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Advancements In Biological Treatment Of Takayasu Arteritis: Efficacy, Safety, And Future Perspectives

Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka,

Marianna Chmiel, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

1. **Mikołaj Biskupski**
   Department of Interventional Cardiology and Cardiac Arrythmias, Teaching Hospital No. 2 of the Medical University of Lodz, Zeromskiego Street 113, 90-549 Lodz
   mikolajbiskupskimed@gmail.com
   https://orcid.org/0009-0009-8103-4053

2. **Marianna Chmiel|**
   Military Clinical Hospital With Polyclinic Spzoz In Wrocław Ul. Rudolfa Weigla 5, 50-981 Wrocław
   https://orcid.org/0009-0001-9571-9477

1.

3. **Aleksandra Cygnarowicz**

Bonifraters Medical Center sp. z. o. o. Branch in Krakow, Trynitarska 11 St., 31-061 Krakow, Poland

o.cygnarowicz@gmail.com

https://orcid.org/0009-0002-2208-0104

4. **Oliwia Maciaszek**

2. Jan Biziel University Hospital No. 2 in Bydgoszcz Ul. Kornela Ujejskiego 75, 85-168 Bydgoszcz, Poland,

oliwia.maciaszek@gmail.com,

orcid: **https://orcid.org/0009-0000-9557-2092**

5. **Aneta Mandziuk**

Independent Public Health Care Facility of the Ministry of Interior and Administration in Białystok/ Fabryczna Street 27 15-471 Białystok, Poland

3. **aneta.mandziuk@o2.pl**
4. **https://orcid.org/0009-0001-2787-9479**

6. **Krystyna Zabojska**

Hospital of Our Lady of Perpetual Help in Wolomin, Gdynska 1/3, 05-200 Wolomin, Poland

k.zabojska@gmail.com

https://orcid.org/0009-0002-6962-0497

7. **Mariola Turemka**

Voivodeship Hospital in Bialystok/Marii Sklodowskiej-Curie 26, 15-278 Bialystok, Poland

mariolaturemka841@gmail.com

https://orcid.org/0009-0001-8219-6515

8. **Artur Tumiński**

Artur Tumiński, Regional Specialized Hospital in Wrocław, Kamieńskiego 73A,

51-124 Wrocław

artur.tuminski1998@wp.pl

https://orcid.org/0009-0001-3646-7142

Abstract

Introduction and Objective

Takayasu's arteritis (TAK) is a chronic autoimmune vasculitis that primarily impacts the aorta and its major branches. The standard treatment has been glucocorticoids; however, their prolonged usage can cause severe side effects, and many patients fail to maintain sustained remission. This review aims to assess the recent advances in utilizing biological drugs for treating TAK, with a focus on their efficacy and safety profiles.

Methods

To conduct this review, we analyzed clinical trials, retrospective studies, and case reports. The databases searched included PubMed, MEDLINE, and Scopus utilizing keywords like "Takayasu arteritis," "biological treatment," and specific medication names.

Brief Description of the Current State of Knowledge

Several biological therapies targeting key inflammatory pathways implicated in TAK have demonstrated promise. These include IL-6 inhibitors (tocilizumab), TNF-alpha inhibitors (infliximab, etanercept), and JAK inhibitors (tofacitinib). Clinical research and case reports indicate these therapies can decrease disease activity, facilitate glucocorticoid tapering, and enhance quality of life in patients who do not sufficiently respond to standard treatment. However, concerns remain about long-term safety, including heightened infection risk and paradoxical inflammatory reactions.

Summary

Biological medications represent a major step forward in TAK treatment, providing hope for individuals unresponsive to conventional approaches. However, additional large-scale, randomized controlled trials are needed to establish their long-term efficacy and safety of the treatment.

Keywords: Takayasu arteritis, biological treatment, IL-6 inhibitors, TNF-alpha inhibitors, JAK inhibitors.

