# The effects of biological agents on vascular structural lesions in Takayasu's arteritis

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**ABSTRACT**

**Objective.** *The aim of the present study was to evaluate the effects of biological disease-modifying anti-rheumatic drugs (bDMARDs) administered to patients with Takayasu's arteritis (TAK) on disease activity and vascular damage.*

**Methods.** *This study included TAK patients who were receiving bDMARDs for at least six months. Disease activity (National Institutes of Health [NIH]), vascular lesions, and vascular damage (Combined Arteritis Damage Score [CARDS]) scores were determined.*

**Results.** *There were 21 TAK patients who received infliximab (INF) and/or tocilizumab (TCZ) (mean age = 38.6±11.8 years; female proportion = 20 [95.2%]). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and NIH disease activity score were found to significantly decrease with bDMARD treatments. There were also significant decreases in the mean CARDS and the total number of vascular lesions after treatment ($p<0.05$). Unlike occlusions, an important decrease was observed in the occurrences of stenosis and aneurysms with bDMARD treatments. Regression was detected in the vascular lesions of 15 (71.4%) patients compared to the last image before bDMARD therapies.*

**Conclusion.** *Our study results indicate that biological agents, such as INF and/or TCZ, that are used in the treatment of TAK are capable of remedying certain vascular lesions and may provide additional benefits to patients with TAK who do not sufficiently respond to conventional synthetic disease-modifying anti-rheumatic drug (DMARD) treatment.*

## Introduction

Takayasu's arteritis (TAK) is a form of large-vessel vasculitis characterised by granulomatous inflammation of the aorta and its major branches (1). Chronic inflammation results in segmental thickening, stenosis, and occlusions in the affected areas. In patients with severe and progressive disease, inflammation can destroy the arterial media, thereby leading to aneurysm formation and vessel rupture (2). The TAK-related mortality rate is 3%-15%, which varies depending on the disease phenotype, disease severity, and medical and surgical therapies administered (3).

Systemic glucocorticoids (GCs) are often the first-line treatment for TAK and are initially administered at high doses, after which the dose is then tapered. The vast majority of patients, however, are resistant to GC monotherapy and experience a relapse after dose reduction (4, 5). Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and/or biological agents (bDMARDs) are thus used as an adjunctive therapy to induce remission and prevent the relapses associated with a reduction in GC doses (6). However, studies have reported limited efficacy for drugs other than GCs, with csDMARDs and biological agents co-administered with GCs reportedly having remission rates of 58–64% and relapse rates of 31–54% (7).

A review of the existing literature shows that immunosuppressive therapies reduce disease activity and levels of inflammatory markers, such as the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level, during the early stages of the disease (7). However, because TAK is a rare disease and there is a paucity of randomised, controlled studies, the long-term effects of the available therapies on the regression or progression of TAK-associated structural vascular damage remain unclear.

The aim of the present study was thus to retrospectively review patients with TAK being treated at our hospital in terms of disease activity and radiological appearance and to evaluate the ef-

fects of the administered bDMARD therapies on the levels of inflammatory markers, scores of disease activity, and development of vascular damage.

## Materials and methods

*Study patients*

Patients who were diagnosed with TAK at the Rheumatology Clinic of Akdeniz University, Turkey, between January 2008 and April 2019 were retrospectively reviewed, and patients who were diagnosed with TAK (n=46) based on the American College of Rheumatology 1990 and/or modified Ishikawa criteria were identified (8, 9). Patients who were administered bDMARDs for at least six months and had at least two images taken before and after treatment were included in the study. A total of 21 patients were included.

*Study design*

The clinical history, vessel involvement patterns, and treatment history of the study patients were determined. The administered csDMARDs (*e.g.* methotrexate [MTX], azathioprine [AZT], cyclophosphamide [CyC], and leflunomide [LEF]) and bDMARDs (*e.g.* tumour necrosis factor [TNF] inhibitors and tocilizumab [TCZ]) were noted. The clinical and laboratory data at the time of diagnosis, the initiation of bDMARD treatment, and the final visit were analysed. The remission status was considered in order to evaluate the response to the treatment.

*Angiographic classification*

The angiographic types were classified using the International TAK Conference in Tokyo 1994 angiographic classification standards (10).

