, due to delays in enrolling the target number of patients, the study protocol was amended in November 2022—at which time 18 patients had enrolled—to facilitate further recruitment. Specifically, 1) the inclusion criteria were changed from patients with an inadequate response to MTX to patients with an inadequate response to csDMARDs; 2) in the IL-6 inhibitor group, initially including only subcutaneous tocilizumab, the options were expanded to include intravenous tocilizumab and subcutaneous sarilumab; 3)

medications not permitted for previous use were revised from all JAK inhibitors and IL-6 inhibitors to filgotinib only; and 4) the week 8 study visit was excluded. These protocol amendments may have influenced some results of the study, compared to the prospective results with the initial plan. However, the study was continued as a randomized trial, maintaining its primary objective of comparing the efficacy of filgotinib and IL-6 inhibitors in patients with active RA. Given this consistency in the main goal of the study, we decided to proceed the trial with the revised protocol. This manuscript presents the final trial report of the study previously described in the published protocol paper, including the results obtained with the original as well as the revised protocols. The final revised methods are described below.

2.3. Patients

The inclusion criteria were as follows: 1) age ≥ 18 years; 2) diagnosis of RA based on the American College of Rheumatology (ACR) /European League Against Rheumatism 2010 RA Classification Criteria (*19*); 3) at least moderate disease activity, defined as a Disease Activity Score 28 (DAS28) – erythrocyte sedimentation rate (ESR) ≥ 3.2 at eligibility evaluation; 4) history of csDMARDs treatment for ≥ 8 weeks before providing consent, including ≥ 4 weeks at the same doses of csDMARDs; and 5) ability and willingness to provide written informed consent and comply with the study protocol requirements.

The exclusion criteria were as follows: 1) concurrent use of a glucocorticoid equivalent to > 5 mg/day of prednisolone; 2) contraindication for filgotinib, tocilizumab or sarilumab; 3) previous use of filgotinib; 4) treatment with a glucocorticoid and csDMARD and change of dose within 4 weeks before providing consent; 5) treatment with a bDMARD or a biosimilar DMARD (such as infliximab, biosimilar of infliximab, adalimumab, biosimilar of adalimumab, golimumab, certolizumab pegol, or abatacept) within 8 weeks before providing consent; 6) treatment with a TNF inhibitor (such as etanercept or biosimilar of etanercept) within 4 weeks before providing consent; 7) use of a prohibited drug or therapy, other than the agents listed, within 4 weeks before providing consent; 8) complications causing musculoskeletal disorders other than RA (such as ankylosing spondyloarthritis, reactive arthritis, psoriatic arthritis, crystal-induced arthritis, systemic lupus erythematosus, systemic sclerosis, inflammatory myopathy, or mixed connective tissue disease); 9) current pregnancy, breastfeeding, or nonadherence to a medically approved contraceptive regimen during and 12 months after the study period; or 10) inappropriateness for study inclusion as determined by the investigator.

2.4. Intervention

Patients were randomized in a 1:1 ratio to receive either 200 mg/day filgotinib or an IL-6 inhibitor (intravenous tocilizumab 8 mg/kg every 4 weeks, subcutaneous tocilizumab 162 mg/biweekly, or subcutaneous sarilumab 200 mg/biweekly) switched from csDMARDs throughout the study period. Randomization was performed using the minimization method, stratified by RA disease duration (< 2 years and ≥ 2 years), disease activity (DAS28-ESR > 5.1 and ≤ 5.1), and body weight (< 60 kg and ≥ 60 kg). Investigators used an electronic data capture (EDC) system (DATATRAK EDC; Fountayn, Datatrak International, Inc., Beachwood, OH, USA), built by an independent data manager, to assign patients to the filgotinib or IL-6 inhibitor group in a 1:1 ratio using computer-generated random numbers automatically.

Patients assigned to the IL-6 inhibitor group received one of the IL-6 inhibitors — intravenous tocilizumab, subcutaneous tocilizumab, or subcutaneous sarilumab — based on the judgment of the study investigator. Patients with a moderate renal dysfunction (estimated glomerular filtration rate 30–60 mL/min/1.73 m^2) were administered 100 mg/day filgotinib. All patients continued receiving the same doses of glucocorticoids that they were receiving before providing consent throughout the study period. During the study period, the following treatments were prohibited: administration of a bDMARD (except tocilizumab and sarilumab) or JAK inhibitor (except for filgotinib); concomitant use of an immunosuppressant (azathioprine, cyclophosphamide, or cyclosporine) or oral glucocorticoids equivalent to ≥ 5 mg/day of prednisolone, in addition to intra-articular glucocorticoid injections in joints; and nonsteroidal anti-inflammatory drug suppositories. During the study period, the dose of any oral nonsteroidal anti-inflammatory drug was modified only within the range of its approved doses in Japan. Although csDMARDs were prohibited, their addition was allowed if clinical disease activity worsened after 12 weeks. For patients receiving subcutaneous tocilizumab, the administration frequency was adjusted from 162 mg every 2 weeks to once weekly. The flowchart of participant selection is shown in Supplementary Figure S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*).

2.5. Patient discontinuation criteria

Participants could be withdrawn prematurely for any of the following reasons: 1) in the filgotinib group, interruption of filgotinib administration for > 7 consecutive days; 2) in the IL-6 inhibitor group, discontinuation of IL-6 inhibitor administration for ≥ 2 consecutive scheduled injections; 3) participant request to withdraw from the trial; 4) participant request to change or discontinue the assigned treatment;

5) adverse events that made continued participation inadvisable; 6) pregnancy; or 7) at the discretion of the principal investigator if continued participation was considered detrimental to the well-being of the participant.

Participants who discontinued were assessed at the time of discontinuation whenever possible, provided the participant cooperated.

2.6. Outcome measurements

Study visits were conducted at baseline and 2, 4, 12, 24, 36, and 52 weeks after the administration of filgotinib or the IL-6 inhibitor. These assessments are shown in Supplementary Table S2 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). Clinical physicians were blinded to the results of the joint assessments that were performed using MSUS.