Introduction

Takayasu's arteritis (TA) is an autoimmune inflammation of the large vessels, mainly involving

the aorta and its large branches [1], [2]. It is a rare disease, with an incidence of 1.11 per million per year [3]. It is most common in young women, under the age of 40 [4], [5]. Vasculitis results in thickening of the vascular wall, fibrosis and narrowing. These changes cause limb numbness, transient ischemic attack, cardiovascular event and renovascular hypertension [6]. Systemic corticosteroids remain the mainstay of treatment, but most patients fail to achieve remission from their use; moreover, these drugs used chronically cause serious side effects, including infections, cardiovascular disease, osteoporosis and growth restriction in children [7]. For this reason, biologic drugs have begun to be used frequently in the treatment of TA after the failure of glucocorticosteroid therapy. This review focuses on recent data on the use of biologic drugs in the pharmacotherapy of TA [5].

Tofacitinib

Immunomechanistic studies showed that dendritic cells located in the blood vessel walls of patients with Takayasu arteritis (TAK) attrack macrophages and T lymphocytes, leading to the development of an inflammatory state. Pro-inflammatory cytokines such as TNF-alpha, IL-6, IL-17, and INF-gamma play an important role in this process [8], [9]. Intracellularly, the signal coming from various pro-inflammatory cytokines is mediated by the Janus kinase (JAK)/STAT pathway. This signaling pathway also plays an important role in the TAK patogenesis [10]. One of the therapeutic options could be Tofacitinib. Tofacitinib (TOF) is a monoclonal antibody that inhibits the Janus kinase signaling pathway. Studies have demonstrated that Tofacitinib can inhibit the production of pro-inflammatory cytokines (IL-17, IL-23, interferon-gamma) and the activation of T lymphocytes. Although therapy using steroids and disease-modifying drugs is effective in most cases, there are still patients who are resistant to such treatment. In these cases, biologic therapy plays a significant role. Numerous clinical cases in which the benefits of using TOF in TAK Patients have been described [11], [12], [13], [14]. One on them is the study conducted by Li et al., where scientists described 5 clinical cases in which they demonstrated the role of biologic therapy using Tofacitinib. They evaluated the efficacy and safety of that treatment. The patients in this group had previously undergone ineffective therapy with steroids, DMARDs, and Tocilizumab. At the beginning of the study all patients exhibited signs of active disease: carotidynia, fever, mialgia, hypertension as well as elevated level of inflammatory parameters. After 4 weeks of treatment, 4 out of 5 patients showed no signs of active disease, and inflammatory markers decreased. In 3 out of 5 cases, a reduction in the use of steroids was observed, along with improvement and stabilization of artery stenosis and mural thickness. This shows that Tofacitinib may be an effective treatment in cases resistant to other therapies [12].

There are some studies which compare the efficiancy and safety of using Tofacitinib and other drugs. One of them is the study conducted by Kong et al. which showed that Tofacitinib was superior to Metotrexat in different categories such as: complete remission induction, possibility to prevent relapse and reduction of the concomitant glucocorticoid dose. 53 Patients with Takayasu arteritis participated in the study- 26 of them were treated with Metothrexat and glucocortykosteroids while 27 Patients used in their theraphy Tofacitinib and glucocorticoids. The treatment effect analysis lasted 12 months. After these time scientists observed that Patients on the TOF theraphy achieved lower relapse rate (11,54% vs 34,78%). Additionally, the duration of remission was prolonged in the TOF vs MTX Patients (11,65+/-0,98 vs 10.48±2.31 months). The complete remition rate turned to be higher in the TOF group (88.46% vs 56.52%). In both groups side effects were comparable and low. There was no difference on imaging in both groups [15]. Another study evaluated the effectiveness of treatment for Takayasu arteritis using Leflunomide and Tofacitinib. Wang and al. assesed the reduction in inflamatory parameters, the rate of remission, changes in imaging, influence on tapering the GCs level, side effects of both terapies as well as disease relapse. Comparing both groups of Patients, after 12 months of observation, the effectivness of both terapies was similar, however the persistent remission was significantly higher in the TOF group (46,88% vs 17,14%). Comparing the laboratory test CRP after 6 months was reduced only in the TOF group. Similar results were achieved in the imaging improvement (25% vs 9,38%). Unfortunately, side effects were also more frequently observed in this group [16].

