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ORIGINAL RESEARCH

# Effectiveness and safety of adalimumab compared with leflunomide in patients with Takayasu arteritis: a retrospective cohort study

Faustino Peron Filho, Andressa de Souza Moreira, Anna Larissa Faria Janes, Alexandre W S de Souza

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Rheumatology Division, Department of Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo, Sao Paulo, Brazil

**Correspondence to**
Dr Alexandre W S de Souza; alexandre_wagner@uol.com.br

## ABSTRACT

**Objective** This study aims to evaluate the effectiveness and safety of adalimumab (ADA) compared with leflunomide (LEF) in patients with Takayasu arteritis (TAK).

**Method** A retrospective cohort study was performed with the following inclusion criteria: the fulfilment of the 2022 American College Classification/European Alliance of Associations for Rheumatology criteria for TAK, age ≥18 years, and written informed consent. Forty-four patients were treated with LEF (n=28) or ADA (n=16) therapy due to relapsing/refractory disease or toxicity from previous therapy. Patients were evaluated at baseline (T0), at a median of 7.0 months (T1) and at 15.0 months of follow-up (T2). Data regarding disease activity, daily dose of prednisone, side effects and angiographic progression were analysed.

**Results** LEF and ADA groups had similar features on the baseline visit. However, intravenous methylprednisolone was more frequently prescribed for the ADA group (p=0.019). On T1 and T2 visits, complete response rates were similar for ADA and LEF groups (75.0% and 88.5%; p=0.397 and 62.5% vs 78.3%; p=0.307), respectively. The differences remained non-significant after adjusting for baseline variables by propensity score matching. Although the ADA group had a higher median daily prednisone on visit T1 (p=0.004), it was similar on visit T2 (p=0.595). Similar rates of angiographic progression were observed in ADA and LEF groups (40% vs 25%; p=0.467). Mild-to-moderate adverse events were observed only in the LEF group (17.9%).

**Conclusion** LEF and ADA had comparable outcomes after a median of 15.0 months of follow-up. However, withdrawal from therapy and mild-to-moderate adverse events were only observed in the LEF group.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ To date, no observational studies have compared the effectiveness of adalimumab to conventional synthetic disease-modifying antirheumatic drugs in the management of patients with Takayasu arteritis (TAK).

### WHAT THIS STUDY ADDS

⇒ Up to a median of 15 months of follow-up, adalimumab and leflunomide had comparable effects in inducing complete response and angiographic progression in TAK, whereas leflunomide was associated with a higher rate of side effects.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In countries with restricted access to biological therapy, leflunomide may be a reasonable option for the treatment of patients with TAK, especially in those who relapsed while under therapy with methotrexate.

## INTRODUCTION

Takayasu arteritis (TAK) is a large-vessel vasculitis involving the aorta, main branches and pulmonary arteries. The inflammatory process in the arterial walls leads to concentric thickening, stenosis, occlusions or aneurysm formation.[1] TAK is a rare disease with a worldwide distribution whose prevalence ranges from 0.9 cases/1 000 000 in the USA to 40 cases/1 000 000 in Japan[2]; recently, the prevalence of TAK in Brazil was reported as 16.9 cases/1 000 000.[3] As a rare disease, the assessment of therapeutic agents for TAK by clinical trials is a challenge and only a few clinical trials have analysed available therapies.[4 5] Currently, the management of TAK is based mostly on the results of non-randomised case series.[6–8] Furthermore, the evaluation of disease activity in TAK is difficult in clinical practice and no reliable tools have been developed for this purpose, since the smouldering arterial inflammation may persist, usually leading to the progression of arterial lesions in previously unaffected arterial territories.[9]

TAK therapy is mostly based on the combination of high-dose glucocorticoids (GC) and

conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biological DMARDs (bDMARDs) during active disease phases.[10] For patients with TAK presenting non-severe manifestations, csDMARDs such as methotrexate (MTX), leflunomide (LEF), azathioprine or mycophenolate mofetil, are added to GC therapy.[11 12] LEF is an immunomodulatory drug that exerts its effects by inhibiting the mitochondrial enzyme, dihydroorotate dehydrogenase, involved in the de novo synthesis of the pyrimidine ribonucleotide, uridine monophosphate. LEF prevents the expansion of activated lymphocytes by interfering with the cell cycle due to insufficient concentration of uridine monophosphate.[13] Previous small case series and observational cohort studies have shown LEF, compared directly with MTX, cyclophosphamide and tofacitinib, as an effective therapy for inducing remission in patients with TAK presenting active disease.[14–20] LEF was shown to be more effective against MTX and cyclophosphamide, but its response rate was similar to that of tofacitinib.[16–18 21]

Patients with TAK presenting severe disease manifestations are recommended to receive bDMARDs, such as tumour necrosis factor inhibitors (TNFi) or tocilizumab.[11 12] Refractory patients and those with multiple relapses may also benefit from TNFi or tocilizumab, and more recently from secukinumab or tofacitinib therapy.[8 10 22] A recent systematic review with meta-analysis and a randomised clinical trial showed similar clinical responses to TNFi and tocilizumab therapies in TAK.[8 23] Although only one randomised controlled trial has assessed the efficacy of TNFi in TAK,[23] these agents are the most frequently analysed therapeutic modalities in observational studies. In these studies, the effectiveness of TNFi in TAK was evaluated as one group including infliximab, etanercept, adalimumab (ADA), golimumab and/or certolizumab pegol.[22 24–32]

To date, no observational studies have analysed the clinical response to ADA individually nor compared the efficacy of ADA to that of csDMARDs such as LEF. Therefore, this study aims to evaluate the effectiveness and safety of ADA in comparison to LEF in patients with TAK in terms of their response rates, GC use, acute phase reactants, disease relapses and angiographic progression.