Clinical disease activity was evaluated by each attending physician (Japan College of Rheumatology-certified rheumatologists) based on the values of the ACR core set, DAS28-ESR, DAS28-C reactive protein (CRP) (*20*), clinical disease activity index (CDAI), and simplified disease activity index (SDAI) levels. For tender (68) and swollen joints (66), improvement in three of the following five assessments defined the ACR response: 1) patient's global assessment, 2) patient's pain assessment, 3) evaluator's global assessment, 4) Health Assessment Questionnaire-Disability Index (HAQ-DI) (*21*), and 5) CRP or ESR. ACR response rates were defined as ACR20, ACR50, and ACR70 responses, based on an improvement of ≥ 20%, ≥ 50%, or ≥70%, respectively. Each patient's global and pain assessments, and the evaluator's global assessment, were performed on a 0–100-mm visual analog scale (VAS). Patient-reported outcomes (PROs) were evaluated using the duration and severity of morning stiffness, EuroQol 5 dimensions 5-level (EQ-5D-5L), and functional assessment of chronic illness-fatigue (FACIT-F).

Participants underwent MSUS at baseline and 4, 12, 24, 36, and 52 weeks, performed by a Japan College of Rheumatology-certified sonographer. A systematic multiplanar grayscale (GS) and power Doppler (PD) examination of each patient's joint was performed using a multifrequency linear transducer (12–24 MHz). A PD was used depending on the most sensitive Doppler modality on the individual machines. Doppler settings were adjusted at each hospital according to the published recommendations (*22*). During the study, no MSUS settings changes or software upgrades occurred. Joint synovitis was assessed using MSUS in the dorsal views of 22 joints: bilateral wrist, 1st–5th metacarpophalangeal (MCP), interphalangeal (IP), and 2nd–5th proximal interphalangeal (PIP) joints. Each joint was scored for GS and PD on a scale of 0 to 3 in a semiquantitative manner. The sum of the GS or PD scores was considered as the total GS or PD score, respectively. We also assessed the Global Outcome Measures in Rheumatology-European League Against Rheumatism Synovitis Score (GLOESS). GLOESS has been combined with synovial hypertrophy, as shown by GS and PD (*23*).

Radiographic imaging of the bilateral hands (posteroanterior view) and feet (anteroposterior view) was conducted. Trained Japan College of Rheumatology-certified rheumatologists (T.K. and T.S.) evaluated joint damage progression based on the van der Heijde-modified total Sharp score (vdH-mTSS) method, as previously described (*24*), including 16 areas in each hand for erosions and 15 areas for joint space narrowing (*25*).

2.7. Biomarker measurements

Serum concentrations of the following biomarkers were measured: rheumatoid factor (RF) was determined using a latex agglutination turbidimetric immunoassay (LZ test "Eiken" RF) (Eiken Chemical Co., Ltd., Tokyo, Japan). Anti-cyclic citrullinated peptide (CCP) antibodies were quantified using a chemiluminescent immunoassay (STACIA MEBLux test CCP) (Medical & Biological Laboratories Co., Ltd., Tokyo, Japan). Matrix metalloproteinase-3 levels were measured using a latex turbidimetric immunoassay (Panaclear metalloproteinase-3 "Latex") (Sekisui Medical Co., Ltd., Tokyo, Japan).

Multiplex cytokine/chemokine bead assays were performed using diluted serum supernatants and the MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel (Merck KGaA, Darmstadt, Germany). Bio-Plex Pro Human Cytokine Assays (Bio-Rad, Hercules, CA, USA) were performed using a Bio-Plex MAGPIX™ Multiplex Reader (Bio-Rad) according to the manufacturer's instructions.

The cytokines/chemokines measured by the bead panel include IL-1α, IL-1β, IL-1 receptor antagonist, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IL-17F, IL-18, IL-22, IL-27, interferon-gamma (IFN-γ), IFN-α2, C-X-C motif chemokine ligand 1 (CXCL1) (growth-related oncogene), granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, C-X3-C motif chemokine ligand 1 (CX3CL1) (fractalkine), flt-3 ligand, fibroblast growth factor-2, eotaxin, epidermal growth factor, vascular endothelial growth factor, platelet-derived growth factor-AA, soluble CD40 ligand, TNF-α, TNF-β, transforming growth factor-α, C-C motif chemokine ligand (CCL)4 (macrophage inflammatory protein-1β), CCL3 (macrophage inflammatory protein-1α), CCL22 (macrophage-derived chemokine), CCL7 (monocyte chemotactic protein-3), CCL2 (monocyte chemotactic protein-1), CXCL10 (IFN-γ-inducible protein-10), vascular cell adhesion

molecule-1, and intercellular adhesion molecule-1. Serum IL-6 and TNF-α levels were measured using specific enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA).

2.8. Study endpoints

The primary endpoint was the ACR50 response at week 12. The secondary endpoints of this study were as follows: 1) ACR responses: ACR50 at weeks 2, 4, 24, 36, and 52, and ACR20 and ACR70 at weeks 2, 4, 12, 24, 36, and 52; 2) clinical disease activity: change from baseline in CDAI, SDAI, DAS28-ESR, and DAS28-CRP at weeks 2, 4, 12, 24, 36, and 52; 3) MSUS scores: change from baseline in total PD and GS scores, and GLOESS at weeks 4, 12, 24, 36, and 52; 4) PROs: change from baseline in patient global and pain VAS scores, HAQ-DI, EQ-5D-5L, FACIT-F, and morning stiffness (duration and activity) at weeks 2, 4, 12, 24, 36, and 52; 5) radiographic assessment: change from baseline in vdH-mTSS at weeks 24 and 52; and 6) biomarkers: change from baseline in serum biomarker levels at weeks 2, 4, 12, 24, 36, and 52. In addition, safety endpoints were adverse events (AEs) and study discontinuation rates.