Unfortunately, further studies on the safety of Tofacitinib in the treatment of Takayasu arteritis are necessary, as existing data suggest that Tofacitinib, compared to TNF-alpha inhibitors, may increase the likelihood of cardiovascular events and cancers [17]. Currently, 5 clinical trials are underway involving a large group of patients with Takayasu arteritis.

Secukinumab

Conducted studies show that Th1 and Th17 lymphocytes are present in increased numbers in patients with Takayasu arteritis, and their levels correlate with disease activity. It has been demonstrated that the addition of serum from patients with TAK to Th lymphocytes from healthy donors led to increased production of IL-17A and IFN-gamma. The study demonstrated that inflammatory infiltrates in patients with Takayasu arteritis contain T cells producing IL-6, IL-17A, and IFN-gamma [18]. This information became the basis for the use of a new drug, Secukinumab, in the therapy of patients with Takayasu arteritis. Secukinumab is a monoclonal antibody that selectively binds to IL-17A, whose role in the pathogenesis of Takayasu arteritis

(TAK) has been proven [18]. So far, it has been used in the treatment of various types of psoriasis, psoriatic arthritis, and ankylosing spondylitis [19], [20]. Currently, its potential use in Takayasu arteritis is being explored. The use of Secukinumab is also being explored in other large vessel inflammations, including GCA (giant cell arteritis) – studies conducted so far show positive effects of this treatment [21]. Unfortunately, so far, only individual cases have been described in which Secukinumab was used to treat Takayasu arteritis (TAK). One of the reports on the effective impact of Secukinumab concerns a 51-year-old woman with Takayasu arteritis, generalized pustular psoriasis, and a history of myocardial infarction. Despite glucocorticoid therapy, the patient still had persistent carotid wall thickening. Proactive therapy using an IL-6 inhibitor led to a reduction in the need for steroids, but after reducing the steroid dose, psoriatic lesions quickly relapsed. After introducing Secukinumab into the treatment, the pustules disappeared, and ultrasound examinations showed a decrease in common carotid artery thickening [22]. There are also studies comparing the effectiveness of Secukinumab with other drugs used in the treatment of Takayasu arteritis. In the study conducted by Tian, scientinsts compare the safety and efectivness of using Secukinumab and TNF-alfa inhibitors in the TAK Patients treatment [23]. The study included patients who did not respond to the previously used treatment consisting of glucocorticoids and two immunosuppressive drugs. In patients treated with Secukinumab, the complete and partial response rates were 31.6% at 3 months and 52.6% at 6 months, while in patients treated with TNF inhibitors, the response rates were 58.8% and 64.7%, respectively. The study showed that both Secukinumab and TNF-alpha inhibitors are effective in treating patients with Takayasu arteritis who did not respond to GC treatment and conventional immunosuppressive therapy [23]. Studies show that Secukinumab may become an alternative treatment for patients in whom previous therapy with glucocorticoids and immunosuppressive drugs has proven ineffective. However, further research on larger patient groups is necessary to assess its efficacy and safety profile.

Tumor Necrosis Factor-α Inhibitors

The number of high-quality studies on the treatment of Takayasu arteritis (TA) with TNF-α inhibitors remains limited. Although the exact pathogenesis of TA is still unclear, it is known that vascular damage occurs due to products released by activated T lymphocytes, γ/δ lymphocytes, NK (natural killer) cells, and macrophages. It appears that TNF-α, which participates in the formation of granulomas responsible for disease progression, is primarily synthesized in these cells [24]. Moreover, the serum level of TNF-α in patients with Takayasu arteritis is significantly higher compared to controls [25]. The involvement of TNF-α in TA