## METHODS

### Study design

This observational monocentre retrospective cohort study was based on a standardised protocol comprising a structured appointment sheet to record TAK-related issues and results of cardiovascular examination, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and imaging studies of patients with TAK followed-up at the Vasculitis Outpatient Clinic of Universidade Federal de São Paulo – Escola Paulista de Medicina. Monthly medical appointments were scheduled for patients presenting active disease, while visits were scheduled every 3–4 months when disease remission was achieved. CT angiography or magnetic resonance angiography of the aorta and main branches, and colour Doppler ultrasound of the carotid and vertebral arteries, were performed yearly and whenever a new disease relapse was suspected.

### Inclusion and exclusion criteria

The inclusion criteria for this study were age ≥18 years, fulfilment of the 2022 American College Classification/European Alliance of Associations for Rheumatology criteria for TAK,[33] prescription of LEF or ADA between 2014 and 2021 at the physician's discretion, minimal follow-up duration of 1 year and informed written consent. Patients with TAK were excluded from the study if they presented chronic infectious diseases, had a history of cancer within the last 5 years or had incomplete clinical data on follow-up.

### Study endpoints

The primary endpoint of this study was a complete response (CR) to therapy on the last follow-up visit (T2), approximately 1 year after the introduction of ADA or LEF. Secondary endpoints were CR on the intermediate visit (T1), CR in low-dose prednisone (ie, <10 mg) on the intermediate (T1) and final visits (T2), changes in daily prednisone dose, ESR and CRP levels during the follow-up, time to relapse, angiographic progression and serious adverse events.

### Study cohort assessments

Patients with TAK who met the inclusion criteria were followed-up from the baseline visit (T0), when either ADA or LEF therapy was started and then reassessed on the intermediate visit (T1) at a median of 7.0 (IQR: 5.0–9.0) months and on the final visit at a median of 15.0 (IQR: 14.0–20.0) months (T2). On each visit, we collected information about disease activity (using Kerr's criteria[34]), ESR, CRP, daily prednisone dose, side effects related to drug therapy and imaging studies performed during the study period. Active disease at baseline and disease relapses were defined as the presence of two or more items in Kerr's criteria in a patient previously thought to be in remission.[34]

CR was defined as the absence of new or worsening systemic symptoms and vascular symptoms or signs, and normalisation of acute phase reactants. CR in low-dose prednisone was considered if the patient presented CR and daily prednisone dose below 10 mg. The refractory disease was defined as the inability to maintain disease remission with a daily prednisone dose below 10 mg.

Angiographic progression was defined as the development of new arterial lesions observed by follow-up imaging in previously unaffected territories.[24 34] The following arterial lesions were evaluated: concentric thickening, stenosis, occlusion, dilatation and aneurysm formation in the common carotid arteries, subclavian arteries, innominate artery, ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, coeliac

trunk, superior and inferior mesenteric arteries, renal arteries and/or common iliac arteries.[35]

### Treatment protocol

At the physician's discretion, patients with TAK were assigned to either ADA or LEF as first-line therapy in association with GC; in patients already under follow-up, one of these agents was prescribed because of disease relapse, refractory disease or unacceptable side effects. Both subcutaneous ADA and oral LEF were given in a fixed dose of 40 mg every other week and 20 mg/day, respectively. Patients presenting active disease also received prednisone at a dose of 0.5–1.0 mg/kg/day (maximum 80 mg), and in severe manifestations of TAK, intravenous pulse therapy with methylprednisolone was added to the therapy. When the symptoms were under control and levels of acute phase reactants had improved, the daily prednisone dose was slowly tapered by 10 mg every other week down to 20 mg and then the daily dose was tapered by 2.5–5.0 mg every 2–4 weeks until complete withdrawal.

Severe disease activity in TAK guided therapeutic decisions and was defined as the presence of at least one life-organ-threatening manifestation of TAK, including the involvement of the coronary arteries, involvement of two or more supra-aortic vessels including the carotid and vertebral arteries causing haemodynamically significant stenosis with risk of cerebral ischaemia, symptomatic subclavian steal syndrome, stroke or transient ischaemic attacks, new onset renal hypertension, vascular kidney failure, intestinal ischaemia, limb ischaemia and symptomatic pulmonary hypertension.[36 37]