2.9. Statistical analysis

The sample size was determined to ensure a statistical power of 0.80 for the primary analysis. Specifically, simulation data were generated through 4,000 random samplings from a binomial distribution B (n, p) (two samples, 2,000 pairs), and the same analytical procedure as in the primary analysis was applied to these data. The minimum value of n for which non-inferiority was demonstrated in at least 1,600 of 2,000 trials (≥ 80%) was selected. Based on previous research, the success probability p was fixed at 0.40 for both groups (*26*). This simulation indicated that 176 patients per group were required for adequate power. Considering an estimated dropout rate of approximately 12% at the time of primary endpoint assessment, the target enrollment was set at 200 patients per group.

Given that the study did not reach the target sample size, the prespecified non-inferiority analysis was deemed inappropriate. Therefore, a confirmatory hypothesis test was not performed, and analyses focused on estimation rather than hypothesis testing. For the primary endpoint, risk differences and risk ratios with 95% confidence intervals (CIs) were calculated. The 95% CI for the risk difference was estimated using the Mee method (*27*), and that for the risk ratio was estimated using a continuity-corrected approach. For continuous outcomes, medians with interquartile ranges were reported. The probability of study continuation in each group was illustrated using Kaplan–Meier curves. The safety analysis set included all patients who received ≥ 1 dose of the study drug. The full analysis set was defined as all patients in the safety analysis set, randomized to either treatment group, and who had available baseline data for the ACR core set. All statistical analyses were performed using R version 4.4.0 (R Project for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patients' characteristics

Between March 3, 2021, and December 4, 2023, the target sample size was not achieved; 26 patients were enrolled and randomized (13 and 13 to filgotinib and IL-6 inhibitor groups, respectively). In the IL-6 inhibitor group, all patients received subcutaneous

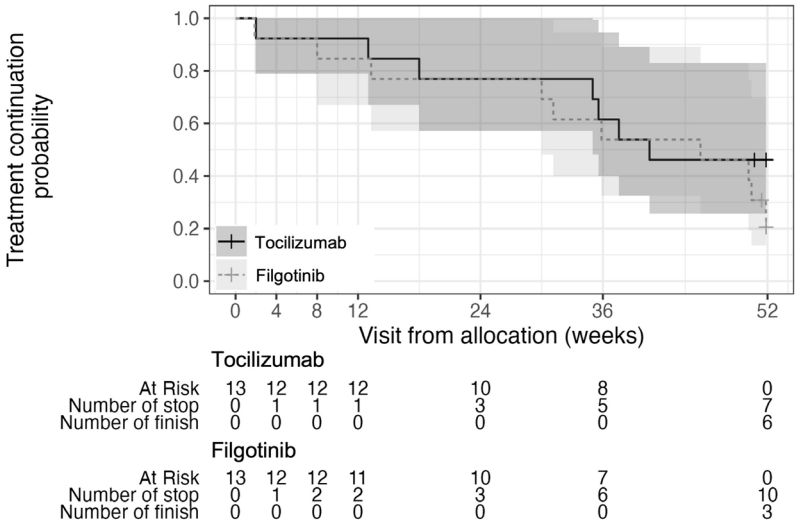

Figure 1. Treatment continuation over 52 weeks. Kaplan–Meier curves show the probability of continuing the assigned study treatment after randomization in the filgotinib (*n* = 13) and tocilizumab (*n* = 13) groups. Shaded areas indicate 95% confidence intervals.

Table 1. Baseline characteristics

Characteristics	Tocilizumab (*n* = 13)	Filgotinib (*n* = 13)
Age (years)[a]	65 (60, 71)	74 (63, 78)
Female[b]	13 (100)	10 (76.9)
Height (cm)[a]	153.6 (152.1, 154.5)	152.6 (150.0, 158.5)
Weight (kg)[a]	51 (46, 63)	48 (42, 65)
Disease duration (years)[a]	4 (0, 13)	2 (0, 5)※
Rheumatoid factor positive history[b]	12 (92.3)	11 (84.6)
Baseline rheumatoid factor (IU/mL)[a]	49 (30, 83)	76 (32, 191)
Anti CCP antibody-positive history[b]	12 (92.3)	8 (61.5)
Baseline anti CCP antibody (U/mL)[a]	92 (15, 143)	12 (6, 373)
Smoking history[b]		
Former smoker	1 (7.7)	2 (15.4)
Current smoker	1 (7.7)	1 (7.7)
Current csDMARDs		
Type of csDMARDs[b]		
MTX	12 (92.3)	13 (100)
Non-MTX	1 (7.7)	0 (0)
MTX dose (mg/week)[a]	9 (7.5, 10.5)※	8 (8, 12)
Pretreatment for rheumatoid arthritis		
Biologics agents[b]	5 (38.5) Infliximab 1, adalimumab 1, etanercept 1, tocilizumab 1, and otilimab 1	3 (23.1) Infliximab 2, and ozoralizumab 1
Concomitant medications		
Glucocorticoid[b]	2 (15.4)	0 (0)
Disease activity[a]		
Tender joint count of 68 joints	8 (7, 13)	8 (3, 22)
Swollen joint count of 66 joints	7 (3, 10)	7 (3, 9)
ESR (mm/h)	40 (12, 44)	38 (17, 66)
CRP (mg/dL)	0.53 (0.12, 0.94)	0.97 (0.5, 1.81)
CDAI	20.8 (18.6, 33)	21.5 (17.7, 28.7)
SDAI	22.2 (18.7, 33)	22.6 (18, 31.3)
DAS28-ESR	5.18 (4.72, 5.94)	5.35 (3.98, 6.33)
DAS28-CRP	4.51 (3.77, 4.93)	4.66 (3.57, 5.57)
Total GS score	13 (8, 15)	12 (7, 24)
Total PD score	5 (1, 10)	7 (4, 19)
GLOESS	14 (9, 15)	13 (7, 29)
Patient global VAS (scale: 0–100)	51.5 (40, 68)	52.9 (23, 80)
Patient pain VAS (scale: 0–100)	53.5 (40, 73)	53.8 (22.1, 80)
Morning stiffness severity (scale: 0–100)	50 (39, 67)	63 (15, 85)
Duration of morning stiffness, minutes	25 (10, 30)	90 (10, 360)
EQ-5D-5L	0.749 (0.636, 0.844)	0.758 (0.653, 0.895)
FACIT-F	39 (34, 47)	38 (33, 41)
HAQ-DI	1 (0.5, 1.25)	0.625 (0.375, 1.62)
vdH-TSS	8.5 (4.5, 31.5)	14 (5, 24.5)