pathogenesis stems from its stimulation of macrophages to produce interleukins (IL-12 and IL-18), which induce T lymphocyte differentiation into Th1 cells and activate NK cells. Additionally, IL-18 leads to macrophage activation, a key component of granuloma formation [26]. These findings may indicate a relationship between the pathogenesis of TA and the TNF-α factor, suggesting that the use of TNF-α inhibitors could be a reasonable therapeutic option for this condition. According to the 2021 American College of Rheumatology (ACR) guidelines, TNF inhibitors (TNFi) are considered one of the first-line treatments for TA [25]. However, the need for further studies and stronger evidence is emphasized. Hoffman et al. conducted a clinical trial to evaluate the efficacy of TNF-α inhibitors (infliximab and etanercept) in patients with TA. The study included individuals with confirmed Takayasu arteritis who required toxic doses of glucocorticoids to maintain remission and, despite conventional and experimental therapies, experienced numerous relapses or refused re-treatment with glucocorticoids. In 10 out of 15 patients (67%), anti-TNF therapy achieved sustained remission (no new vascular lesions and complete discontinuation of glucocorticoids) for 1–3.3 years. Four patients (27%) achieved partial remission, with a ≥50% reduction in glucocorticoid dose. After 12 months, the median daily prednisone dose among patients decreased from 20 mg/day to 0 mg/day. In one patient, anti-TNF therapy was ineffective—this individual also failed to achieve remission with previous treatments. Subsequent imaging studies showed new vascular lesions in 5 patients (2 with complete remission, 2 with partial response, 1 with no improvement) during a median observation period of 12 months. Nine out of 14 responders (64%) required an increased anti-TNF dose to maintain sustained remission. In one patient who achieved complete remission, new stenoses of the axillary artery appeared after 23 months; doubling the etanercept dose halted further lesion progression for another 28 months. Two other patients experienced relapses during therapy interruptions, but remission was quickly restored after resuming anti-TNF therapy [26]. These results suggest that this treatment method may be a valuable therapeutic component for TA patients. Additionally, the patient cohort in this study comprised individuals who were particularly resistant to standard TA treatment. However, due to the small number of patients, this study is insufficient to draw definitive conclusions regarding the use of TNF-α inhibitors in TA. It remains possible that the observed remissions were unrelated to the introduced treatment. Furthermore, the long-term efficacy and toxicity of such therapy have not been fully assessed [26]. Comarmond et al. analyzed the clinical history of 84 patients (5 from their own experience and 79 from the available literature) with TA that was refractory to treatment. Before receiving anti-TNF, these patients had been treated with non-prednisone

immunosuppressive drugs: methotrexate (69%), azathioprine (30%), cyclophosphamide (28.5%), mycophenolate mofetil (9.5%), cyclosporine A (6%), aminosalicylates (5%) due to Crohn's disease or pancolitis, and tacrolimus (3.5%). The introduction of anti-TNF therapy achieved complete remission in 31 out of 84 patients (37%), while 45 patients (53.5%) showed a partial response. Unfortunately, 8 patients (9.5%) did not respond to anti-TNF-α therapy. In 30% of patients, it was possible to discontinue or reduce the doses of previously used immunosuppressive drugs entirely. After starting anti-TNF therapy, the median minimal daily prednisone dose required to maintain remission dropped from 20 mg to 4 mg. Overall, 40% of the patients completely discontinued prednisone, and 52% reduced its dose following the initiation of anti-TNF therapy. In 32% of patients, it was necessary to increase the dose of the TNF inhibitor due to inadequate disease control. It is important to note that one of the main limitations of this analysis is the fact that published data largely come from case reports or small case series, which vary in follow-up duration and endpoints. Adverse events were observed in 17 patients during therapy, primarily infectious complications. After a median follow-up of 10 months, there were no reported deaths; however, anti-TNF therapy was discontinued in eight patients due to severe complications [24]. Souabni et al. described the case of a 58-year-old patient with spondyloarthritis (SpA) in whom anti-TNF-α therapy was initiated because of an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs). The patient developed asthenia and severe back pain, along with elevated inflammatory markers (ESR of 82 mm and CRP of 192 mg/L). Based on MRI findings showing thickened large vessels, Takayasu arteritis was diagnosed. Discontinuation of anti-TNF-α agents and the introduction of glucocorticoids enabled an 8-month symptom-free follow-up. This case suggests an association between TA and spondyloarthritis, as well as the risk of developing TA in SpA patients following anti-TNF therapy [27]. Analyzing the results raises the question of the relationship between the onset of TA and anti-TNF therapy. It appears that anti-TNF agents might have contributed to TA development in this case, as earlier CT studies had not shown any signs of TA [27]. The authors propose a possible "paradoxical effect," defined as the emergence of a new autoimmune inflammatory disease after initiating TNF inhibitor therapy, which is otherwise used to treat similar conditions [28]. Nicola Mariani, Alexander So, and Bérengère Aubry-Rozier also reported two cases of TA developing during anti-TNF therapy. The first involved a 43-year-old patient with rheumatoid arthritis (RA) treated with adalimumab and methotrexate. Laboratory tests showed elevated inflammatory markers (C-reactive protein [CRP] 41 mg/L, erythrocyte sedimentation rate [ESR] 73 mm/h). Suspecting TA, the patient