### Statistical analysis

Continuous variables were presented as means and SD or as medians and IQR according to the distribution. Categorical variables were presented as numbers and percentages. Groups were compared by the $\chi^2$ test or Fisher's exact test for categorical variables and by Student's t-test or the Mann-Whitney U test for continuous variables. Propensity score analysis was applied to control baseline variables between LEF and ADA groups for primary endpoint analysis to minimise potential sources of selection bias. The covariates included in the analysis were intravenous methylprednisolone, disease duration, severe disease manifestations at baseline, refractory disease and ADA associated or not associated with csDMARDs. Results were displayed as ORs with 95% CIs. Longitudinal analyses for daily prednisone dose and acute phase reactants between groups were performed using the general linear model. Relapse-free survival was analysed by the Kaplan-Meier analysis and the log-rank test was used to compare differences between LEF and ADA groups. Relapse risk between LEF and ADA groups was estimated by the HR with 95% CI. Paired analyses regarding the proportion of patients presenting active disease between baseline and visits T1 or T2 were performed by the McNemar test. A p value<0.05 was considered significant. Statistical analysis was carried out by the IBM SPSS V.21.0 for Windows (Armonk, New York, USA) and graphs were built by the GraphPad Prism V.9.00 for Windows (La Jolla, California, USA). The R software V.4.3.1 (R Core Team, 2020) was used to analyse the propensity score matching.

## RESULTS

### Characteristics of patients with TAK at baseline

We evaluated 44 patients with TAK, 16 in the ADA group and 28 in the LEF group and they were assessed at T1 and T2. Five (17.9%) patients in the LEF group discontinued therapy in comparison to no patient in the ADA group (p=0.141). Four patients discontinued LEF due to a combination of adverse events and relapse while an adverse event was the reason for discontinuing LEF in one patient (figure 1). Table 1 describes the comparison of demographics and baseline features between patients with TAK under ADA and LEF therapy. Both groups had similar demographic features, levels of acute phase reactants, disease duration, active disease and severe disease manifestations at baseline (table 1).

The reason for adding ADA or LEF to the therapy of patients with TAK varied, with disease relapse observed in half of the patients in both groups. Intolerance to a previous agent seemed to be associated with therapy changes from other agents to LEF (eg, gastrointestinal intolerance and elevated liver function tests), while ADA seemed to be more often prescribed for refractory disease compared with LEF. Both agents were prescribed for only two patients in each group as first-line therapy in association with prednisone for patients with TAK. Previous therapy with MTX or azathioprine was observed in up to 85% of patients in the LEF group, but no relevant associations with previous agents were found in the ADA group. Although the median daily prednisone dose was similar between ADA and LEF groups, intravenous pulse therapy with methylprednisolone was more frequently prescribed at baseline to patients who received ADA more than LEF (table 1). ADA was prescribed as a monotherapy in 5 patients (31.3%) and in association with a csDMARD in 11 patients (68.7%), including LEF in 7 patients and MTX in 4 patients.

### Response rates in ADA and LEF groups

CR rates were similar between ADA and LEF groups in the T1 (75.0% vs 88.5%; p=0.397, respectively) and T2 assessments (62.5% vs 78.3%; p=0.307, respectively). CR with prednisone <10 mg/day was also similar between ADA and LEF groups in the T1 (37.5% vs 44.4%; p=0.655, respectively) and T2 assessments (37.5% vs 56.5%; p=0.242, respectively) (figure 2). When propensity score matching analysis was applied, the p values remained non-significant as follows: CR rate in the T1 assessment (p=0.411), CR rate in the T2 assessment (p=0.782), CR in low-dose prednisone in the T1 assessment (p=0.728), CR in low-dose prednisone in the T2 assessment (p=0.498).

Propensity score analysis was applied to adjust for potential confounding factors such as intravenous