Values are presented as median (IQR) for continuous variables[a] and *n* (%) for categorical variables[b]. CCP, cyclic citrullinated peptide; CDAI,Clinical Disease Activity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; EQ-5D-5L, EuroQol 5 Dimension 5-Level; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GLOESS, Global the global Outcome Measures in Rheumatology-European League Against Rheumatism Synovitis Score; GS, grayscale; HAQ-DI, Health Assessment Questionnaire-Disability Index; IQR, interquartile range; MTX, methotrexate; PD, power Doppler; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; VAS, Visual Analog Scale; vdH-TSS, van der Heijde-modified total Sharp score. ※*n* = 12 (1 missing).

tocilizumab 162 mg/biweekly. Therefore, this group would hereafter be referred as the tocilizumab group. All 26 patients were included in both the full and safety analyses sets. During the follow-up period, 10 patients in the filgotinib group and 7 in the tocilizumab group discontinued the study (Figure 1 and Supplementary Figure S1, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). In the filgotinib group, the reasons for discontinuation were AEs in two patients, withdrawal of consent in two, and the investigator's judgment of inappropriateness for study continuation in six. In the tocilizumab group, one patient discontinued due to withdrawal of consent, one due to a violation of inclusion/exclusion criteria, and five due to the investigator's judgment of inappropriateness for study continuation. After week 12, one patient in the tocilizumab group received iguratimod as rescue therapy. Eighteen patients were

enrolled before the amendment of the study protocol (ddetails are provided in Section 2.2. Changes from the previously published protocol), and eight patients were enrolled after the amendment.

Baseline characteristics were similar between the two groups, with some differences (Table 1). The median age was 74 and 65 years and the proportion of females was 76.9 and 100% in the filgotinib and tocilizumab groups, respectively. Most patients in both groups were positive for RF, and anti-CCP positivity was observed in 61.5 and 92.3% of patients in the filgotinib and tocilizumab groups, respectively. All patients in the filgotinib group and 12 patients (92.3%) in the tocilizumab group were receiving MTX at baseline. The remaining patients in the tocilizumab group, who were not receiving MTX, were treated with bucillamine 100 mg/day and tacrolimus 1 mg/day. Glucocorticoids were concomitantly administered in two patients (15.4%) in the tocilizumab group (prednisolone 5 and 3 mg/day, respectively). No patient had prior exposure to JAK inhibitors, whereas one patient in the tocilizumab group had previously received tocilizumab.

3.2. Primary endpoint

For the primary endpoint, an ACR50 response at week 12 was achieved in 38.5% (5/13) of patients in the filgotinib group and 46.2% (6/13) of those in the tocilizumab group. The risk difference was −7.69% (95% CI, −42.26–28.8), and the risk ratio was 0.83 (95% CI, 0.36–1.98) (Table 2).

3.3 Secondary endpoints

The responses for ACR20, ACR50, and ACR70 at each assessment time point are presented in Table 2. No apparent differences were observed in the achievement proportions between the filgotinib and tocilizumab groups.

Disease activity measures (CDAI, SDAI, DAS28-ESR, and DAS28-CRP) decreased from baseline to as early as week 2 in both groups (Figure 2 and Supplementary Table S3, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). CDAI remission (CDAI ≤ 2.8) was achieved in 7.7% (1/13) of patients in the filgotinib group and 0% (0/13) in the tocilizumab group at week 2. At week 4, CDAI remission was observed in 7.7% (1/13) of patients in both groups. At week 12, CDAI remission rates were 38.5% (5/13) in the filgotinib group and 23.1% (3/13) in the tocilizumab group. At week 24, CDAI remission was achieved in 15.4% (2/13) of patients in the filgotinib group and 30.8% (4/13) in the tocilizumab group. However, no apparent between-group differences were observed in the estimated values at any time point (Supplementary Table S4, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*).

Similarly, MSUS scores (total GS score, total PD score, and GLOESS) decreased from baseline, and their median values, respectively, at week 52 were 0 in both groups, although the number of evaluable patients at this time point was limited (filgotinib group, n = 3; tocilizumab group, n = 6) (Figure 2). Notably, reductions in these scores were observed from week 4 in the filgotinib group, but from week 12 in the tocilizumab group (Supplementary Table S3, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). However, no apparent between-group differences were observed at any time point (Supplementary Table S4, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*).

PROs (patient global VAS score, patient pain VAS

Table 2. Proportions of patients achieving ACR20/50/70 responses

	Filgotinib (n = 13)	Tocilizumab (n = 13)	Risk Difference (95% CI)	Risk Ratio (95% CI)
ACR20				
Week 2	5/13 (38.5)	6/13 (46.2)	-7.69 (-42.26, 28.80)	0.83 (0.36, 1.98)
Week 4	9/13 (69.2)	6/13 (46.2)	23.08 (-14.58, 54.95)	1.50 (0.76, 2.81)
Week 12	9/13 (69.2)	10/13 (76.9)	-7.69 (-40.37, 26.45)	0.90 (0.58, 1.42)
Week 24	8/13 (61.5)	9/13 (69.2)	-7.69 (-41.56, 27.94)	0.89 (0.52, 1.53)
Week 52	3/13 (23.1)	6/13 (46.2)	-23.08 (-54.37, 13.49)	0.50 (0.19, 1.55)
ACR50				
Week 2	2/13 (15.4)	0/13 (0.0)	15.38 (-9.27, 42.23)	Inf (0.26, 94.69)
Week 4	4/13 (30.8)	4/13 (30.8)	0.00 (-34.26, 34.26)	1.00 (0.34, 2.91)
Week 12	5/13 (38.5)	6/13 (46.2)	-7.69 (-42.26, 28.80)	0.83 (0.36, 1.98)
Week 24	7/13 (53.8)	8/13 (61.5)	-7.69 (-42.26, 28.80)	0.87 (0.47, 1.65)
Week 52	3/13 (23.1)	5/13 (38.5)	-15.38 (-47.59, 20.08)	0.60 (0.21, 1.93)
ACR70				
Week 2	0/13 (0.0)	0/13 (0.0)	0.00 (-22.81, 22.81)	0.00 (0.00, Inf)
Week 4	2/13 (15.4)	2/13 (15.4)	0.00 (-30.33, 30.33)	1.00 (0.21, 4.87)
Week 12	4/13 (30.8)	4/13 (30.8)	0.00 (-34.26, 34.26)	1.00 (0.34, 2.91)
Week 24	4/13 (30.8)	4/13 (30.8)	0.00 (-34.26, 34.26)	1.00 (0.34, 2.91)
Week 52	3/13 (23.1)	5/13 (38.5)	-15.38 (-47.59, 20.08)	0.60 (0.21, 1.93)

