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PEDIATRIC RHEUMATOLOGY (S OZEN, SECTION EDITOR)

Wind of Change in the Treatment of Childhood-Onset Takayasu Arteritis: a Systematic Review

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Abstract

Purpose of Review We lack evidence-based data for the treatment of childhood-onset Takayasu arteritis (c-TA) since it is a rare disease in children. In this systematic literature review, we aimed to evaluate the treatment choices in c-TA patients and integrate our experience for the treatment of our patients in the recent years/in the biologic era.

Recent Findings We reviewed 24 articles addressing treatments of 413 c-TA patients. Steroids were given to 352 patients (85.2%) as the main immunosuppressive therapy. Other immunosuppressive agents included methotrexate (37.3%), cyclophosphamide (24.5%), azathioprine (16.9%), and mycophenolate mofetil (7.9%). Besides, various biological agents were used, including tumor necrosis factor-alpha inhibitors in 70 of 107 c-TA patients (65.4%) and interleukin-6 inhibitors in 33 of them (30.8%). Biologics are increasingly used in our center as well. Even in severe patients, CYC is switched to either anti-TNF or antiIL6 once disease control is achieved.

Summary Recently, in addition to conventional immunosuppressants, biologics are increasingly used in c-TA. We have revised our treatment protocol to start with 1–3 doses of high-dose steroids and CYC, in a child with TA with types III–V involvement and high acute phase reactants; once clinical features subside and CRP normalizes, biologics should be started to replace CYC while decreasing the steroid dose.

Keywords Childhood-onset Takayasu arteritis · Pediatric Takayasu · Treatment · Tumor necrosis factor-alpha inhibitors · Interleukin-6 inhibitors

Introduction

Takayasu arteritis (TA) is a chronic granulomatous, inflammatory disease of the aorta and its major branches at their origin [1]. TA is characterized by dilatation, occlusion, stenosis, or aneurysm formation of the affected arteries [2]. The childhood-onset TA (c-TA) subset affects any age group, from young infants to late adolescents [3, 4].

The findings range from systemic nonspecific symptoms, such as malaise, myalgia, weight loss, and fever, to vascular and ischemic manifestations, such as stroke, syncope, limb claudication, pulselessness, hypertension, and vascular bruit [5, 6]. Although hypertension is the most common form of presentation in children and adults, the overall clinical spectrum at the presentation of children with TA may differ from that in adults [3, 4, 7].

The Ankara 2008 criteria used in classification for pediatric patients were endorsed by the European League Against Rheumatism (EULAR), the International Trials of Pediatric Rheumatology (PRINTO), and the European Association of Pediatric Rheumatology (PRES) [1, 8•]. However, diagnostic delay in children is typical and almost certainly contributes to worse outcomes [9].

Although TA is suggested to be the third most common vasculitis in children, management is challenging because of the delay in diagnosis and difficulty assessing disease activity. Studies on the management of TA patients are rare and different approaches are available. Adequate therapy in c-TA is

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essential to prevent irreversible vessel damage with the resulting insufficiency of vital organs. Ongoing evidence reveals that biological therapies could be effectively used in refractory cases or even in first-line management. The aim of this paper is to systemically review the literature to evaluate the treatment options in c-TA patients. We also aimed to analyze our treatment approach in c-TA patients in the recent years, along with the relevant literature. As a secondary objective, we have compared the outcome (activity index) of the c-TA patients in our center before and after the use of biologics.

Methods

Protocol for Systematic Review

This systematic review was reported by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [10].

Search Strategy

We reviewed the literature using Pubmed/MEDLINE and Scopus between January 1, 1990, to January 31, 2021, combining the following keywords: "Takayasu arteritis," "Takayasu disease," "large vessel arteritis," "aortic arch syndromes," "arteritis brachiocephalica," "occlusive thromboaortopathy," "pulseless disease," "young female arteritis," "brachiocephalic ischemia," "idiopathic arteritis of Takayasu," and "reverse coarctation." We restricted our research to English articles. Case reports, original research articles, editorials, and review articles about TA were analyzed. The articles, which include data about the treatment of patients with c-TA, have been included in the final analysis. Two reviewers (OB, SS) performed the literature searches independently based on inclusion and exclusion criteria, deleting irrelevant literature, abandoning duplications, and screening titles and abstracts.