*Disease activity*

Disease activity was assessed using the proposed National Institute of Health (NIH) study criteria: (1) systemic features (*i.e.* fever, myalgia, weight loss), (2) elevated erythrocyte sedimentation rate or CRP, (3) features of vascular ischaemia or inflammation (*i.e.* carotidynia, claudication, diminished or absent pulse, asymmetric blood pressure in either upper and/or lower limbs, bruit), and (4) angiographic changes (1). Remission was indicated by a NIH disease activity score of <2 and an administration of prednisolone at a dose of <7.5 mg/day (11).

**Table I.** Characteristics of TAK patients.

| Patient Demographics | n=21 | |
|---|---|---|
| Female, n (%) | 20 (95.2) | |
| Age, years (mean±SD) | 38.6 ± 11.8 | |
| Age at diagnosis, years (mean±SD) | 31.2 ± 11.9 | |
| Disease duration (months) | | |
| Mean±SD | 84.7 ± 63.2 | |
| Median (min-max) | 62 (15-300) | |
| Period of untreatment (months) (mean±SD) | 7.76 ± 20.15 | |
| Duration of csDMARDs (months) (mean±SD) | 27.9 ± 32.5 | |
| Duration of csDMARDs plus bDMARDs (months) (mean±SD) | 37.1 ± 22.3 | |
| GC treatment duration (months) (mean±SD) | 44.1 ± 27.2 | |
| Initial dose of GC (mg/day) | | |
| Mean±SD | 37.1 ± 16.2 | |
| Median (min-max) | 32 (4-64) | |
| Discontinuation of GC, n (%) | 15 (71.4) | |
| Classification of TAK, n (%) | | |
| I | 6 (28.6) | |
| IIA | 4 (19) | |
| IIB | 2 (9.5) | |
| III | 1 (4.8) | |
| IV | 0 | |
| V | 8 (38.1) | |
| csDMARDs, n (%) | Previously | Currently |
| MTX | 17 (80.9) | 13 (61.9) |
| AZT | 10 (47.6) | 4 (19.0) |
| CYC | 4 (19.0) | - |
| LEF | 2 (9.5) | - |
| Use of antiaggregant, n (%) | 8 (38.1) | |
| Surgery, n (%) | 4 (19.0) | |
| Endovascular interventions, n (%) | 3 (14.3) | |
| Infections, n (%) | 3 (14.3) | |

SD: standard deviation; csDMARDs: conventional disease-modifying ant-rheumatic drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs; GC: glucocorticoid; MTX: methotrexate; AZT: azathioprine; CyC: cyclophosphamide; LEF: leflunomide.

*Vascular assessment*

Radiographic images of the patients at the time of the initial diagnosis, before treatment upon adding the biological agent, and at the final control visit after treatment were examined to assess the vascular damage. An intima-media thickness (IMT) of the carotid artery of >0.8 mm was considered to indicate an active lesion (12).

Computed tomography angiography (CTA) imaging was used to evaluate the vascular changes. The rates of mild stenosis, moderate-to-severe stenosis, occlusions, and aneurysms (and dilation) were calculated using CTA. The carotid artery, vertebral artery, brachiocephalic artery, subclavian artery, axillary artery, ascending aorta, aortic arch, descending aorta, abdominal aorta, celiac artery, superior mesenteric artery, renal artery, iliac artery, bilateral pulmonary artery, and coronary artery, including the right coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and left main trunk arterial region were evaluated to detect stenosis (mild = <50%, moderate-to-severe = 50–99% narrowing), occlusions, and aneurysms (including dilation). The Combined Arteritis Damage Score (CARDS), proposed by Nakagomi *et al*. (13), was used to analyse vascular damage in large-vessels. The formula of the CARDS score is as follows: number of mild stenosis x 0.6 + number of moderate and severe stenosis x 1.2 + number of occlusions × 1.6 + number of aneurysms x 0.8.

The vascular outcome was classified into the categories of *stable* (absence of

**Table II.** Disease activity and radiological outcomes at the diagnosis and during the treatment.

| | At time of diagnosis | Before bDMARDs | After bDMARDS | $p^*$ | $p^\dagger$ |
|---|---|---|---|---|---|
| **ESR (mm/h)** (mean ± SD) | 59.0 ± 37.4 | 43.9 ± 40.5 | 15.7 ± 14.2 | <0.001 | 0.002 |
| **CRP (mg/dl)** (mean ± SD) | 6.0 ± 6.1 | 3.4 ± 2.3 | 0.6 ± 0.7 | <0.001 | 0.008 |
| **NIH score** (mean ± SD) | 3.4 ± 0.7 | 1.8 ± 1.4 | 0.4 ± 0.9 | <0.001 | 0.001 |
| **CARDS** (mean ± SD) | 3.8 ± 3.2 | 4.4 ± 3.1 | 3.4 ± 2.9 | 0.526 | 0.014 |
| **IMT, n (%)** | 18 | 19 | 17 | 0.080 | 0.352 |