Values are presented as number (%). ACR, American College of Rheumatology; CI, confidence interval.

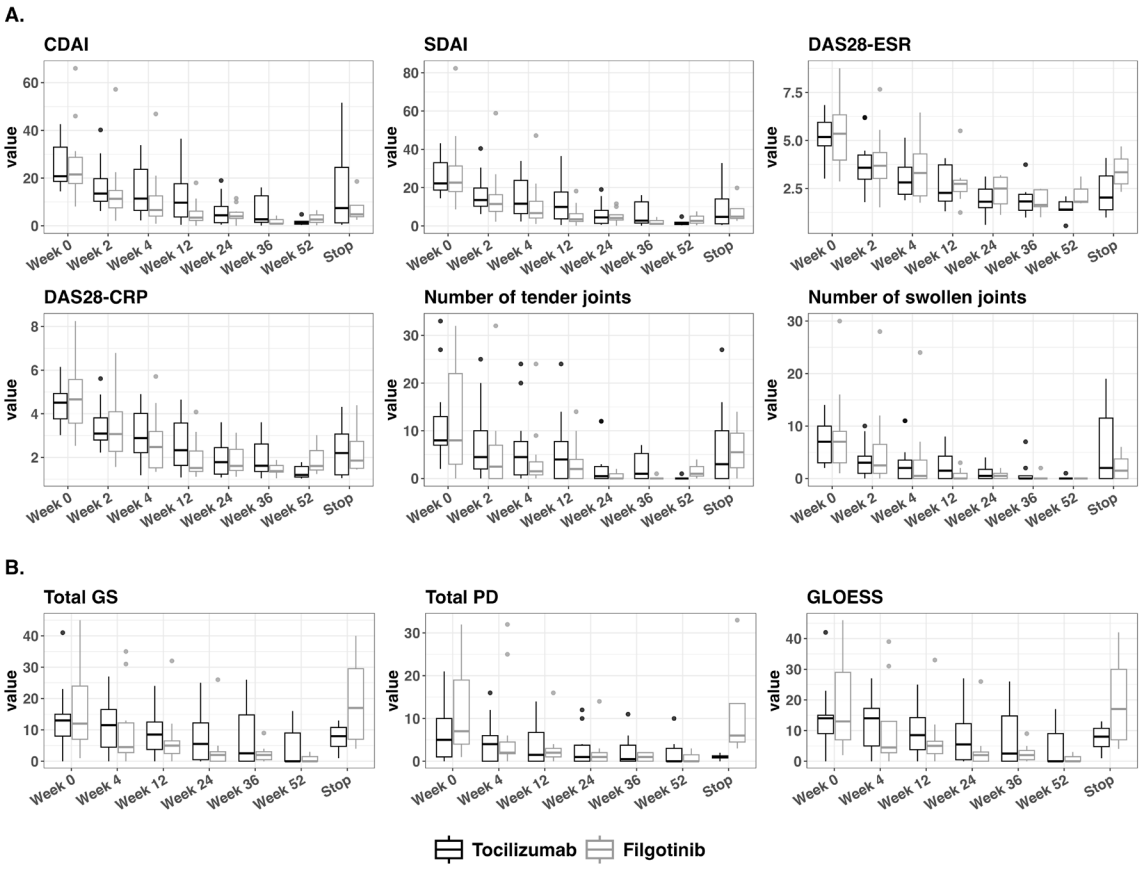

Figure 2. Values in clinical disease activity and MSUS during the study period. A. clinical disease activity and **B**. musculoskeletal ultrasound scores. Horizontal bar: median; boxes: 25th and 75th percentiles; bars: 5th and 95th percentiles. Black box/bar indicates the tocilizumab group, and gray box/bar indicates the filgotinib group. The numbers of evaluable patients at each time point were as follows. In **A**, in the tocilizumab group, the numbers were identical for CDAI, tender joint count, and swollen joint count: week 0, *n* = 13; week 2, n = 12; week 4, n = 12; week 12, n = 12; week 24, n = 10; week 36, n = 8; week 52, n = 6; and stop, n = 7. For SDAI, DAS28-ESR, and DAS28-CRP in the tocilizumab group, the numbers were week 0, n = 13; week 2, n = 12; week 4, n = 12; week 12, n = 12; week 24, n = 10; week 36, n = 8; week 52, n = 6; and stop, n = 6. In the filgotinib group, the numbers were identical across all assessments: week 0, n = 13; week 2, n = 12; week 4, n = 12; week 12, n = 11; week 24, n = 10; week 36, n = 7; week 52, n = 3; and stop, n = 4. In **B**, the numbers in the tocilizumab group were week 0, n = 13; week 4, n = 12; week 12, n = 12; week 24, n = 10; week 36, n = 8; week 52, n = 6; and stop, n = 4, whereas those in the filgotinib group were week 0, n = 13; week 4, n = 12; week 12, n = 11; week 24, n = 9; week 36, n = 7; week 52, n = 3; and stop, n = 4. Abbreviations: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; GLOESS, Global OMERACT-EULAR Synovitis Score; GS, grayscale; PD, power Doppler; SDAI, Simplified Disease Activity Index; MSUS, musculoskeletal ultrasound scores.

score, morning stiffness severity, duration of morning stiffness, EQ-5D-5L, FACIT-F, and HAQ-DI) also showed early improvement in both groups (Figure 3 and Supplementary Table S3, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). At week 2, the patient global VAS scores were lower in the filgotinib group than in the tocilizumab group (− 20.96; 95% CI, − 40.16 – −1.76); however, this difference was not observed after week 4 (Table 3). In addition, other PROs showed no apparent differences between the groups at any time point (Table 3).