Inclusion and Exclusion Criteria

Inclusion criteria were set in the literature about c-TA patients' treatment, including randomized controlled trials (RCTs), cohort study, case series, case report, review, and pilot study. Exclusion criteria were as follows: (1) no information on the treatment of patients with c-TA; (2) animal researches; (3) literature about epidemiology, mechanism, diagnosis (variable biomarkers, radiological techniques, etc.), and evaluation (disease activity, radiological assessment, etc.); and (4) case reports fewer than three cases.

Data Extraction

Two reviewers (OB, SS) independently extracted data from the included studies, including information such as genders, ages, previous and current treatments, relapses, and outcomes. Disagreements between the reviewers were resolved by consensus.

Patients from Our Center

We retrospectively evaluated the medical treatment records of 25 c-TA patients followed between August 2005 and January 2021 at the Pediatric Rheumatology Department of Hacettepe University Faculty of Medicine, Ankara, Turkey. All c-TA patients fulfilled the EULAR/PReS/PRINTO-endorsed Ankara 2008 criteria [8•]. Patients were evaluated in two groups as those who received treatment before and after the date that we started to use biologic drugs to treat TA. Treatment regimens in the disease course were compared between the two groups. Severe disease was defined as types III–V involvement according to the Numano classification of angiographic findings, and all had high acute phase reactants [9].

The activity of TA was assessed with the Indian Takayasu's Clinical Activity Score (ITAS).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, NY, USA). Quantitative variables are expressed as mean and standard deviation (SD). Student's T-test was used to compare continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results

Literature Search

The selection process for the studies included in this review is shown in Fig. 1. Electronic searches resulted in 339 articles that were potentially relevant to eliminating duplicates. After excluding studies that did not include case reports (<3 cases) or medical treatment information of c-TA patients, 24 articles meeting the research criteria remained were analyzed in detail.

Medical Treatments in Childhood-Onset Takayasu Arteritis

Clinical characteristics of c-TA patients in the literature are presented in Table 1. We identified 24 articles describing 413 c-TA patients (excluding case series with <3 patients) during our literature search [4, 6, 11–32]. Two hundred ninety-seven