underwent a chest angio-CT scan, which strongly indicated Takayasu arteritis. Discontinuation of adalimumab and the initiation of methylprednisolone, followed by prednisone, normalized the inflammatory response. The second case concerned a 32-year-old patient diagnosed with HLA-B27-negative spondyloarthritis, treated with golimumab. Physical examination revealed an absent left radial pulse and a systolic murmur over the right subclavian artery. Laboratory tests showed elevated inflammatory markers (CRP 19 mg/L, ESR 92 mm/h). Angio-CT demonstrated changes characteristic of TA. Golimumab was discontinued, and treatment with methylprednisolone was initiated, followed by prednisone, which reduced inflammatory markers and mitigated Takayasu arteritis activity on PET and angio-MRI [28]. These and other studies indicate that autoimmune phenomena in patients receiving TNF-α inhibitors are not isolated incidents, with vasculitis and drug-induced lupus being the most frequently observed systemic manifestations [28]. The authors suggest that blocking TNF-α in patients whose immune system is already imbalanced might lead to the development of vasculitis. Additionally, based on reports of two similar cases of TA in patients with Crohn's disease treated with infliximab, there is a suspicion that this adverse effect may not be limited to a single inflammatory disorder [29], [30]. Available data suggest that TNF-α inhibitors are a promising therapeutic option for patients with Takayasu arteritis (TA) that is resistant to conventional treatment, allowing dose reduction of glucocorticoids and enabling many patients to achieve sustained or partial remission [24], [26], [27]. At the same time, there are reports of paradoxical TA development during anti-TNF therapy in predisposed patients with other inflammatory conditions [27], [31]. Underscoring the need for careful monitoring and individualized treatment strategies. Ultimately, determining the full benefit-risk profile of TNF-α inhibitors requires further long-term studies involving larger patient populations, as well as a better understanding of the factors responsible for this paradoxical effect.

Tocilizumab

Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor monoclonal IgG1 antibody, produced using DNA recombinant technology in Chinese hamster ovary cells. Many studies have proved that this interleukin is involved in the pathophysiology of Takayasu's arteritis (TA). The strong expression of IL-6 was shown to actually occur in the aortic tissue of patients with TA [32]. Tocilizumab specifically binds to interleukin-6 (IL-6) receptors, both soluble and membrane-bound (sIL-6R and mIL-6R). IL-6 is a pro-inflammatory cytokine produced by T and B lymphocytes, monocytes, fibroblasts and other cells. It is involved in many physiological processes, for example T-cell activation, induction of immunoglobulin secretion, stimulation of

acute-phase protein production in the liver, and promotion of hematopoiesis. TCZ has been shown to inhibit signal transduction mediated by sIL-6R and mIL-6R receptors. Case reports and case series since 2008 have reported this mechanize as effective in TK [33], [34]. The expression level of IL-6 has been noticed to be greatly elevated in patients with Large Vassel Vasculitis (LVV) and to directly correlate with disease activity [35]. In addition, several studies have reported that IL-6 receptor blockade with the IL-6R monoclonal antibody tocilizumab might be effective for the treatment of patients with refractory TA [36], [37], [38]. Since January 2009 to January 2016 was conducted a large retrospective study of 46 patient with TA [39]. All data were assessed at baseline, at the initiation of each treatment regimen, and subsequently at 3, 6, 12, and 18 months, as well as at 3 years after each treatment line and the most recent follow-up visit. They analyzed the efficacy of:

- **d) treatment with TCZ alone or associated without DMARDs (methotrexate, azathioprine, mycophenolate mofetil)**
- **d) TCZ as first-line therapy or in treatment-experienced patients**
- **d) the event free survival after the therapy with TCZ**
- **d) cumulative incidence of relapses of TCZ compared to a control group (patients treated by DMARDs therapy).**