Changes in the vdH-mTSS were minimal, with a median change from baseline of 0 at both weeks 24 and 52 in each group (Supplementary Table S3, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*).

Supplementary Figure S2 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*) shows the changes in serum cytokine and chemokine biomarkers. Serum IL-6 levels showed a sustained decrease from week 2 to week 52 in the filgotinib group, whereas the levels increased in the tocilizumab group during the same period. Moreover, from week 2, lower serum IL-6 levels were observed in the filgotinib group than in the tocilizumab group. Other than serum IL-6, no biomarkers showed consistent changes from baseline or any clear differences between the treatment groups (Supplementary Table S5, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*).

3.4. Subgroup analysis

The results of ACR20, ACR50, and ACR70 responses stratified by the randomization factors — disease duration of RA (< 2 years and ≥ 2 years), disease activity (DAS28-ESR > 5.1 and ≤ 5.1), and body weight (<

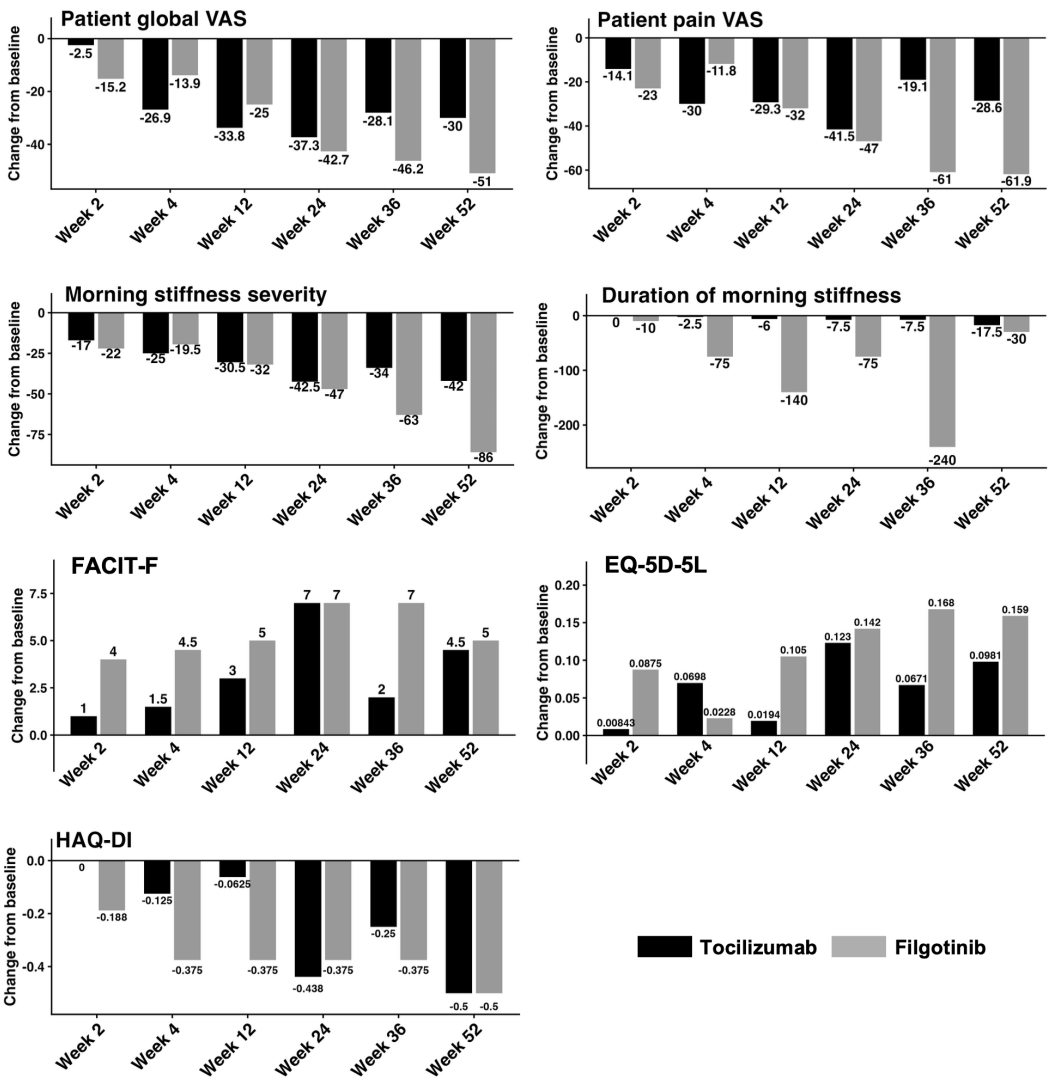

Figure 3. Changes in patient-reported outcomes during the study period. Bar graphs show the median change from baseline at each time point. The black bar indicates the tocilizumab group, and the gray bar indicates the filgotinib group. The numbers of evaluable patients at each time point were as follows. In the tocilizumab group, the numbers were identical for patient global VAS scores, patient pain VAS scores, and HAQ-DI: week 2, *n* = 12; week 4, n = 12; week 12, n = 12; week 24, n = 10; week 36, n = 8; week 52, n = 6; and stop, n = 7. For morning stiffness severity, duration of morning stiffness, FACIT-F, and EQ-5D-5L in the tocilizumab group, the numbers were week 2, n = 12; week 4, n = 12; week 12, n = 12; week 24, n = 10; week 36, n = 8; week 52, n = 6; and stop, n = 6. In the filgotinib group, the numbers were identical for patient global VAS scores, patient pain VAS scores, morning stiffness severity, duration of morning stiffness, FACIT-F, and HAQ-DI: week 2, n = 12; week 4, n = 12; week 12, n = 11; week 24, n = 10; week 36, n = 7; week 52, n = 3; and stop, n = 4. For EQ-5D-5L in the filgotinib group, the numbers were week 2, n = 11; week 4, n = 12; week 12, n = 11; week 24, n = 10; week 36, n = 7; week 52, n = 3; and stop, n = 4. Abbreviations: EQ-5D-5L, EuroQol 5 Dimension 5-Level; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; VAS, Visual Analog Scale.