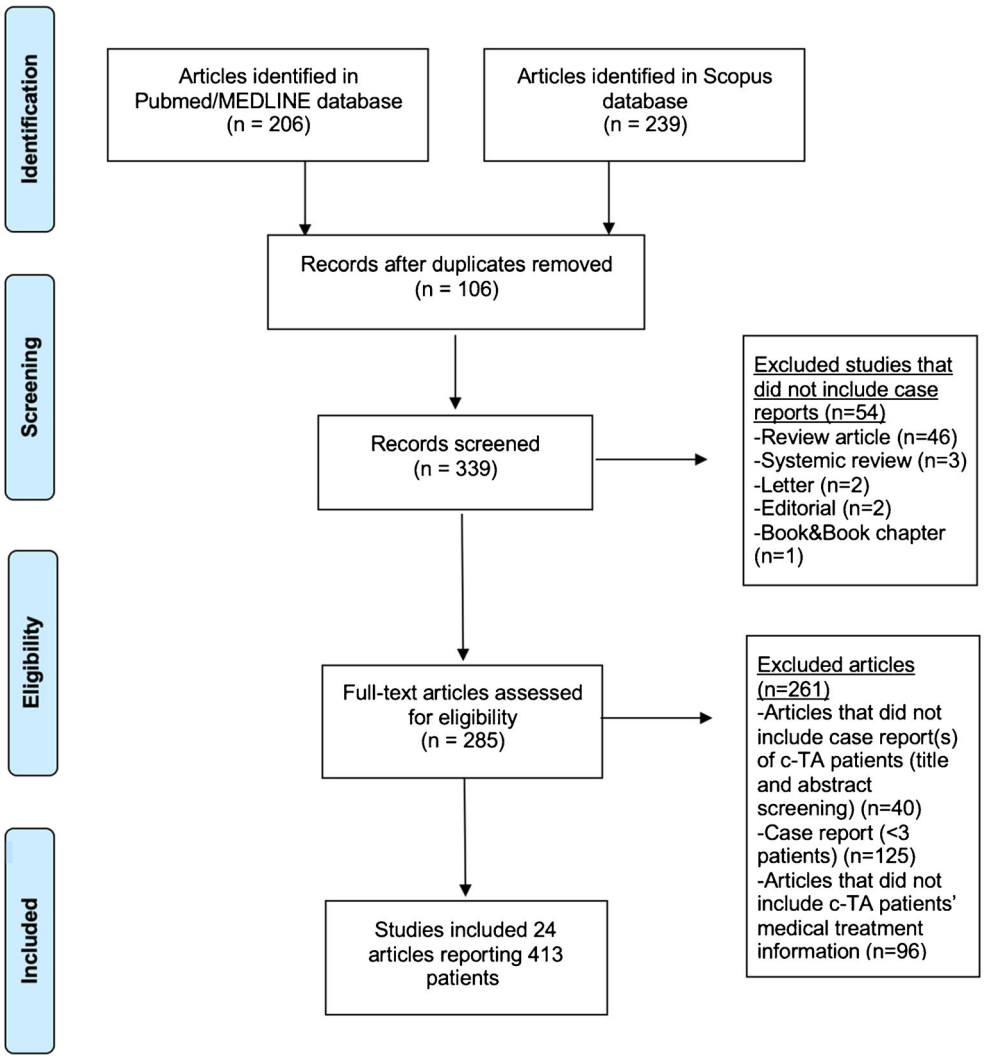

Fig. 1 Schematic overview of the studies included in literature research for childhood-onset Takayasu arteritis

patients were female. The patients' median age was 12.6 years (range 0.1–18). The median follow-up was of 2.4 years (range 0.1–16).

Detailed treatments for c-TA patients are summarized in Table 2 [4, 6, 11–32]. Steroids were given to 352 patients (85.2%) as the main immunosuppressive therapy. Other immunosuppressive agents included methotrexate (MTX) (n = 154, 37.3%), cyclophosphamide (CYC) (n = 101, 24.5%), azathioprine (AZA) (n = 70, 16.9%), mycophenolate mofetil (MMF) (n = 33, 7.9%), leflunomide (LEF) (n = 8, 1.9%), and cyclosporine A (CSA) (n = 2, 0.5%). One hundred seventy of 232 c-TA patients (73.3%) received 5-ASA as antiaggregant treatment. The pediatric centers tend to give more aggressive treatment for severe patients; however, severe patients are defined as those with involvement on both sides of the diaphragm and high acute phase reactants.

Biological agents were increasingly used in the treatment of 107 c-TA patients in the last 10 years [4, 6, 15–17, 20–22, 24–26, 27•, 30–32]. Seventy (65.4%) of 107 patients received anti-tumor necrosis factor-alpha (TNF-α) therapy [4, 6, 15–17, 22, 24–26, 30, 32]. Among the anti-TNF-α agents, infliximab (IFX) was often the first choice. Thirty-eight (54.3%) of 70 c-TA patients received IFX, 7 (10%) received adalimumab (ADA), and three patients (4.3%) were treated with etanercept (ETA). Another commonly used biological agent was tocilizumab (TCZ), an anti-interleukin (IL) 6 receptor antibody. Thirty-three c-TA patients (30.8%) were treated with TCZ [4, 20, 21, 25, 26, 27•, 30–32]. Three patients received anakinra, which is an anti-IL-1 agent [6], and one patient was treated with rituximab (RTX) [22].