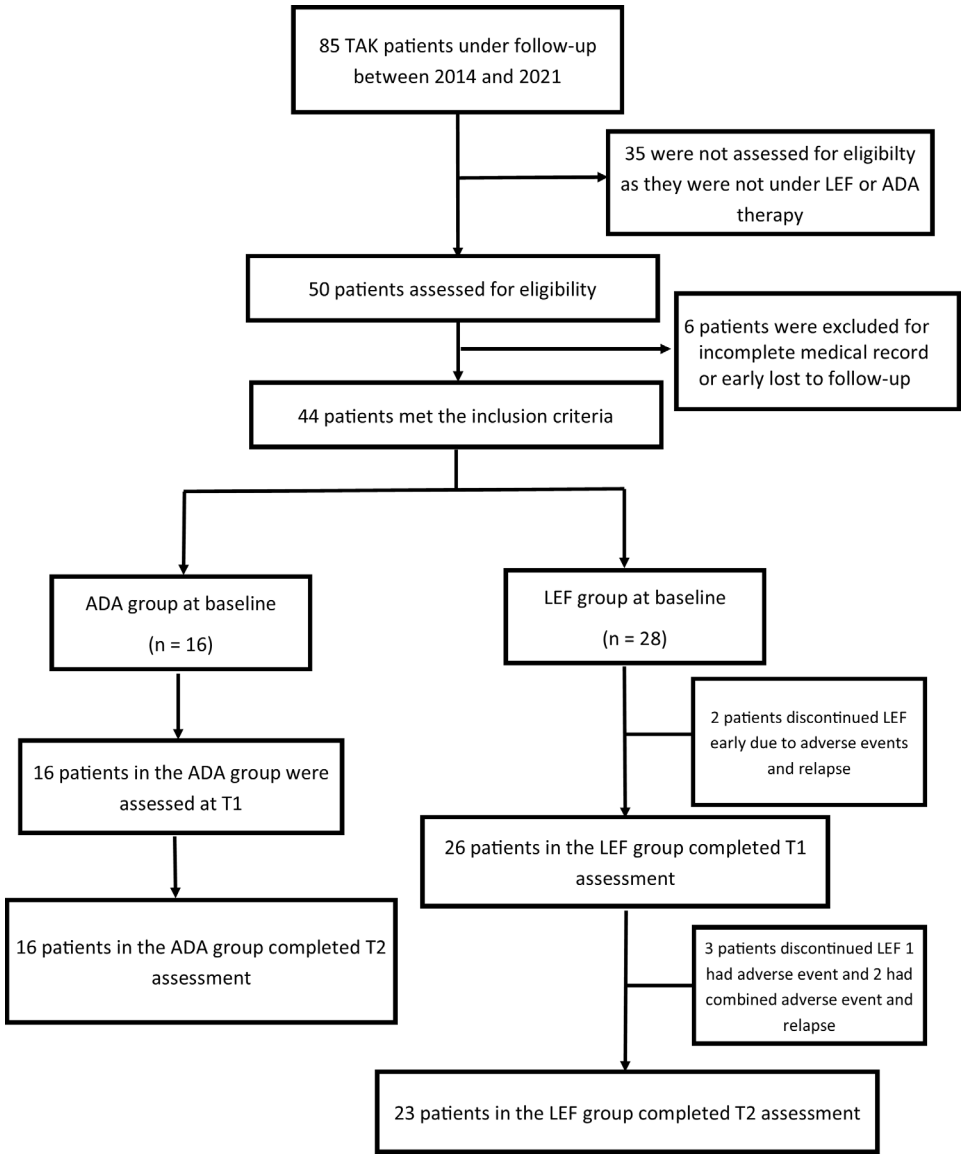


**Figure 1** Flowchart of follow-up of the participants. The flowchart depicts the number of participants and the reasons for withdrawals in study groups at each assessment visit. ADA, adalimumab; LEF, leflunomide; TAK, Takayasu arteritis.

methylprednisolone, disease duration, severe disease manifestations at baseline, refractory disease and ADA use associated or not associated with csDMARDs. The differences between ADA and LEF groups for being in remission on the final visit T2 were non-significant before (OR: 1.20; 95% CI: 0.32 to 4.37; p=0.782) and after matching for baseline variables (OR: 0.56; 95% CI: 0.05 to 4.72; p=0.592).

In the whole cohort of patients with TAK, the proportion of patients presenting active disease at baseline, T1 and T2 visits were as follows: 84.1%, 15.9% and 25.0%, respectively. Paired comparisons yielded significant results between baseline and T1 visit (p<0.0001) and between baseline and T2 visit (p<0.0001). When analysing each group separately, the proportion of patients presenting active disease at baseline, T1 and T2 visits were 87.5%, 25.0% and 37.5% in the ADA group and 82.1%, 11.5% and 21.7% in the LEF group, respectively. Significant decreases in the proportion of patients with TAK presenting active disease between baseline and T1 visit (p<0.05) and between baseline and T2 visit (p<0.05) were observed in the ADA and LEF groups.

### Longitudinal analysis for acute phase reactants

ESR and CRP levels were similar between ADA and LEF groups at baseline (p=0.964 and p=0.540, respectively). During the follow-up period, the median ESR levels were similar between ADA and LEF groups on the T1 (17.0 (9.0–35.5) mm/hour vs 16.0 (8.0–33.0) mm/hour; p=0.741, respectively) and T2 visits (20.0 (10.0–39.5) mm/hour vs 24.0 (8.3–30.3) mm/hour; p=0.915, respectively), with a p value=0.650 for between-groups comparisons at all time points (figure 3A). In addition, the frequency of ESR levels above 20 mm/hour (ie, the upper level of the normal range) was similar between ADA and LEF groups