60 kg and ≥ 60 kg)—are shown in Supplementary Table S6 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=302*). No apparent between-group differences were observed for any of these subgroups.

3.5. Safety

During the 52-week treatment period, AEs were reported in three patients (23.1%) in the filgotinib group and seven patients (53.8%) in the tocilizumab group (Table 4). There were 9 AEs in the filgotinib group, including 4 serious AEs: urinary tract infection, heart failure, bacteremia, and tumor-forming pancreatitis. Treatment was discontinued in two patients in the filgotinib group due to the AEs. In the tocilizumab group, 12 AEs were reported, none of which were serious. The most common AEs were stomatitis (*n* = 4) and infections, including one case each of *Pseudomonas aeruginosa* pneumonia, periodontal disease, and upper respiratory tract infection. Treatment-related AEs occurred in 33.3% (3/9) of events in the filgotinib group and 83.3% (10/12) of events in the tocilizumab group.

Medication adherence was high in both groups, with

Table 3. Differences in patient reported outcomes between the filgotinib group and tocilizumab group

Parameter	Difference	95% CI Lower	95% CI Upper
Patient global VAS (scale: 0–100)			
Week 0	-1	-23.82	21.83
Week 2	-20.96	-40.16	-1.76
Week 4	-0.66	-21.55	20.23
Week 12	-0.49	-20.89	19.91
Week 24	3.69	-14.17	21.54
Week 36	-14.81	-35.91	6.29
Week 52	-0.99	-30.78	28.8
Patient pain VAS (scale: 0–100)			
Week 0	-3.28	-28.01	21.45
Week 2	-16.08	-37.08	4.92
Week 4	-0.26	-22.48	21.96
Week 12	-1.92	-22.21	18.38
Week 24	2.69	-12.69	18.07
Week 36	-18.34	-43.43	6.75
Week 52	1.76	-22.06	25.58
Morning stiffness severity (scale: 0–100)			
Week 0	3.38	-22.76	29.53
Week 2	-11.33	-35.26	12.59
Week 4	-3.75	-26.81	19.31
Week 12	-5.83	-25.56	13.9
Week 24	-3.6	-18.21	11.01
Week 36	-22.14	-49.57	5.28
Week 52	-1	-12.84	10.84
Duration of morning stiffness, minutes			
Week 0	275	-2.98	552.98
Week 2	37.08	-121.29	195.46
Week 4	-87.25	-349.92	175.42
Week 12	-106.01	-369.14	157.13
Week 24	124.7	-199.18	448.58
Week 36	-188.3	-610.26	233.65
Week 52	5.83	-23.86	35.53
EQ-5D-5L			
Week 0	-0.04	-0.23	0.16
Week 2	0.09	-0.13	0.3
Week 4	-0.04	-0.18	0.09
Week 12	0.06	-0.05	0.17
Week 24	-0.02	-0.16	0.11
Week 36	0.13	-0.01	0.26
Week 52	0	-0.29	0.29
FACIT-F			
Week 0	-4.62	-13.78	4.55
Week 2	-2.5	-13.60	8.6
Week 4	-1.75	-12.01	8.51
Week 12	-0.93	-9.6	7.74
Week 24	-0.9	-7.65	5.85
Week 36	6.23	-2.11	14.57
Week 52	-0.33	-23.97	23.31
HAQ-DI			
Week 0	0.16	-0.44	0.77
Week 2	-0.08	-0.73	0.57
Week 4	-0.1	-0.64	0.43
Week 12	-0.11	-0.61	0.4
Week 24	0.19	-0.48	0.85
Week 36	-0.18	-0.76	0.4
Week 52	-0.1	-1.24	1.03

Data shown the difference (Filgotinib – Tocilizumab) in each timepoint from baseline. CI, Confidence interval; EQ-5D-5L, EuroQol 5 Dimension 5-Level; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; VAS, Visual Analog Scale.

median adherence rates of 98.4% (95% CI, 94.7–99.7) in the filgotinib group and 96.3% (95% CI, 92.9–100) in the tocilizumab group.

4. Discussion

This randomized controlled trial compared the efficacy and safety of filgotinib and subcutaneous tocilizumab monotherapies in patients with RA and an inadequate response to csDMARDs. Although the planned sample size was not achieved and a formal non-inferiority

Table 4. Summary of adverse events

Event	Tocilizumab (*n* = 13)	Filgotinib (*n* = 13)
Patients with adverse event, *n* (%)[a]	7 (53.8)	3 (23.1)
Number of adverse events	12	9
Number of serious adverse events	0	4
Number of infection (serious infection)	3 (0)	3 (3)
Adverse events by severity, *n* (%)[b]		
Mild	2 (16.7)	2 (22.2)
Moderate	10 (83.3)	3 (33.3)
Severe	0 (0.0)	3 (33.3)
Life-threatening	0 (0.0)	1 (11.1)
Death	0 (0.0)	0 (0.0)
Treatment-related adverse events, *n* (%)	10 (83.3)	3 (33.3)
Patients discontinuing due to adverse events	0	2
Adverse events of special interest		
Infection	3	3
Serious infection	0	3

[a]proportion per patient, [b]proportion per event.

analysis could not be performed, the results provide meaningful insights into the comparative performance of these two therapeutic strategies. Both groups demonstrated rapid and sustained improvement in disease activity, with no apparent difference in radiographic progression between the treatments.