In two studies, a striking feature was the switch between biological agents [4, 11]. In a study by Eleftheriou et al. with 11 c-TA patients, ADA was used in one patient because there was no response to IFX, and TCZ was used in another patient who was unresponsive to ADA [4]. In another study conducted by Filocamo et al., two patients were switched to ADA because there was no response to IFX, and complete remission was achieved with ADA treatment [17].

Eighty-five (28.3%) patients relapsed during follow-up. Two hundred thirty-seven of 357 (66.4%) patients achieved complete

Table 1 The demographic features, treatments, and outcomes of childhood-onset Takayasu arteritis (n = 388) in the literature review

Authors	Year	No.	Sex (F/M)	Age, years, median, (min-max)	Follow-up, years, median, (min-max)	5-ASA, n (%)	Steroid, n (%)	Other immunosuppressive agents, n (%)	Anti-TNF-α agents, n (%)	Other biologics, n (%)	Outcome	Relapse	Exitus
Singh et al. [11]	1999	6	6/0	9.8 (5–11)	NA	NA	5 (83.3)	AZA = 2 (33.3)			NA	NA	1
Aluquin et al. [12]	2001	3	2/1	12.7 (11–14)	NC	NA	3 (100)	MTX = 2 (66.7) CYC = 2 (66.7)			2 CR 1 PR	1	0
Ozen et al. [13]	2006	6	4/2	15.2 (12–17)	2.5 (0.1–7)	NA	6 (100)	MTX = 5 (83.3) CYC = 4 (66.7) MMF = 1 (16.7)			5 CR	0	1
Al Abrawi et al. [14]	2008	4	2/2	11.5 (8–15)	6.3 (3–10)	1 (25)	4 (100)	MTX = 3 (75) MMF = 1 (25)			4 CR	1	0
Çakar et al. [15]	2008	3	2/1	13.7 (13–14)	2.2 (0.5–3)	NA	3 (100)	MTX = 1 (33.3) AZA = 2 (66.7)	IFX = 1 (33.3)		3 CR	0	0
Çakar et al. [16]	2008	19	14/5	12.8 (8–17)	2.9 (0.1–14)	NA	19 (100)	MTX = 11 (57.9) CYC = 9 (47.4) AZA = 5 (26.3)	IFX = 1 (5.3)		12 CR 6 PR	1	1
Filocamo et al. [17]	2008	4	3/1	11.3 (7–15)	2.7 (1.3–4.8)	NA	4 (100)	MTX = 1 (25) CYC = 3 (75) AZA = 2 (50)	IFX = 4 (100) ADA = 2 (50)		3 CR 1 PR	4	0
Hijazi et al. [18]	2009	3	1/2.	2.3 (1.3–2.9)	3.9 (1.7–8)	NA	3 (100)	CYC = 1 (33.3) MMF = 3 (100)			2 CR 1 PR	NA	0
Jales-Neto et al. [19]	2010	17	11/6	16 (1–18)	8.37 ± 5.72	NA	13 (76.5)	MTX = 9 (52.9) CYC = 1 (5.9) AZA = 5 (29.4) MMF = 5 (29.4)			4 CR 11 PR	4	2
Cañas et al. [20]	2014	3	3/0	14.3 (12–17)	1.3 (1–1.5)	NA	3 (100)	MTX = 2 (66.7) AZA = 1 (33.3)		TCZ = 3 (100)	2 CR 1 PR	1	0
Kumar et al. [21]	2014	40	26/14	12.5 (1–16)	1.1 (0.3–16)	NA	34 (85)	MTX = 9 (22.5) AZA = 9 (22.5) MMF = 3 (7.5)		TCZ = 3 (7.5)	23 CR 16 PR	15	1
Stern et al. [22]	2014	23	14/9	15.7 ± 6.0	NA	16 (69.6)	20 (86.9)	MTX = 17 (73.9) CYC = 19 (82.6) MMF = 1 (4.3) CSA = 2 (8.7)	IFX = 11 (47.8)	RTX = 1 (4.3)	13 CR 7 PR	NC	3
Szugye et al. [6]	2014	21	15/6	13 (0.1–17)	2.3 ± 2.5	18 (85.7)	8 (38.1)	MTX = 14 (65.7) CYC = 5 (23.8) MMF = 3 (14.3)	IFX = 9 (42.9) ETA = 2 (9.5)	Anakinra = 3 (14.3)	19 CR 2 PR	NA	0
Misra et al. [23]	2015	29	19/10	13 (11–15)	2.4 (1.5–5.1)	16 (55.2)	NA	MTX = 13 (65) AZA = 6 (30) MMF = 2 (10)			18 CR 2 PR	6	1
Eleftheriou et al. [4]	2015	11	7/4	11.8 (1.3–17)	1.3 (0.5–14)	6 (54.5)	9 (81.8)	MTX = 8 (72.7) CYC = 4 (36.4) AZA = 1 (9.1)	IFX = 3 (27.3) ADA = 4 (36.4)	TCZ = 1 (9.1)	7 CR 1 PR	1	3
Conkar et al. [24]	2016	4	4/0	14.5 (13–16)	0.6 (0.3–1)	4 (100)	4 (100)	MTX = 1 (25) CYC = 2 (50) AZA = 1 (25)	NC = 2 (50)		2 CR 2 PR	NA	0