**Table 1** Comparison of baseline features in patients with Takayasu arteritis treated with leflunomide and adalimumab

| Variables | ADA (n=16) | LEF (n=28) | P value |
|---|---|---|---|
| Demographics | | | |
| Age at baseline, years | 35.0 (22.5–41.8) | 40.5 (32.0–48.8) | 0.063 |
| Females, n (%) | 15 (93.8) | 25 (89.3) | 1.000 |
| Disease duration, months | 51.0 (15.0–114.0) | 108.0 (27.0–240.0) | 0.183 |
| ESR, mm/hour | 21.0 (6.8–35.3) | 20.5 (10.3–32.0) | 0.964 |
| Elevated ESR at baseline*, n (%) | 7 (50.0) | 12 (50.0) | 1.000 |
| CRP, mg/L | 8.6 (2.6–14.5) | 6.5 (1.3–11.8) | 0.540 |
| Elevated CRP at baseline†, n (%) | 6 (66.7) | 12 (60.0) | 1.000 |
| Active disease at baseline according to Kerr's criteria,[34] n (%) | 14 (87.5) | 23 (82.1) | 1.000 |
| Severe disease manifestations at baseline, n (%) | 11 (68.8) | 12 (42.9) | 0.098 |
| Reason for prescribing ADA or LEF at baseline | | | |
| Therapy at disease presentation, n (%) | 2 (12.5) | 2 (7.1) | NA |
| Disease relapse with other agents‡, n (%) | 8 (50.0) | 14 (50.0) | |
| Intolerance to a previous agent, n (%) | 1 (6.3) | 10 (35.7) | |
| Refractory disease§, n (%) | 3 (18.8) | 2 (7.1) | |
| Other reasons¶, n (%) | 2 (12.5) | 0 (0.0) | |
| Therapy before inclusion | | | |
| Methotrexate, n (%) | 3 (18.8) | 14 (50.0) | NA |
| Azathioprine, n (%) | 2 (12.5) | 10 (35.7) | |
| Mycophenolate mofetil, n (%) | 1 (6.3) | 0 (0.0) | |
| Leflunomide, n (%) | 4 (25.0) | -- | |
| Cyclophosphamide, n (%) | 1 (6.3) | 0 (0.0) | |
| TNFi**, n (%) | 2 (12.5) | 1 (3.6) | |
| Tocilizumab††, n (%) | 1 (6.3) | 1 (3.6) | |
| Glucocorticoid therapy | | | |
| Prednisone, mg/day | 33.5 SD 22.9 | 30.0 SD 18.6 | 0.622 |
| MTP intravenous pulse therapy, n (%) | 6 (37.5) | 2 (7.1) | 0.019 |

*Two missing values in adalimumab group and four in leflunomide group.
†Seven missing values in adalimumab group and eight in leflunomide group.
‡Disease relapses were defined as the presence of two or more items in Kerr's criteria in a patient previously thought to be in remission.
§Refractory disease was defined as the inability to maintain disease remission with a daily prednisone dose below 10 mg.
¶Other reason refers to the temporary unavailability of the medication in the public health system.
**Two patients in the adalimumab group had previously used infliximab for a period of 5 and 17 months, respectively. One patient in the leflunomide group had previously used adalimumab for 36 months.
††One patient in each group had previously used tocilizumab for a period of 12 and 24 months, respectively.
ADA, adalimumab; CRP, C reactive protein (the upper limit of the normal range is 5.0 mg/L); ESR, erythrocyte sedimentation rate (the upper limit of the normal range is 20 mm/hour); LEF, leflunomide; MTP, methylprednisolone; n, number of patients; NA, not analysed; TAK, Takayasu arteritis; TNFi, tumour necrosis factor inhibitors.

at T1 (46.2% vs 38.1%; p=0.643) and T2 (44.4% vs 55.0%; p=0.700) visits, respectively.

During the follow-up period, the median CRP levels were also similar between ADA and LEF groups on the T1 visit (1.00 (0.06–12.26) mg/L vs 2.11 (0.44–8.40) mg/L; p=0.463, respectively) and on the T2 visit (7.1 (3.5–11.1) mg/L vs 3.5 (2.3–10.0) mg/L; p=0.287, respectively). The p value was 0.833 for between-group comparisons at all time points (figure 3B). The frequency of patients presenting CRP levels above 5 mg/L (ie, the upper level of the normal range) was similar between ADA and LEF groups at T1 (36.4% vs 30.0%; p=0.999) and T2 (75.0% vs 41.2%; p=0.202) visits, respectively.

## Daily prednisone dose

Although the daily prednisone doses were similar between groups at baseline (p=0.622), the median daily prednisone dose on the T1 visit was significantly higher in the ADA group compared with the LEF group (20.0 (10.6–40.0) mg vs 5.0 (5.0–15.0) mg; p=0.004, respectively). However, the median daily prednisone doses were similar between the ADA and LEF groups on the