*At time of diagnosis *vs*. after bDMARDs.
†Before bDMARDs *vs*. after bDMARDs.
bDMARDs: biological disease-modifying anti-rheumatic drugs; SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NIH: National Institute of Health; CARDS: Combined Arteritis Damage Score; IMT: intima-media thickness.

**Table III.** Comparison of TAK patients treated with bDMARDS.

| | Infliximab (n=9) | Tocilizumab (n=6) | Infliximab+ Tocilizumab (n=6) | *p* |
|---|---|---|---|---|
| **ΔESR (mm/h) (mean±SD)** | -31.0 ± 37.7 | -18.2 ± 12.3 | -34.0 ± 48.9 | 0.732 |
| **ΔCRP (mg/dl) (mean±SD)** | -3.59 ± 5.54 | -0.82 ± 0.52 | -3.54 ± 4.35 | 0.443 |
| **ΔNIH score (mean±SD)** | -1.22 ± 2.05 | -1.17 ± 0.98 | -1.67 ± 1.63 | 0.850 |
| **ΔCARDS (mean±SD)** | -1.11 ± 1.83 | -1.40 ± 0.98 | -0.00 ± 1.08 | 0.224 |
| **Remission, n(%)** | 8 (88.9) | 5 (83.3) | 3 (50.0) | 0.223 |

bDMARDs: biological disease-modifying anti-rheumatic drugs; SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NIH: National Institute of Health; CARDS: Combined Arteritis Damage Score.

any change in the total lesion number and CARDS score), *progression* (increase in the total lesion number and/or CARDS score), and *regression* (decrease in the total lesion number and/or CARDS score).

*Ethical considerations*

The bDMARDs were administered in accordance with the permission of the Turkish Medicines and Medical Devices Agency, and every patient who planned to use these treatments signed an informed consent form before this retrospective analysis. This study was performed with the approval of the local ethical committee (Approval number: 12.06.2019/535).

*Statistical analysis*

The data were analysed using Windows SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to evaluate the samples and results. Differences in the categorical data were analysed using the chi-square test or Fisher's exact test. McNemar's test was used to compare differences between the groups in terms of dichotomous variables before and after treatment. Student's *t*-test was used to compare parametric variables between the groups, whereas the Mann-Whitney U-test was used to compare non-parametric variables. The Wilcoxon signed-rank test was used to determine the significance of the changes within each group before and after treatment. A *p*-value of <0.05 was considered statistically significant.

## Results

*Baseline characteristics of the study patients*

There were 21 TAK patients who received bDMARDs. INF and TCZ were given to 12 (57.1%) and 9 (42.6%) patients, respectively. Both INF and TCZ in conjunction were administered to 6 patients. Three of them were switched from INF to TCZ, and the other 3 from TCZ to INF.

The mean age of the patients was 38.6±11.8 years, and 20 (95.2%) of the patients were females. The most common angiographic pattern was the type 5 pattern (n=8, 38.1%). The mean diagnosis age was 31.2±11.9 years, the mean initial GC dose was 37.1±16.2 mg/day, the mean duration of the GC treatment was 44.1±27.2 months, and the discontinuation rate was 71.4%. The median disease duration was 62 months (min = 15; max = 300).

Before their bDMARD therapies, all the patients received corticosteroids and at least one conventional immunosuppressive agent. Seventeen patients (80.9%) received MTX, 10 (47.6%) received AZT, and 4 (19.1%) received CyC. Additionally, 2 patients (9.2%) were treated with LEF. The mean follow-up time for csDMARD therapy was 27.9±32.4 months, and 2 patients were administered INF as first-line treatment due to their accompanying ankylosing spondylitis (AS) and ulcerative colitis. Seventeen patients (80.9%) were still continuing with the combination regimens (csDMARDs + bDMARDs) in their last visits, and the other patients were only using bDMARDs. Four patients underwent arterial bypass surgery and three patients had endovascular interventions. The number of patients using antiaggregant agents was 8 (38.1%), concomitant with the bDMARDs. The clinical characteristics of the TAK patients are summarised in Table I.