The conclusions after the study are that tocilizumab can lead patients with DMARDS-refractory TA to remission in 80% at 6 months. Moreover, TCZ have significant steroid sparing effect and a relatively good safety profile for those patients. Event-free survivals after TCZ treatment were 81% (at 12 months) and 72% (at 24 months), respectively considering clinical improvement, relapse and steroid sparing effect. This drug seems to have similar efficacy when considered in monotherapy and with associated DMARDs. The daily prednisone dose also decreased during the therapy. This large study shows very promising conclusions that tocilizumab is efficient and may reduce the incidence of relapses. TAK has been conventionally treated with glucocorticoids (GCS) but relapses are frequently observed [40]. Symptom improvement is typically achieved with GCS therapy. However, relapses are often observed during dose tapering [41]. Chronic morbidity and disabilities occur in most patients. Moreover, advanced arterial lesions lead to: aortic regurgitation, visual loss, cerebral infarction, and aortic aneurysms, some of which require surgery. In patients with steroid-resistant or steroid-dependent Takayasu arteritis, the addition of disease-modifying anti-rheumatic drugs (DMARDs) to glucocorticoid therapy often facilitates improved disease control and enables steroid tapering [41]. According to G. S. Hoffman et al. [41] approximately half of all Takayasu

arteritis (TA) patients experience chronic active disease for which glucocorticoid (GC) monotherapy fails to achieve sustained remission, preventing treatment withdrawal. In their study, patients were treated with weekly prednisone combined with low-dose methotrexate (MTX). Sixteen patients were followed over an average period of 2.8 years. Remission was achieved in 81% (13 out of 16) of the patients following weekly GC and MTX administration. However, 7 patients experienced relapses as GC doses were tapered to or near discontinuation. Retreatment successfully restored remission in these cases, and 3 of the 7 patients in this group were able to discontinue GC therapy entirely. Among those who achieved remission, 8 patients (50%) maintained sustained remission for 4–34 months, with 4 of them requiring neither GC nor MTX therapy for 7–18 months. Despite treatment, 3 patients showed disease progression. Conclusions contained above indicate that IL-6R inhibition with tocilizumab might be a future treatment option for TA. From the other hand, despite all the positive effect, researchers noticed that after discontinuation of TCZ therapy the potential development of cytokine storm is very possible. Yoh Arita et. all [42] presented a case with a TAK patient (27-years old woman) who showed a recurrence of TAK after cessation of TCZ with elevation of inflammatory cytokines, which is called “cytokine storm”. She was initially treated with prednisone and after this she became free from all symptoms. Since a subsequent reduction in the prednisone dosage it was followed by an increase of CRP. Subsequently a treatment with TCZ was initiated. After a single administration of TCZ, the serum levels of CRP were normalized. During the 19 times of TCZ infusion, the prednisone dosage progressively reduced without any observed worsening of the thickened arterial lesions. The serum IL-6 levels normalized after the 10th TCZ infusion. This therapy was discontinued at the 20th infusion, accompanied by an increase in increase the prednisone dosage. Unfortunately, symptoms of TA recurred with elevated levels of CRP at 9 weeks after cessation of TCZ. Despite doubling the prednisone dose, the patient's condition did not improve. She was again treated with the 21st infusion of TCZ with similar effects. Within a month after resumption of TCZ infusion, symptoms were again normalized. The prednisone dosage was gradually tapered with each infusion of TCZ ultimately leading to successful discontinuation of TCZ treatment without any flare-up. During the 2-year observation after cessation of TCZ, she had no symptoms and shown no signs of recurrence. The researchers observed that serum IL-6 levels increased with symptom relapse and returned to baseline levels after TCZ rechallenge. These results suggest that the cytokine storm occurred due to TCZ discontinuation. Serum IL-6 levels were found to correlate with TAK disease activity. This case highlights that that a flare-up with a cytokine storm could occur in the patients with TAK after

abrupt discontinuation of TCZ. However to confirm this finding we need future multicenter studies.