Table 1 (continued)

Authors	Year	No.	Sex (F/M)	Age, years, median, (min-max)	Follow-up, years, median, (min-max)	5-ASA, n (%)	Steroid, n (%)	Other immunosuppressive agents, n (%)	Anti-TNF-α agents, n (%)	Other biologics, n (%)	Outcome	Relapse	Exitus
Batu et al. [25]	2016	4	4/0	14.5 (4–16)	2.5 (0.6–1.1)	NA	4 (100)	MTX = 2 (50) CYC = 3 (75) AZA = 1 (25)	ETA = 1 (25)	TCZ = 4 (100)	4 CR	0	0
Aeschlimann et al. [26]	2017	27	20/7	12.4 (9.1–14.4)	2.1 (1.2–5.5)	15 (55.6)	27 (100)	MTX = 16 (59.3) LEF = 3 (11.1) CYC = 10 (37.1) AZA = 8 (29.6) MMF = 1 (3.7)	IFX = 9 (33.3) ADA = 1 (3.7)	TCZ = 2 (7.4)	14 CR 11 PR	13	2
Şahin et al. [27•]	2018	16	12/4	12.9 (1.4–16.6)	2.9 (0.1–14.8)	NA	16 (100)	MTX = 6 (37.5) CYC = 10 (62.5) AZA = 15 (93.8) MMF = 1 (6.3)		TCZ = 6 (37.5)	NA	NA	0
Fan et al. [28]	2019	101	77/24	14 (12–16)	2.4 (0.7–6.1)	73 (72.3)	79 (78.2)	MTX = 3 (2.9) LEF = 2 (1.9) CYC = 2 (1.9) MMF = 5 (49.5)			71 CR 27 PR	27	3
Vijayvergiya et al. [29]	2019	6	2/4	9.7 (2–14)	2.6 (1.5–7)	5 (100)	3 (60)	MTX = 3 (60) MMF = 2 (40)			4 CR 2 PR	NA	0
Aeschlimann et al. [30]	2019	29	22/7	12.1 (9.8–13.8)	2.6 (1.8–6.4)	16 (55.2)	26 (89.7)	MTX = 12 (41.4) CYC = 7 (24.1) AZA = 5 (17.2) MMF = 1 (3.4)	NC = 8 (27.6)	TCZ = 2 (6.9)	18 CR 9 PR	11	2
Lei et al. [31]	2020	9	8/1	14.3 ± 3.3	1.7 (0.5–2.9)	NA	8 (88.9)	CYC = 4 (44.4) MMF = 4 (44.4)		TCZ = 2 (22.2)	7 CR	NA	2
Bölek and Akça et al. [32]	2020	25	19/1	12.8 ± 4.6	3.2 (4.8)	NA	25 (100)	MTX = 16 (66.7) LEF = 3 (12.5) CYC = 15 (62.5) AZA = 7 (29.2)	NC = 12 (50)	TCZ = 10 (41.7)	NA	NA	2