During the follow-up, three patients developed serious infections. One patient who was being administered infliximab therapy also developed tuberculous lymphadenitis, and another patient died due to colonic malignancy.

*Disease activity*

The mean ESR levels, CRP levels, and NIH disease activity at the time of diagnosis were 59.0±37.4 (mm/h), 6.0±6.1(mg/dl), and 3.4±0.7, respectively. After treatment, there was a statistically significant decrease in the mean ESR levels, CRP levels, and NIH disease activity scores (*p*-value <0.001 for all at the time of diagnosis *vs*. after bDMARDs; and *p*-value <0.05 for all before *vs*. after bDMARDs) (Table II).

The patients were divided into three groups according to the bDMARD drugs they had used (Table III). There were no significant differences between the groups in terms of the decreases in their ESR levels, CRP levels, or NIH scores compared with pre-treatment levels. Between the groups, a similar number of patients achieved remission.

**Table IV.** Changes of vascular outcomes with bDMARDs treatment in TAK patients.

| Patients No: | Drugs | bDMARDs Treatment Duration (months) | Previous Treatments | Before bDMARD's Therapy | | | | | | After bDMARD's Therapy | | | | | | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Stenosis | | Occlusion | **Aneurysm** | Totally Score | CARDS | Stenosis | | Occlusion | **Aneurysm** | Totally Score | CARDS | |
| | | | | Mild | Moderate Severe | | | | | Mild | Moderate Severe | | | | | |
| 1 | IFX | 84 | ETN, ADA | 1 | 4 | 1 | 0 | 6 | 7.0 | 1 | 2 | 1 | 0 | 4 | 4.0 | Regression |
| 2 | IFX | 47 | AZT | 2 | 2 | 0 | 0 | 4 | 3.6 | 3 | 1 | 0 | 0 | 4 | 3.0 | Regression |
| 3 | IFX | 60 | CYC, AZT | 0 | 3 | 1 | 0 | 4 | 5.2 | 0 | 1 | 2 | 0 | 3 | 4.4 | Regression |
| 4 | IFX | 24 | MTX, AZT | 0 | 2 | 2 | 0 | 4 | 5.6 | 0 | 0 | 3 | 0 | 3 | 4.8 | Regression |
| 5 | IFX | 84 | MTX, CYC | 0 | 1 | 1 | 0 | 2 | 2.8 | 0 | 0 | 0 | 0 | 0 | 0.0 | Regression |
| 6 | IFX | 51 | AZT, MTX | 0 | 1 | 0 | 0 | 1 | 1.2 | 0 | 1 | 0 | 0 | 1 | 1.2 | Stable |
| 7 | IFX | 50 | MTX | 0 | 6 | 1 | 0 | 7 | 8.8 | 3 | 2 | 1 | 0 | 6 | 5.2 | Regression |
| 8 | IFX | 50 | MTX, CYC | 0 | 2 | 0 | 0 | 2 | 2.4 | 0 | 0 | 1 | 0 | 1 | 1.6 | Regression |
| 9 | IFX | 12 | MTX | 0 | 0 | 0 | 0 | 0 | 0.0 | 0 | 2 | 0 | 0 | 2 | 2.4 | Progression |
| 10 | TCZ | 26 | MTX | 1 | 2 | 0 | 0 | 3 | 3.0 | 1 | 0 | 0 | 0 | 1 | 0.6 | Regression |
| 11 | TCZ | 6 | MTX, AZT | 0 | 1 | 0 | 0 | 1 | 1.2 | 0 | 0 | 0 | 0 | 0 | 0.0 | Regression |
| 12 | TCZ | 12 | AZT | 1 | 0 | 0 | 0 | 1 | 0.6 | 0 | 0 | 0 | 0 | 0 | 0.0 | Regression |
| 13 | TCZ | 8 | MTX | 1 | 2 | 4 | 0 | 7 | 9.4 | 0 | 1 | 3 | 0 | 4 | 7.6 | Regression |
| 14 | TCZ | 32 | MTX | 3 | 0 | 1 | 0 | 4 | 3.4 | 3 | 0 | 1 | 0 | 4 | 3.4 | Stable |
| 15 | TCZ | 33 | MTX | 0 | 3 | 1 | 0 | 4 | 5.2 | 0 | 0 | 1 | 0 | 1 | 2.8 | Regression |
| 16 | IFX /TCZ | 15 | MTX, AZT | 0 | 2 | 1 | 0 | 3 | 4.0 | 0 | 1 | 1 | 0 | 2 | 2.8 | Regression |
| 17 | IFX / TCZ | 38 | MTX, LEF | 0 | 0 | 0 | 0 | 0 | 0.0 | 0 | 0 | 0 | 0 | 0 | 0.0 | Stable |
| 18 | IFX / TCZ | 52 | AZT, MTX | 0 | 1 | 2 | 3 | 6 | 6.8 | 2 | 3 | 1 | 0 | 6 | 6.4 | Regression |
| 19 | TCZ / IFX | 37 | MTX | 0 | 1 | 5 | 0 | 6 | 9.2 | 0 | 3 | 3 | 0 | 6 | 8.4 | Regression |
| 20 | TCZ / IFX | 21 | AZT, MTX, LEF | 0 | 0 | 2 | 0 | 2 | 3.2 | 1 | 0 | 2 | 0 | 3 | 3.8 | Progression |
| 21 | TCZ / IFX | 36 | MTX, AZT | 3 | 0 | 3 | 3 | 9 | 9.0 | 2 | 2 | 4 | 1 | 9 | 10.8 | Progression |
| The total number of vascular lesions | | | | 12 | 33 | 25 | 6 | 76 | | 16 | 19 | 24 | 1 | 60 | | |