Rituximab

Rituximab (RTX) is approved by the FDA in 1997, chimeric murine/human monoclonal antibody. It is directed against the CD20 antigen which is a glycosylated transmembrane protein, present on the surface of normal and most malignant B cells during their development from pre-B to mature B lymphocytes. The antibody is composed of human IgG1 constant region sequences, murine light and heavy chain variable region sequences. Rituximab was primary designed as a drug to treat patients with B-cell Non-Hodgkin's Lymphoma (NHL) and chronic lymphocytic leukaemia. However, now it is used, with success, for a variety of autoimmune conditions. After binding rituximab triggers antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity against CD20-positive cells, causing depletion in CD20-positive cells count [43], [44]. The utilization of rituximab is based on the principle that the pathophysiology of TAK depend not only on T-cell, but also on B-cell infiltration into the outer vessel membrane and high blood levels of activated B-cell subsets. Data suggests that B-cell dysfunction involves stimulated by interleukin (IL)-6 and B cell activating factor (BAFF) expansion in the population of plasmablasts, elevated memory to naive B cells ratio and production of autoantibodies by circulating B cells [45], [46], [47], [48]. To date, several case reports regarding rituximab therapy in TAK has been published [45], [49], [50], [51], [52], [53], [54], [55]. Despite promising favourable outcomes from case reports, especially in a group of refractory TAK, results of cohort studies remain inconclusive. Three retrospective case series have been reported. First by Pazzola et al. included seven patients with active disease (Kerr index $\geqslant$2). Despite RTX treatment, 4/7 patients had evidence of persistent disease activity and/or radiographic disease progression and only 3/7 patients achieved complete remission (all 3 patients received RTX as rescue therapy [56]. However, in series by Nakagomi et al. 7/8 patient achieved clinical response [57]. Recently published work by Mekinian et al. assessed the effectiveness and safety of 6 months rituximab therapy. It involved 11 patients from BIOTAK registry with active disease defined as NIH score $\geq$ 2. In 2 patients RTX was used as first-line therapy, 9 patients have previously received DMARDs (MTX, CYC, MMF), 5 had previously received anti-TNF therapy, and 2 were treated with tocilizumab. Clinical response was defined as a combination of NIH score < 2 and prednisone daily dose < 10 mg at 6 months follow-up. Only 1/11 patient achieved remission after 6 months of treatment. NIH score reduction and CRP reduction were not statistically significant [58]. Unfortunately,

aforementioned studies are susceptible to multiple biases like incoherent patterns of previously and actual used co-treatments, small patient cohorts without a control group for comparison, often unspecified response criteria, and inconsistently reported imaging response criteria Noteworthy is a case report by Sugita et al. presenting late onset TAK supposedly associated with RTX treatment for other indications [59]. Available data remains inconclusive about rituximab efficacy, but it remains a viable treatment option, especially in cases resistant to conventional therapy. However, further research assessing rituximab use as a primary biologic therapy in TAK patients, particularly randomized clinical trials, is urgently needed.

Ustekinumab

Il-12 and Il-23 play an important role in cytokine signaling between antigen-presenting cells (APCs) and Th1 and Th17 lymphocytes involved in the inflammatory response in the pathogenesis of Takayasu arteritis. As a result of stimulation of antigen-presenting cells by dendritic cells present in the adventitia, CD4+ T lymphocytes polarize towards Th1 and Th17 [60], [61]. Cytokines IL-12 and IL-23, which share a common subunit (p40), play a key role in the polarization process of these lymphocytes. Ustekinumab is a humanized monoclonal anti-p40 antibody. Its use allows for simultaneous disruption of immune responses of both Th1 and Th17 lymphocytes, and thus interrupting the signaling pathway that causes chronic inflammation and remodeling in Takayasu arteritis [61]. The theoretical basis for the effectiveness of Ustkinumab in treating patients with TAK was demonstrated in a 2015 study involving three patients with a confirmed diagnosis [62]. The study revealed a genetically determined association of elevated levels of the IL-12p40 variant in these patients compared to the general population [62]. In a 2020 clinical trial, among three patients undergoing Ustekinumab therapy, a small reduction in inflammatory marker levels and the total dose of glucocorticoids used was observed [63]. After a 44-month follow-up, no side effects of the therapy were shown, however, two patients discontinued treatment due to disease activity relapse [63]. The effectiveness of Ustekinumab was further demonstrated in a case-control study involving a young Caucasian woman with a long-standing history of refractory TAK, who required glucocorticoids therapy using >40 mg/d of prednisone from the onset of the disease. Disease symptoms could not be alleviated despite attempts at immunosuppressive therapy with methotrexate and azathioprine, as well as biological treatment using infliximab, rituximab and tocilizumab [64]. Treatment with Ustekinumab, 90 mg subcutaneously at weeks 1 and 4, for severe psoriasis in this patient resulted in the normalization of inflammatory markers and the resolution of symptoms. Applied treatment achieved both clinical and