ASA aminosalicylic acid, *MTX* methotrexate, *LEF* leflunomide, *CYC* cyclophosphamide, *MMF* mycophenolate mofetil, *CSA* cyclosporine A, *IFX* infliximab, *ADA* adalimumab, *ETA* etanercept, *TCZ* tocilizumab, *RTX* rituximab, *TNF-α* tumor necrosis factor-alpha, *F* female, *M* male, *min* minimum, *max* maximum, *NA* not assessed, *NC* not clear

Table 2 Treatment of patients with childhood-onset Takayasu arteritis in the literature

Immunosuppressive agents, n (%)	
Steroid	352 (85.2)
MTX	154 (37.3)
LEF	8 (1.9)
CYC	101 (24.5)
AZA	70 (16.9)
MMF	33 (7.9)
CSA	2 (0.5)
Biological agents, n (%)	
Anti-TNF-α	70/107 (65.5)
IFX	38/70 (54.3)
ADA	7/70 (10)
ETA	1/70 (4.3)
NC	22/70 (31.4)
TCZ	33/107 (30.8)
Anakinra	3/107 (2.8)
RTX	1/107 (0.9)

MTX methotrexate, *LEF* leflunomide, *CYC* cyclophosphamide, *MMF* mycophenolate mofetil, *CSA* cyclosporine A, *TNF-α* tumor necrosis factor-alpha, *IFX* infliximab, *ADA* adalimumab, *ETA* etanercept, *TCZ* tocilizumab, *RTX* rituximab; *NC* not clear

remission, and 99 (27.7%) of them were partial responders. Death was reported in 24 (5.8%) of all c-TA patients.

Assessment of Patients from Hacettepe University Department of Pediatric Rheumatology

Twenty-five c-TA patients have been followed up in our Department of Pediatric Rheumatology. Most of the patients were judged to have severe disease since they had types III–V involvement according to the Numano classification, and all had high acute phase reactants. Corticosteroid, the main therapeutic agent of TA treatment, was administered to all patients. MTX was given to 16 patients, CYC to 15, AZA to seven, MMF to one, and LEF to three of our patients.

In recent years, we have started to use biological agents in treating c-TA patients. Until today, we have used biological agents in 18 c-TA patients. These patients initially received two or rarely three doses of CYC and switched to biologics once no new clinical symptoms and inflammatory markers returned to normal. While 13 of our 25 patients received anti-TNF-α treatment, 10 received TCZ. Among the anti-TNF-α agents, we preferred ADA in 12 patients and ETA in one patient.

Due to the progression of MR angiography findings or the persistent elevation in acute phase reactants, biologic agent switch was made between ADA and TCZ in six patients. Four patients were switched from TCZ to ADA treatment, and ADA to TCZ switch was performed in two patients.

We used the Indian Takayasu's Clinical Activity Score (ITAS-2010) to evaluate disease activity in our c-TA patients [33]. In treatment selection, we applied steroids only or steroids + CYC combination for those with severe disease at the beginning. When acute phase reactants decreased, and disease activity scores (ITAS-2010) returned to normal during follow-up, we switched to biological agent therapy. There was no statistically significant difference in post-treatment disease activity scores (ITAS-2010) between the patients treated with conventional immunosuppressive agents and those switched to biological agents ($p = 0.876$; mean ITAS-2010 for conventional immunosuppressants and biological agents was 0.5 ± 0.53 and 0.56 ± 0.92 respectively).

Discussion

This systematic literature review suggests that biologic agents are effective alternatives in treating c-TA patients. The primary goal of treatment in c-TA is to prevent complications and disease progression. However, delay in diagnosis due to non-specific early symptoms continues to be a significant therapeutic challenge. TA leads to significant and sometimes irreversible damage even in the phase before diagnosis [4].

