STUDY PROTOCOL

Official Title:

Cessation of Biologic Treatment in Patients With Takayasu Arteritis in Sustained Remission

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Background and Rationale	Takayasu arteritis (TAK) is a rare, chronic granulomatous large-vessel arteritis affecting mainly aorta and its major branches. In addition to glucocorticoids, non-biologic agents such as methotrexate, azathioprine, and mycophenolate mofetil can be chosen in the treatment. However, prospective and retrospective studies have shown the efficacy of biologic agents in refractory and relapsing patients. Treatment choices are typically guided by observational studies and expert opinions, yet there is a notable lack of literature providing recommendations on when it is safe to discontinue treatment. In a review assessing the efficacy of tocilizumab in patients with Takayasu arteritis, it was found that six out of 13 patients (46%) who received tocilizumab for a median duration of six months experienced a relapse after a median of five months (range: 2-9) following the discontinuation of treatment. The study indicated that the duration of tocilizumab therapy was comparable between relapsing and non-relapsing patients[1]. Additionally, in a separate study comparing anti-TNF agents and tocilizumab in Takayasu arteritis patients, biologic treatments were discontinued in seven patients (comprising four on infliximab, two on tocilizumab, and one on adalimumab) upon achieving permanent remission. Among these, one patient (50%) from the tocilizumab

	group relapsed 26 months after treatment cessation, while three patients (60%) from the anti-TNF group relapsed after a median of 18 months (range: 7-60) following discontinuation[2]. When examining other inflammatory diseases treated with biologic agents, the GiACTA study on giant cell arteritis found that a significant number of patients who received tocilizumab for one year were able to maintain drug-free remission for two years after stopping the treatment[3]. In contrast, for rheumatoid arthritis, discontinuing biologic disease-modifying anti-rheumatic drugs (bDMARDs) and/or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) in patients who have been in remission for six months or more after tapering off glucocorticoids often leads to exacerbations. Therefore, it is usually advisable to consider either a dose reduction or an increase in the interval between doses[4]. Similarly, for ankylosing spondylitis, it is recommended to develop a treatment plan that includes a reduction in bDMARD doses to effectively maintain treatment responses in patients who have been in remission for at least six months[5].
Study Duration	Dose tapering period: 3 months; Post-withdrawal follow-up period: 12 months
Study Design	This is a prospective, observational cohort study designed to evaluate the outcomes of biologic treatment withdrawal in patients with Takayasu arteritis who have received TNF inhibitors or tocilizumab for at least 3 years and are in long-standing clinical and radiologic remission. Eligible patients will undergo a 3-month biologic dose tapering period**.** Patients who do not experience a relapse during this phase will discontinue biologic therapy at the end of 3 months. All patients will then enter a 12-month post-withdrawal follow-up period**.** Clinical and laboratory evaluations will be conducted at 1 month following cessation and every 3 months thereafter. Prior to tapering, carotid and thoracoabdominal CT or MR angiography will be performed in patients who have not undergone vascular imaging within the previous 12 months. In case of clinical suspicion, re-imaging is planned at the discretion of the physician. Active disease and major/minor relapse evaluation of patients is planned to be performed according to the 'EULAR 2018 Large Vessel Vasculitis (LVV) Treatment Recommendations' consensus report.

[1] Decker vd., "Tocilizumab and Refractory Takayasu Disease".
[2] Alibaz-Oner vd., "Biologic Treatments in Takayasu's Arteritis".
[3] Stone vd., "Long-Term Effect of Tocilizumab in Patients with Giant Cell Arteritis".
[4] Smolen vd., "EULAR Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biologic Disease-Modifying Antirheumatic Drugs".
[5] Ramiro vd., "ASAS-EULAR Recommendations for the Management of Axial Spondyloarthritis".

Primary Objective	To evaluate whether patients with Takayasu arteritis who have been in long-standing clinical and radiologic remission and have received biologic therapy (TNF inhibitors or tocilizumab) for at least 3 years can maintain remission following planned treatment discontinuation
Primary outcome	• The proportion of patients maintaining remission at month 12 following treatment withdrawal
Secondary Objective	• The proportion of patients experiencing disease relapse (major or minor) during the 3-month dose tapering phase or the 12-month post-treatment withdrawal period • The time to first disease relapse (major or minor) following biologic treatment withdrawal
Primary and Secondary Outcome Measures	**Remission:** The absence of new or worsening clinical symptoms and signs together with acute phase response within normal limits. **Active disease:** 1. The presence of typical signs or symptoms of active LVV 2. At least one of the following: 1. Current activity on imaging or biopsy 2. Ischaemic complications attributed to LVV 3. Persistently elevated inflammatory markers (after other causes have been excluded) **Major relapse:** Recurrence of active disease with either of the following: 1. Clinical features of ischaemia (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication) 2. Evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis or dissection. **Minor relapse:** Recurrence of active disease, not fulfilling the criteria for a major relapse
Eligibility Criteria	Participants must meet all of the following criteria to be eligible for enrollment:

	1. Diagnosis of TAK according to the 2022 American College of Rheumatology/EULAR Classification Criteria for Takayasu Arteritis 2. To have received biologic therapy (TNF inhibitors and/or tocilizumab) for at least 3 years 3. There is no evidence of activation in clinical evaluation, current vascular imaging and laboratory values 4. Patients who have had no change in treatment in the last 1 year and who have not received glucocorticoid treatment in the last 6 months will be included 5. Willing and able to provide written informed consent
Exclusion Criteria	1. Presence of additional diseases (inflammatory bowel disease, ankylosing spondylitis, etc.) in the active period that require the use of biologic agents 2. Patients who cannot attend the planned control visits after dose reduction and treatment discontinuation 3. Pregnancy or planning to become pregnant during the study period
Treatment Description	Eligible patients with Takayasu arteritis who have received biologic therapy (TNF inhibitors or tocilizumab) for at least 3 years and are in sustained clinical and imaging remission will undergo a predefined dose tapering protocol over a 3-month period. The dose reduction schedules are as follows: <u>Treatment dose reduction protocol;</u> - Infliximab 3 mg/kg/6-8 w iv (according to previous dose range) - Adalimumab 40 mg sc/3 w - Certolizumab pegol 200 mg sc/3 w - Tocilizumab 162 mg sc/2 w -Tocilizumab 8 mg/kg iv/6 w • Patients who do not relapse during the dose tapering phase will have biologic treatment discontinued completely at the end of 3 months. • csDMARDs (e.g., methotrexate, azathioprine, mycophenolate mofetil) may be continued if stable for at least 12 months prior to tapering.

Statistical analysis	Descriptive statistics will be used to summarize baseline demographic and clinical characteristics. The primary outcome—the proportion of patients maintaining remission at month 12 following treatment withdrawal—will be analyzed using the Kaplan-Meier method to estimate remission maintenance over time. The corresponding 95% confidence interval will be calculated. Secondary outcomes, including the rate and timing of major and minor relapses during the dose tapering and 12-month post-withdrawal periods, will be evaluated using survival analysis techniques. Time-to-event data will be compared using the log-rank test where applicable. Cox proportional hazards regression models may be used to assess the impact of baseline variables on relapse risk. Subgroup analyses will be performed based on biologic agent type (e.g., TNFi vs tocilizumab) and concomitant DMARD use. A p-value < 0.05 will be considered statistically significant.
Ethical Considerations	The study will be conducted in accordance with the Declaration of Helsinki. Written informed consent will be obtained from all participants. Ethics committee approval was obtained from the Marmara University Faculty of Medicine Clinical Research Ethics Committee prior to patient enrollment (Approval No: 09.2023.1564).