radiological remission, with the resolution of inflammation in the aortic walls, while also allowing for the reduction of prednisone dosage to 30 mg/day [64]. The safety and efficacy of Ustekinumab use are supported by the report of Saur et al. on a patient with refractory Takayasu arteritis treated with this therapy, who showed clinical improvement, normalization of inflammatory markers, and reduction of inflammation in the abdominal aorta in MRI scans [65]. The authors of the these studies emphasize the need to conduct large, double-blind, randomized studies to assess the efficacy and safety of this therapy, as the current data are based on studies of small patient populations and do not provide sufficient clinical evidence.

Abatacept

Abatacept, a chimeric protein construct consisting of a fragment of a human IgG1 and the extracellular domain of CTLA-4, that exhibits an affinity for binding to CD80 and CD86 receptors located on the membranes of antigen-presenting cells, thereby modifying activation signals through the CD28 pathway on T lymphocytes [60], [66]. The result of this action is the blockade of B-T cell costimulation. Research has explored its hypothesized impact on the immune modulation of Th1 and Th17 cell populations, which play a crucial role in the pathogenesis of Takayasu's arteritis [66] following a 3-month induction therapy period using prednisone and achieving remission, patients were divided into a treatment group using abatacept and a control group with placebo [67]. As a result of the therapy, the authors did not demonstrate a significant advantage of combined therapy with glucocorticoids and abatacept over glucocorticoid monotherapy with placebo in prolonging the relapse-free survival (22% vs. 40%; p= 0.853) [67]. No significant differences in the occurrence of side effects were found between the two study groups. Due to the small number of patients in the study and the limited number of studies conducted on the treatment of TAK with abatacept therapy, the authors of the article emphasize the need for larger randomized trials with a broader patient population. In the 2021 American College of Rheumatology/Vasculitis Foundation Guidelines for the Management of Giant Cell Arteritis and Takayasu Arteritis, abatacept is not recommended for use in patients with Takayasu arteritis due to the limited clinical data and the lack of demonstrated effectiveness in small randomized trials [68].

Summary

The treatment of Takayasu arteritis (TAK) continues to be associated with a significant number of adverse effects that negatively impact patients' quality of life. The time required to achieve clinical remission is often considered insufficient. Therefore, further investigation into the pathomechanisms of TAK and studies involving larger patient cohorts are essential. Such

research could pave the way for innovations in targeted and biologic therapies, improving future treatment methods and significantly enhancing the quality of life for patients with TAK.

Authors' Contribution

Authors' Contributions Statement:

Conceptualization: Aleksandra Cygnarowicz, Mariola Turemka, Marianna Chmiel, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

Data Curation: Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

FormalAnalysis Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka, Marianna Chmiel, Krystyna Zabojska

Investigation: Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka, Marianna Chmiel, Artur Tumiński, Aneta Mandziuk

Methodology: Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka, Marianna Chmiel, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

Project Administration: Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski

Resources: Marianna Chmiel, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

Software: Aleksandra Cygnarowicz, Mariola Turemka, Marianna Chmiel, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

Supervision: Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

Validation: Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka, Marianna Chmiel,

Visualization: Aleksandra Cygnarowicz, Aneta Mandziuk, Krystyna Zabojska

Writing–Original Draft: Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka, Marianna Chmiel, Artur Tumiński, Aneta Mandziuk

Writing– Review & Editing: Aleksandra Cygnarowicz, Oliwia Maciaszek, Mikołaj Biskupski, Mariola Turemka, Marianna Chmiel, Artur Tumiński, Aneta Mandziuk, Krystyna Zabojska

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