bDMARDs: biological disease-modifying anti-rheumatic drugs; CARDS: Combined Arteritis Damage Score; IFX: infliximab; TCZ: tocilizumab; ETN: etanercept; ADA: adalimumab; AZT: azathioprine; CyC: cyclophosphamide; MTX: methotrexate; LEF: leflunomide.

**Table V.** Comparison of the parameters in Takayasu's arteritis patients with vascular regression and non-regression.

| | Patients with regression of vascular lesions (n=15) (Mean±SD) | Patients with non-regression of vascular lesions (n=6) (Mean±SD) | *p* |
|---|---|---|---|
| Age, years | 38.67 ± 11.18 | 38.33 ± 14.26 | 0.876 |
| Age at diagnosis, years | 31.80 ± 11.06 | 32.33 ± 15.00 | 0.845 |
| Disease duration (months) | 89.73 ± 74.02 | 72.17 ± 18.66 | 0.785 |
| Basal ESR (mm/h) | 69.33 ± 39.54 | 33.17 ± 10.03 | 0.086 |
| Basal CRP (mg/dl) | 6.68 ± 5.32 | 4.35 ± 7.78 | 0.161 |
| Basal NIH score* | 3.60 ± 0.51 | 3.00 ± 0.89 | 0.064 |
| Basal CARDS score | 4.09 ± 2.97 | 2.97 ± 3.80 | 0.388 |
| Initial dose of GC (mg/day) | 35.47 ± 12.03 | 41.33 ± 14.46 | 0.545 |
| Duration of GC treatment (months) | 43.27 ± 29.29 | 46.00 ± 23.34 | 0.726 |
| Duration of cDMARDs (months) | 28.53 ± 35.46 | 26.50 ± 26.41 | 0.969 |
| Time from diagnosis to bDMARD's treatment (months) | 39.40 ± 47.18 | 26.00 ± 26.83 | 0.725 |
| Duration of bDMARDs (plus cDMARDs) treatments (months) | 39.20 ± 25.01 | 31.67 ± 13.66 | 0.612 |

SD: standard deviation; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NIH: National Institute of Health; CARDS: Combined Arteritis Damage Score; GC: glucocorticoid; csDMARDs: conventional synthetic disease-modifying ant-rheumatic drugs; bDMARDs: biological disease-modifying anti-rheumatic drugs.