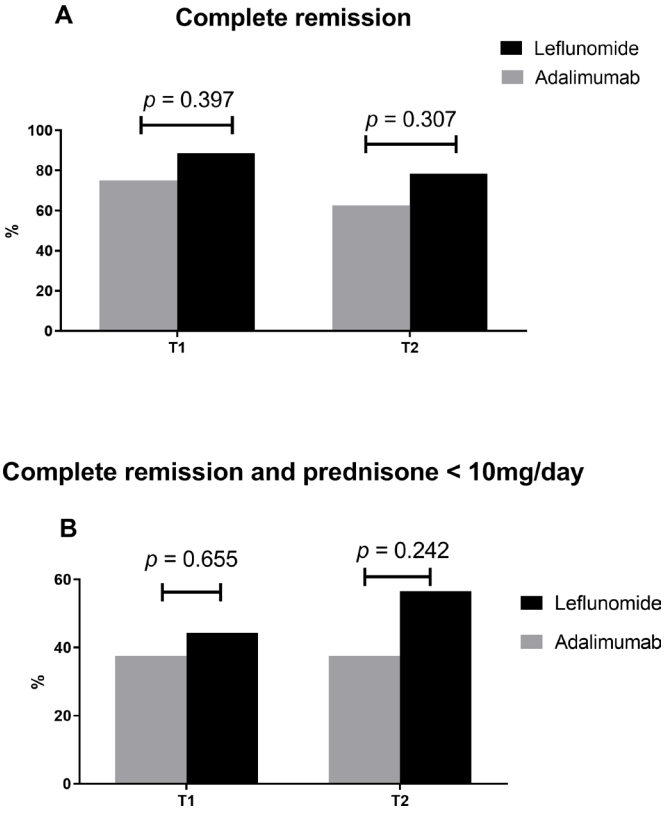


**Figure 2** Proportion of patients with complete remission during follow-up. (A) Compares the proportions of patients with TAK in complete remission in the ADA and LEF groups at T1 and T2. (B) Compares the proportions of patients with TAK in complete remission and taking daily doses of prednisone below 10 mg in the ADA and LEF groups at T1 and T2. T1 is the assessment of patients with TAK at a median of 7 months of follow-up and T2 is the assessment of patients with TAK on the final visit (ie, at a median of 15 months of follow-up). ADA, adalimumab; LEF, leflunomide; TAK, Takayasu arteritis.

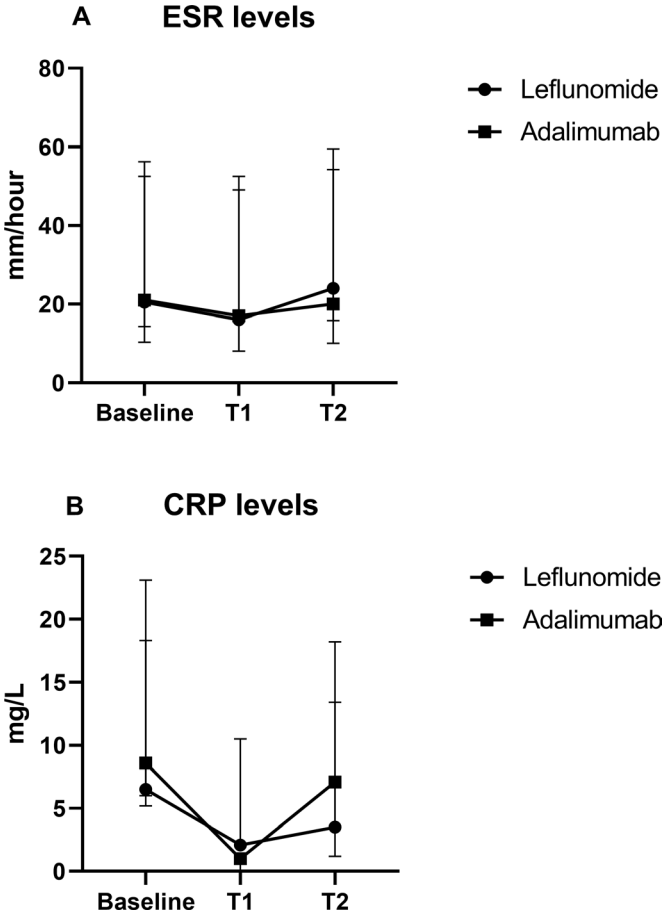


**Figure 3** Longitudinal analysis of acute phase reactant levels between ADA and LEF groups. Median ESR (A) and CRP (B) levels were similar during follow-up between ADA and LEF groups of patients with TAK at baseline T1 and T2. T1 is the assessment of patients with TAK at a median of 7 months of follow-up and T2 is the assessment of patients with TAK on the final visit (ie, at a median of 15 months of follow-up). ADA, adalimumab; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LEF, leflunomide; TAK, Takayasu arteritis. In the whole group of participants, the number of patients with available results for baseline, T1 and T2 were 38, 34 and 29 for ESR levels and 29, 31 and 25 for CRP levels, respectively.

T2 visit (10.0 (8.8–12.5) mg vs 5.0 (3.0–11.3) mg; p=0.595, respectively) (figure 4). Although non-significant, the proportion of patients with TAK patients who were off GC therapy at the end of follow-up was higher in the ADA group compared with the LEF group (62.5% vs 35.7%; p=0.086).

### Disease relapses and angiographic progression

The frequencies of disease relapse were similar between both groups, as it was observed in 6 (37.5%) patients in the ADA group and 10 (35.7%) patients in the LEF group (p=0.906). Moreover, the mean time to relapse was 8.7 (SD 2.9) months in the ADA group and 7.9 (SD 5.7) months in the LEF group (p=0.765). The Kaplan-Meier curve showed no differences in relapses between ADA and LEF groups (HR: 1.007 (95% CI: 0.366 to 2.768)), with a non-significant log-rank test (p=0.989) (figure 5).

Follow-up imaging studies were performed in 35 (79.5%) patients from the whole cohort: 15 out of 16 patients in the ADA group and 20 out of 28 patients in the LEF group. Angiographic progression was observed in 11 (31.4%) patients in the whole cohort, and this was associated with a relapse in 10 cases (90.9%). The remaining 24 patients (68.6%) who underwent serial vascular imaging had stable arterial lesions. No significant differences between ADA and LEF groups were found regarding the development of new angiographic lesions (40.0% vs 25.0%; p=0.467, respectively).