The mainstay of treatment is steroids, with the EULAR 2019 guidelines suggesting high-dose glucocorticoid therapy (40–60 mg/day prednisone-equivalent) for induction of remission in active TA. Adjunctive treatment using tocilizumab was recommended in selected patients (refractory or relapsing disease, presence of an increased risk for glucocorticoid-related adverse events or complications). Moreover, the recommendations suggest the use of non-biological glucocorticoid-sparing agents combined with glucocorticoids in all patients with TA and biological agents in refractory or relapsing patients [34••].

Due to the rarity of the disease in childhood and lack of solid evidence in children, we rely on the adult recommendations for treatment endorsed by EULAR [34••]. On the other hand, children tend to have a more inflammatory disease course. This was reflected in our study comparing pediatric and adult TA patients. A recent study showed that children had a more inflammatory disease, and the use of immunosuppressive drugs and the need for additional immunosuppressive on top of steroids were more common in c-TA compared to adult patients [32].

Although corticosteroids remain the mainstay for remission induction, relapse is frequent during dose tapering, and long-term use of high-dose corticosteroids needs to be avoided in children [35••, 36]. Pediatricians want to spare their growing children from the side effects of high-dose corticosteroids for long periods. Thus steroid-sparing immunosuppressives have been traditionally used in children, which is reflected in this literature review. The aim is to lower the steroid dose while preventing relapse when the steroid dose is reduced or stopped

[13]. Therefore, it is recommended to add corticosteroid-sparing agents to the treatment [26, 35••, 36]. The use of immunosuppressant drugs, such as MTX, CYC, AZA, and MMF, has been suggested to be safe and effective, to achieve sustained remission, improve vascular lesions, and decrease steroid dose in c-TA therapy [25, 35••, 36]. CYC is traditionally used in children with extensive or life-threatening disease or critical organ perfusion, whereas MTX, AZA, and MMF are used in less severe cases [37].

After the year 2008, in addition to conventional immunosuppressants, biological agents have been increasingly used in the treatment of adult patients [36, 38]. Several studies have also reported beneficial effects of biological agents on clinical and laboratory responses in patients with c-TA [17, 38]. Their use was included in the recent European consensus-based recommendations [36]. Among biological agents, especially, TNF-α inhibitors (IFX, ADA, ETA) have been used in c-TA treatment, and very successful results have been obtained [4, 6, 15–17, 22, 24–26, 30, 32]. The largest series reporting on TNF inhibitors in c-TA to date studied 23 children in a combined American–Brazilian cohort [22]. In this study, 11 of 23 c-TA patients were given IFX treatment. Nine out of 16 c-TA patients who received CYC did not respond during follow-up; 6 of them were switched to IFX, and five (83%) subsequently experienced stabilization of disease activity. Seven of the 11 patients who received IFX, including those who switched from CYC (n = 6), responded, while four cases worsened [22]. In another study, Szugye et al. [6] treated two of 21 c-TA patients with only prednisone, 7 of them with MTX and prednisone alone. Biological agents were used in addition to conventional immunosuppressive agents in 10 patients. IFX, which was used in 9 c-TA patients (42.9%), was the most commonly used medication when disease activity was still present despite prednisone and methotrexate use. Besides, ETA was also used in the treatment of two c-TA patients. Complete remission was achieved in 19 patients, and there was partial remission in the other two patients [6].