*Radiological outcomes*

Control CTA imaging after bDMARD therapies was available for all patients. Carotid intima-media thickness (IMT) has been documented in most patients. There was no statistically significant change in the IMT ratio after treatment (Table II). The mean CARDs score was 3.8±3.2 at the time of diagnosis and continued to increase until the bDMARD treatments were initiated (from 3.8±3.2 to 4.4±3.1). But there was a statistically significant decrease in the CARDS score (from 4.4±3.1 to 3.4±2.9, $p$=0.014) after the bDMARD treatments (Table II). There was no significant difference between the treatment groups (INF, TCZ, and INF+TCZ) in terms of the decreases in CARDS scores compared with pre-treatment levels (Table III). There was no correlation between CARDS score and age, disease duration, basal ESR levels, basal CRP levels, basal NIH activity score, and duration of csDMARD or bDMARD treatment (data not shown). The total number of vascular lesions (mild stenosis + moderate-to-severe stenosis + occlusions + aneurysms) was lower in the last CTA imaging scan compared to before the bDMARD treatments. The total number of aneurysms decreased from 6 to 1 without surgery or endovascular interventions in 2 patients. The transformation between severe stenosis and occlusions was also observed in some patients. While there was no statistically significant change in the number of occlusion (from 25 to 24, $p$=1.00), aneurysms (from 6 to 1, $p$=0.171), and mild (from 12 to 16, $p$=0.296) and moderate-to-severe stenosis (from 33 to 19, $p$=0.085), a statistically significant decrease in the total number of lesions (from 76 to 60, $p$=0.008) was observed with bDMARD treatments (Table IV).

Regression was detected in the vascular lesions of 15 patients (71.4%) compared to the last image before bDMARD therapies. Although bDMARDs were administered for a long time, at a mean of 37.1±22.3 months, vascular progression was continued in 3 patients (14.3%). Three (14.3%) patients were radiologically stable. Vascular regression was achieved in 7 out of 9 (77.7%) and 5 out of 6 (83%) patients using only INF and TCZ, respectively (Table IV).

Comparing vascular regression patients with those who showed non-regression, there were no significant differences for parameters such as age for the diagnosis, disease duration, dose of GC, or the duration of the csDMARD and/or bDMARD treatments (Table V).

## Discussion

The results of this study show that bDMARDs are effective at treating regression of vascular damage, systemic inflammation, and disease activity in TAK patients with inadequate response to csDMARDs. Given that bDMARDs are a csDMARD-resistant group to begin with, adding bDMARDs is effective at decreasing the number of vessels involved.

The main purpose of TAK treatment is to control disease activity and prevent the development of structural vascular damage. While there are certain recommendations for the follow-up and treatment of TAK, there is no consensus in this area, and the effect of bDMARDs on vascular damage was not very well known beforehand. There is currently no validated and approved scoring system for evaluating the damage that occurs in TAK. Although the Takayasu Arteritis Damage Score has been used in two studies and is described as specifying in assessing TAK damage, its original content has not been published (14, 15). Nakagomi *et al*. developed CARDS as an imaging score to evaluate long-term vascular damage (13). This damage index has not yet been used in any study to evaluate patients' responses to treatment. In the present study, we calculated the pre-treatment and post-treatment CARDS scores of patients receiving bDMARDs and compared the treatment effectiveness. The present study also evaluated the relationship of changes in CARDS to acute-phase reactant (ESR and CRP) levels and NIH disease activity scores. Our findings demonstrate that bDMARDs significantly reduced the CARDS scores in addition to the ESR levels, CRP levels, and NIH scores in TA patients. For these patients, bDMARDs are effective not only on in-

flammation markers but also on vascular structural lesions.

In the present study, the total number of lesions was obtained by summing the stenosis (mild, moderate-to-severe), occlusion, and aneurysm numbers in all arteries in each patient. The total number of lesions decreased after bDMARD treatment. This finding was quite remarkable, as it suggested that for patients who were resistant to csDMARD treatment, adding bDMARD agents seemed to be effective in decreasing the number of vessels involved. Additionally, most of the regressed lesions were stenosis or aneurysms. This may suggest that adding bDMARD agents in earlier stages even to csDMARD-responsive patients may have an even bigger impact on the decreasing numbers of vessels involved. Based on these findings, the administration of bDMARD agents may begin in earlier stages, especially if there are not any occlusions. The marked improvement of aneurysms with bDMARDs, without surgery or endovascular interventions, is one of the most important findings of this study. This result shows that the formation of aneurysms in TAK is related to active inflammation and can be resolved with the appropriate treatments.

There was no statistically significant change in the carotid IMT values after bDMARD treatment. In the present study, however, the IMT was not evaluated in the other arteries due to the lack of standardised IMT values for said arteries. Therefore, we could not comment on the IMT status of the other arteries. There is a need for further studies to evaluate the effects of bDMARDs on the carotid and other arteries regarding IMT.