### Adverse events

Mild-to-moderate adverse events were reported only by 5 (17.9%) patients in the LEF group and led to the discontinuation of the drug at the physician's discretion. The events included peripheral neuropathy (n=2), abnormal liver functional tests (n=1), worsening of hypertension (n=1) and stomatitis (n=1). No serious adverse events such as severe infections were observed in the cohort.

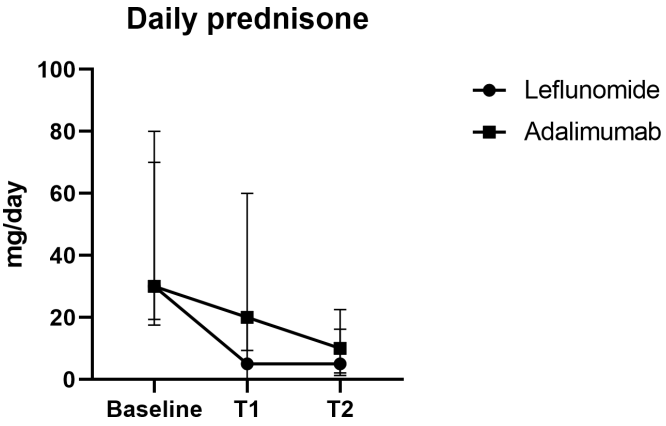


**Figure 4** Longitudinal analysis of daily prednisone dose between ADA and LEF groups. The median daily prednisone dose was compared between ADA and LEF groups at baseline, T1 and T2 follow-up visits. The median daily prednisone dose was significantly higher in ADA compared with LEF (p=0.004) on the T1 visit. However, no significant differences were found between the median daily prednisone dose between ADA and LEF groups on the baseline visit or on the final visit T2. T1 is the assessment of patients with TAK at a median of 7 months of follow-up and T2 is the assessment of patients with TAK on the final visit (ie, at a median of 15 months of follow-up). ADA, adalimumab; LEF, leflunomide; TAK, Takayasu arteritis.

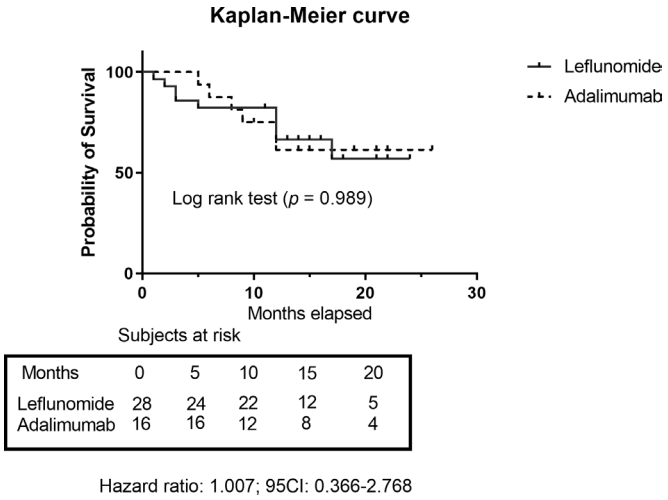


**Figure 5** The Kaplan-Meier estimator curve to analyse relapse-free survival between ADA and LEF groups. No significant differences were found between patients with TAK under ADA or LEF therapy regarding the time to relapse. ADA, adalimumab; LEF, leflunomide; TAK, Takayasu arteritis.

## DISCUSSION

In this observational study, we compare for the first time the response to therapy between a bDMARD and a csDMARD (ie, ADA and LEF, respectively) in patients with TAK for a median follow-up time up to 15 months. During the observational period of this study, all outcome measures (ie, CR rate, complete remission and daily prednisone <10 mg, daily prednisone dose, ESR and CRP levels, time to relapse, angiographic progression) were similar between patients with TAK under ADA and LEF therapy. However, mild-to-moderate adverse events and withdrawals of therapy were observed only in patients in the LEF group. In both groups, a high CR rate was achieved at a median follow-up time of 7 and 15 months. Nonetheless, clinical relapses and angiographic progression occurred in a significant proportion of patients, indicating to some extent a failure of both agents to warrant sustained remission without GC during follow-up. No important safety issues were found in patients with TAK under ADA and LEF therapy, and only patients under LEF had to withdraw the medication due to mild-to-moderate side effects.

To date, the efficacy of biological agents has been analysed against placebo only in three clinical trials assessing ADA, tocilizumab and abatacept in patients with TAK respectively.[4 5 23] In two studies, the response rates to the addition of tocilizumab or abatacept alone to the therapy of patients with TAK presenting active disease were not analysed, as these two trials included patients with active TAK who received high-dose GC and were then randomised to the test drug or to placebo only after achieving remission.[4 5] On the other hand, in another randomised trial, ADA was compared with tocilizumab in patients with TAK presenting severe active disease and even though ADA was superior to tocilizumab at 6 months, the efficacy rate was similar between both agents at 9 and 12 months.[23]

In most observational studies, biological agents (ie, TNFi or tocilizumab) were added to the therapy when disease activity could not be controlled by another therapy, especially csDMARDs. Different TNFi, such as infliximab, etanercept, ADA, certolizumab and golimumab, have been used to treat patients with TAK. Etanercept has been frequently associated with treatment failure, whereas most patients under infliximab therapy require dose escalation to achieve disease control.[24 25]