Serum IL-6 levels of patients with TA have been significantly higher than those of controls and higher in the active disease group than in the stable disease group [39]. Besides its role as a biomarker in TA, IL-6 has profibrotic effects on aortic adventitial fibroblasts, and this stimulation has been demonstrated in TA patients [40]. TCZ has shown promising results as a treatment option for TA in numerous observational studies and subsequent systematic reviews of such studies [41]. In a study by Batu et al. [25] examining the short-term effectiveness of TCZ in c-TA, TCZ treatment was given to a total of 12 patients. TCZ effectively induced remission in all ten patients with refractory c-TA and the remaining two patients who received TCZ as first-line therapy. No recurrence was observed in the patients during the follow-up period, and imaging studies demonstrated vascular improvement in two of these patients and stable disease in four; these patients had been assessed among our patients. In one RCT, the safety and efficacy of TCZ in refractory TA were investigated. Although TCZ failed to meet the primary endpoint, the study results recommended that TCZ was favored over placebo in the per-protocol set. [42, 43••]. Kong et al. [44] evaluated response to treatment with TCZ and CYC in patients with TA and explored the mechanism by analyzing their impact on various cytokines. They found no significant improvement in the vascular stenosis, thickness, and enhancement scores in both groups. However, they showed decreased ESR, CRP level, significantly reduced matrix metalloproteinase (MMP)-9 level, and increased MMP-2 level in the TCZ group than in the CYC group [44]. It should be emphasized that biologic inflammation may be suppressed, and disease activity scores that include acute phase reactants may not be sensitive enough for accurate detection [45, 46]. Consequently, recent data support the use of biologic pathway–targeting agents, such as TNF-α or IL-6 inhibitors, for c-TA patients with critical organ perfusion or end-organ damage at diagnosis and those showing severe, refractory disease [37].

The reflection of the aforementioned literature is evident in our practice as well. Since we have obtained excellent results with our recent treatment strategy in severe patients (types III–V with involvement on both sides of the diaphragm), we now suggest switching CYC to biologic agents in the early phases of the disease and maintaining the remission with low-dose corticosteroids. Thus, in a child with TA with types III–V involvement and high acute phase reactants, which is often the case, two doses — maximum of three — of CYC should accompany the pulse steroid. Once clinical features subside and CRP normalizes, biologics should be started to replace CYC while decreasing the steroid dose.

Different biological agents such as RTX and anakinra have also been used in c-TA patients in a few studies [6, 22]. However, results regarding the post-treatment state of the patients were not reported, and therefore, the place of these agents in c-TA treatment remains unclear. Recent studies have shown that interferon-gamma expression (IFN-γ) is increased in aortic tissue from TA patients with active inflammation [47]. A study conducted on an animal model by Zhang et al. [48] has suggested the efficacy of JAK-STAT signaling inhibition with tofacitinib in suppressing tissue-resident memory T lymphocytes, inhibiting microvascular angiogenesis, and intima proliferation. These data support the notion that JAK inhibitors could be potentially effective in patients with LVV. After that, some clinicians used tofacitinib in refractory TA patients [49–51]. Kuwabara et al. [49] had a successful outcome with tofacitinib in an adult patient with TA who did not respond to anti-TNF and anti-IL-6 therapy. In another case report [51], complete remission was achieved with tofacitinib in an adult TA patient who did not respond to glucocorticoids, immunosuppressants, TNF-α blockers, and TCZ.

Therapies other than immunosuppressive drugs are commonly used in the management of TA. There is an increased

risk of atherosclerosis and hypercoagulation due to increased platelet aggregation with excessive thromboxane A2 release in TA. Therefore, antiplatelet therapy such as 5-ASA or full anticoagulation might be indicated in c-TA patients [35••, 36, 52•, 53–54]. Hypertension is one of the most common symptoms, especially in c-TA, and antihypertensive agents may also be needed for the treatment [3, 55].

There are some limitations in this study. First of all, it is too difficult to manage RCTs in medical treatments of c-TA patients to obtain high-quality evidence. Second, existed evidence derived from retrospective, small-sample, and single-center cases with discrepancies in treatment alternatives are weak since standardized guidelines in c-TA are limited. Third, there is no consensus on evaluation and follow-up indicators to assess the therapeutic efficacy and safety, so that it is challenging to perform a valuable systematic review. Another limitation is that the included studies address mainly adult patient populations. We were unable to extract the pediatric cases for all the studies.

Conclusion

In conclusion, the use of biological agents in the treatment of c-TA is gradually increasing. Studies support the efficacy of biological agents such as TNF-α or IL-6 inhibitors, especially in cases of c-TA resistant to conventional therapies. On the other hand, multicenter studies are needed to judge the need for steroid pulses and limited doses of CYC at the induction phase of the severe disease.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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