The introduction of bDMARDs and JAK inhibitors has greatly advanced the RA therapeutic landscape, offering multiple treatment options with distinct mechanisms of action. However, as these options have expanded, the question of how to optimally select among them has become an important clinical issue. Several studies comparing JAK or IL-6 inhibitors with TNF inhibitors show that both JAK (including filgotinib) and IL-6 inhibitors can achieve efficacy comparable to or greater than TNF inhibitors in patients with inadequate response to csDMARDs (*7-10,28-30*). Regarding comparative studies of JAK and IL-6 inhibitors, one retrospective analysis using propensity score matching reported that baricitinib and tocilizumab led to comparable improvements in DAS28-CRP, joint counts, and CRP levels at 24 weeks (*31*). Nevertheless, no randomized controlled trial has directly compared the efficacy and safety of JAK inhibitors and IL-6 inhibitors. The comparison of these two therapeutic classes holds particular scientific significance given their overlapping mechanisms of action. JAK inhibitors provide therapeutic effects through direct inhibition of the JAK-STAT signaling pathway, whereas IL-6 inhibitors indirectly suppress this pathway by blocking IL-6 signaling. Furthermore, our study addresses a clinically relevant scenario, as both filgotinib and tocilizumab demonstrate lower MTX dependency than TNF inhibitors, making monotherapy comparison particularly meaningful.

Notably, in our study, the patient global VAS score was lower in the filgotinib group than in the tocilizumab group at week 2. Recently, PROs, including the patient global VAS score, have been increasingly emphasized in RA management, as early improvements in PROs correlate with long-term pain persistence and radiographic progression (*32,33*). Previous randomized control trials have shown that baricitinib and upadacitinib lead to significantly greater and faster improvements in the patient global VAS scores than bDMARDs such as adalimumab and abatacept (*9,10,34*). A post hoc analysis of a randomized control trial showed that, among patients with an inadequate response to MTX, 200 mg filgotinib plus MTX resulted in a significantly greater improvement in the patient global VAS score at week 12 than adalimumab plus MTX (*35*). Consistent with these findings, a propensity-matched retrospective comparison between baricitinib and tocilizumab demonstrated a greater patient global VAS score improvement with baricitinib at 24 weeks (*31*). However, in our study, this early difference between the filgotinib and tocilizumab groups diminished over time, and no difference was observed in radiographic progression. Therefore, the clinical significance of early PRO improvement with filgotinib compared to tocilizumab requires further investigation.

We also evaluated MSUS findings, which are increasingly recognized as valuable tools for monitoring disease activity in RA. Previous studies demonstrate that both bDMARD and JAK inhibitor therapies improve synovial inflammation detectable by MSUS, even at early stages (*36,37*). Although clinical remission remains the primary therapeutic target to prevent joint destruction, radiographic progression occurs in 15–20% of patients with clinical remission (*38,39*). Approximately 60% of patients in clinical remission demonstrate persistent power Doppler-positive synovitis on MSUS, which represents a risk factor for subsequent joint destruction (*13,40,41*). These observations underscore the importance of performing MSUS assessment with clinical evaluation. Despite the limited sample size, both treatment groups in our study demonstrated MSUS improvement and suppression of radiographic progression as measured by the vdH-mTSS.

Multiple serum cytokines and chemokines were examined. Among all evaluated parameters, serum IL-6 was the only biomarker demonstrating consistent changes from baseline in all visits and between-group differences from week 2. Serum IL-6 levels decreased early in the filgotinib group while increasing in the tocilizumab group, with between-group differences maintained throughout the study. The elevation in serum IL-6 levels observed in the tocilizumab group is consistent with the mechanism of receptor blockade, which reduces IL-6 clearance and leads to the accumulation of circulating IL-6, correlating with receptor occupancy and antibody concentration (*42,43*). Persistently elevated serum IL-6 levels through week 52 suggest adequate antibody exposure throughout the study. In contrast, the filgotinib

group demonstrated IL-6 reduction, presumably through JAK-STAT pathway blockade. However, no definite changes were observed in other cytokines involved in the JAK–STAT pathway, including IFN-α, possibly reflecting the limited sample size and highlighting the need for further investigation.

Regarding safety, multiple AEs were observed in both groups. Although large post-marketing studies have raised concerns regarding malignancy and major adverse cardiovascular events associated with JAK inhibitors, none of these events occurred in our study (*44*). However, the limited sample size and 52-week observation period preclude conclusions regarding long-term safety. Notably, several serious AEs, including serious infections, were observed in the filgotinib group, warranting careful monitoring in clinical practice.

This study has some important limitations. First, although the study was randomized, the open-label design introduced potential treatment bias. Second, failure to achieve the predetermined target sample size precluded the planned non-inferiority analysis, limiting the analysis to descriptive comparisons. Consequently, this study does not provide definitive guidance regarding treatment selection for specific patient populations. Despite these limitations, our study provides valuable comparative data on two important therapeutic options, evaluating not only clinical activity but also MSUS findings, PROs, and biomarker profiles.

In conclusion, although the planned sample size was not attainable and robust between-group effect estimation was not feasible, both filgotinib and subcutaneous tocilizumab monotherapies led to early and sustained improvements in disease activity, including MSUS findings and PROs in patients with csDMARD-refractory RA. Although no new safety signals were identified, the occurrence of several serious AEs with filgotinib warrants careful monitoring. This trial was terminated early and represents a descriptive analysis of an underpowered randomized study. Larger, adequately powered studies are required to confirm these findings and clarify the optimal therapeutic positioning of JAK and IL-6 inhibitors in RA management.

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This was an investigator-initiated study. The study protocol was designed by the authors and reviewed by Gilead Sciences, Inc. for feasibility before funding approval. Gilead Sciences, Inc. provided financial support for the study but had no role in the study design; data collection; data analysis or interpretation; or the decision to submit the manuscript for publication. The sponsor was given the opportunity to review the manuscript; no comments were provided. The authors had full access to all data and take final responsibility for the content of the manuscript.

Institutional Review Board Statement: The study protocol was approved by the certified review board of Nagasaki University (Reference number: CRB20-026).

Informed Consent Statement: Written informed consent was provided by the patients before enrollment.

Data Availability Statement: The datasets used or analyzed (or both) during the current study are available from the corresponding author upon reasonable request.

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