In some other studies, a few patients were treated with ADA as TNFi therapy and the response to ADA therapy was analysed together with other TNFi such as infliximab, etanercept, certolizumab pegol and even golimumab.[22 26–32] Thus, the current observational study is the first to analyse ADA solely as a TNFi in patients with TAK. The overall CR rates to TNFi therapy in most observational studies ranged from 44% to 90%, which falls within the CR rate observed in our study (ie, 75% and 62.5% at a median of 7 and 15 months, respectively). In addition, the CR rates were similar between assessments at 6 (56–76%) and 12 (56–77%) months of follow-up in different studies evaluating TNFi in TAK.[22 24–28 30 31 38] Likewise, the effectiveness of therapy with LEF had a CR rate of 67.8–75.5% at 6 months[16 19 21] and ranged from 68.7% to 84.6% between 9 and 12 months in observational studies assessing patients with TAK.[14 16 17 19 21] These figures are similar to the response rates observed at 7 months (85.2%, respectively) and 15 months (66.7%) in our study. A meta-analysis of three uncontrolled studies showed a 75.0% (95% CI: 0.64% to 0.84%) pooled clinical

response to LEF.[20] In previous comparison studies, LEF had a comparable response rate to tofacitinib at 6 and 12 months, whereas it was more effective than MTX at 6 months of therapy and cyclophosphamide at 6, 9 and 12 months.[16–18 20 21] Combining our results and the literature findings in other observational studies, it seems that LEF and TNFi demonstrate similar effectiveness in controlling disease activity in TAK.

In this study, we also analysed if the addition of csDMARD to ADA had any impact on the response to therapy, since the addition of csDAMRD to bDMARD therapy has been shown to decrease the development of anti-drug antibodies and to improve the efficacy of bDMARDs in other inflammatory diseases.[39–41] Nonetheless, regarding the CR rate in our study, the addition of csDMARD to ADA therapy in TAK did not yield significant differences. This is in line with a previous multicentre study including 209 patients with TAK which found no differences in the relapse rates when csDMARD was added to TNFi or tocilizumab therapy (HR: 1.52 (95% CI: 0.93 to 2.47)).[27] Conversely, another group of researchers showed that the retention rate of infliximab was higher when csDMARD was added to bDMARD therapy in patients with TAK.[28]

As TAK is a relapsing-remitting disease, relapses are relatively common in patients with TAK regardless of the therapy.[42] In this study, ADA and LEF groups had similar but high relapse rates (ie, 37.5% and 35.7%, respectively) at a relatively short mean follow-up time of 7 and 8 months, respectively. In the literature, the relapse rate with TNFi therapy in TAK has been reported to be up to 44% within 1 year,[22] and the cumulative incidence rate of relapses in TAK under TNFi may reach 66% in up to 28 months of follow-up.[25] Conversely, the relapse rate in patients with TAK under LEF therapy was as low as 7.2% at 12 months in one study,[16] whereas the treatment failure reached 58.3% with LEF use by patients with TAK at a mean of 43 months of follow-up in another study.[15] A randomised clinical trial is underway comparing LEF versus placebo to analyse the role of this agent in TAK therapy.[43] In summary, observational studies have shown that both TNFi and LEF therapies have high long-term treatment failures in patients with TAK.

Angiographic progression (ie, the development of angiographic lesions in previously unaffected territories) is an issue in patients with TAK as it may ensue even in patients thought to be in remission.[44] In this study, up to one-third of patients with TAK developed angiographic progression during the median follow-up time of 15 months. In most of our patients with TAK who presented angiographic progression, the issue was associated with a clinical relapse. Although no significant differences were found between ADA and LEF groups, a study performed in Norway observed angiographic progression in only 10% of patients with TAK under TNFi therapy compared with 40% of patients under csDMARD therapy within 2 years of initiation of therapy.[45] Nonetheless, the rate of angiographic progression described in the literature within 1 year of TNFi therapy ranges between 11% and 33%,[24 25 30 38] while LEF use is associated with angiographic progression in 7.3–10.0% of patients with TAK within 1 year.[16 21] Recently, a systematic review with meta-analysis assessing LEF use in TAK showed angiographic stabilisation in 86% of patients (95% CI: 0.77 to 0.94) in three uncontrolled observational studies.[20]

We acknowledge some limitations to this study due to its retrospective nature, the relatively low number of patients in the ADA group and the lack of randomisation. On the other hand, this study has the strengths of being a real-world study analysing a fair number of patients under ADA as an individual TNFi therapy, and it included patients with TAK who were refractory or intolerant to other csDMARD or bDMARD therapy. Propensity score matching helped to control baseline features for confounding factors due to the lack of randomisation.

## CONCLUSIONS

We have demonstrated that ADA and LEF present similar effectiveness in inducing remission in patients with TAK within a median follow-up time of up to 15 months, and that both agents have comparable effects on tapering GC, decreasing ESR and CRP, as well as preventing disease relapses and angiographic progression. Mild-to-moderate side effects that led to drug discontinuation were observed only in the LEF group.

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**ORCID iD**

Alexandre W S de Souza http://orcid.org/0000-0001-7681-6215

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