In their meta-analysis, Barra *et al*. reported similar remission rates for csDMARDs and bDMARDs (58% and 64%, respectively). In both groups, a significant decrease was observed in the steroid dose (-17.2 mg/day and -11.1 mg/day, respectively), ESR levels (-16.3 mm/h and -47 mm/h, respectively), and CRP levels (-14.1 mg/L, -20 mg/L, and -21.8 mg/L for csDMARDs, anti-TNF agents, and TCZ, respectively) (7). Among our TA patients, the GC discontinuation rate was high (71.4%), and the decreases in the ESR and CRP levels after bDMARD therapy were statistically significant. The NIH disease activity scores also decreased with bDMARD treatments. However, there were no statistical differences for the ESR levels, CRP levels, or NIH scores in patients receiving TCZ, INF, or both. TA begins with inflammation (*e.g*. aortitis) in the large arteries and gradually progresses to radiologically identifiable vessel wall changes (16, 17). The acute phase response reflects the inflammation in the vessel wall in TA and other rheumatic diseases. In inflammatory diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), cytokine inhibitors including anti-TNF and anti-IL6 are effective at controlling inflammation (18). This decreased inflammation is related to the regression of the symptoms. However, their effectiveness in reversing the structural damages to the joints has not been clearly demonstrated (19, 20). Similar to the permanent damage observed in the joints of patients with RA and AS, inflammation in TAK results in structural damage to the arterial walls. In untreated patients, the number of vascular lesions is expected to increase during the natural course of TAK (21). The results of the present study show that certain arterial wall changes in TAK can be reversed using biological agents. Treatments in TA patients initially suppress systemic inflammation, and the prevention of vascular damage requires a longer treatment duration. There may be a need for studies evaluating the effects of the long-term use of biological agents on radiological damage.

Studies have shown that new lesions appear in 19%, 13.3%, and 33% of patients with TAK who use MTX, LEF, and CYC, respectively (22-24). These studies also show that while AZT is observed to halt lesion progression, it does not lead to lesion regression (25). In a study performed using TNF inhibitors, it was observed that 10/15 patients (66.7%) achieved sustained remission with no new lesions, while 5/15 patients (33.3%, 3/8 INF, 2/7 Etanercept) developed new lesions (26). In another study, 2/13 (15%) patients who were treated with INF showed an improvement, and 2/13 (15%) showed new lesions. And there was no correlation between disease activity, as measured by BVAS, and radiological changes (27). Gudbrandsson *et al*. observed that patients who received more aggressive treatment regimens such as TNF inhibitors had reduced vascular damage (number of new lesions; TNFi *vs*. csDMARDs, 10%, and 40%, respectively) and higher sustained remission rates (TNFi *vs*. csDMARDs, 44%, and 20%, respectively) by the second year of their treatment (28). In a study involving TCZ use, the angiographic assessments at the end of a 6-month period showed 40% vascular activity, while the rest remained stable, whereas, in another study, 3/7 (42.8%) patients (those who achieved a complete response) showed improvement or stabilisation of all vascular lesions without disease progression. And in both studies, although acute phase reactants were normal, cases with vascular progression were reported (29, 30). The results as to whether the treatments for TAK prevent the long-term development of structural vascular damage are contradictory. In our study, as a result of the radiographic evaluation, we observed that vascular lesions regressed in 71.4% of the patients, while only 14.8% had vascular progression. The vascular improvement achieved with bDMARDs was higher than the rates in the literature.

In this study, it was found that in the period before bDMARD treatments began, the CARDS score, which reflects vascular damage, continued to increase, even though the csDMARD treatments improved the ESR levels, CRP levels, and NIH scores. Initiating the bDMARD treatments resulted in a decrease of the CARDS score together with the ESR levels, CRP levels, and NIH scores. Furthermore, there was no difference in the effects of INF, TCZ, or both.

The present study has certain limitations, the first being the low number of patients. The lack of statistical significance in certain comparisons may have been caused by the small sample size. Second, this was designed as a retro-

spective study, and the decision to initiate biological agents was based on the experience of the clinicians. Third, the study did not include a control group due to its retrospective design. The strengths of the present study are that the patients and radiological findings were evaluated at a single centre and that the study reflects real-life experiences.

In conclusion, our preliminary results reveal that bDMARD therapies may provide additional benefits to patients who are unresponsive to csDMARD treatments. More detailed studies are needed to investigate the effects of earlier administration of biological agents on the development of vascular damage in TAK patients.

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