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Invited Review

Childhood-onset Takayasu Arteritis

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Abstract

Childhood-onset Takayasu Arteritis (cTAK) is a rare, large-vessel type of vasculitis seen in children, mainly affecting the aorta and its major branches. Clinical manifestations are often severe and arise as a result of systemic and local inflammation, along with end-organ ischemia. Disease flares are common and the disease burden is high, with a significant rate of morbidity and mortality. Recent advances in understanding the underlying disease pathobiology resulted in the use of pathway-targeting agents, such as TNF- or IL-6 inhibitors with improved disease control. Nonetheless, the prognosis often remains guarded and the accrued damage is significant. This review aims at summarizing the recent evidence and observations regarding this condition, with a focus on pediatric publications.

Keywords: Childhood vasculitis, Takayasu Arteritis, large-vessel vasculitis

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Introduction

Takayasu Arteritis (TAK) is the most common form of large-vessel vasculitis in children and is characterized by granulomatous inflammation of the aorta and its major branches. Vessel wall inflammation leads to thickening, stenosis, and thrombus formation, and aneurysms and dissections are also often observed. Symptoms result from systemic inflammation, local inflammatory processes, and organ dysfunction secondary to ischemia. This disease may also be life-threatening. The diagnosis is based on analyzing clinical criteria and angiographic abnormalities, and is supported by laboratory findings. Recent advances in understanding the disease pathobiology have resulted in the use of cytokine-targeting agents and better control of the disease. Although the treatment outcomes seem improved, long-term follow-up is lacking and the prognosis remains guarded.

Since the comprehensive review on TAK in children and adolescents published by Brunner and colleagues in 2010 was published, additional pediatric cohorts have been reported (1-12). The aim of this article is to provide a review of childhood-onset TAK (cTAK) with a focus on recent pediatric observations.

Epidemiology

TAK was initially described in Japan, and although its incidence rates are higher in Asia, South America, and the Mediterranean basin, the disease is known to occur worldwide. TAK most commonly affects young women between 20-40 years of age, and its onset in childhood is far less frequent. The prevalence depends on the geographic region studied and varies in adults between 4.7 per million in UK to 29 per million in Korea (13, 14).

The epidemiologic data on cTAK are scarce. The annual incidence rate for cTAK was estimated to be 0.4 (CI 0.0, 1.1) per million in Southern Sweden in 2015 (15). The prevalence in Korea varied depending on the age group, between 0.04 (CI 0.00, 0.08) for younger patients and 0.63 (CI 0.36, 0.91) per 100,000 for older children, and seems to have been increasing over the last decade (14). The female preponderance of cTAK is lower than in adult-onset TAK; around 2.5:1 for the pediatric population (1-8, 10, 11, 16). The peak age of onset in children is around 12 years (1-11), although cases of early onset in infancy have been described in the literature (3, 6, 8, 10, 11, 17-20).

Pathogenesis

The etiology of TAK remains poorly understood, and the current knowledge is extrapolated from adult TAK patients and animal models of large-vessel vasculitis (21). Both the innate and adaptive immune systems seem to be involved in the pathogenesis of TAK (22). The inflammatory process usually involves the vasa vasorum, the adventitia, and the outer part of the media and results in vessel wall damage with laminar necrosis and elastic fiber fragmentation, which is eventually replaced by fibrosis and arterial remodeling

(23). Inflammatory infiltrates of the arterial wall consist of macrophages and lymphoid cells (aß CD4+ and CD8+ cells, gδ T-cells, NK cells, and B cells) (24). Th1 and Th17 responses seem to play an important role as demonstrated by an increased expression of Th1 and Th17 immunity in TAK-related inflammation that correlates with disease activity (25). Furthermore, recent data have shown a role of the mTORC1 pathway in T-cell activation and development of vascular lesions (26). Insights in these newly recognized pathways that have been implicated in the pathobiology of TAK may guide us toward future therapeutic targeted options.

The involvement of humoral immune mechanisms is evidenced by the presence of circulating anti-endothelial cell antibodies and autoantibody-producing B cells in inflammatory TAK lesions that may cause vascular dysfunction (27, 28). TAK patients have also been shown to generate a significantly large number of plasmablasts, which correlate with disease activity (29). These results lend support to the use of anti B-cell agents in the treatment of TAK.

Proinflammatory cytokines seem to play an important role in the pathogenesis of TAK (30). Elevated serum levels of TNFa, IFNa, IL-6, IL-8, IL17A, and IL-18 have been observed in patients with TAK as compared to controls, with serum IL-6 and IL-18 levels correlating with increased disease activity (25, 31, 32). Identification of key proinflammatory cytokines lead to the use of cytokine-targeting agents, such as TNF or IL-6 inhibitors.

Main Points

- Despite increasing literature on childhood-onset Takayasu Arteritis, most of the available evidence is derived from adult observational cohorts.
- Early diagnosis and effective treatment using biologic agents can reduce morbidity and mortality in childhood Takayasu Arteritis.
- Acute phase reactants have limited utility, and novel biomarkers are required to distinguish between active inflammation and non-inflammatory lesions in Takayasu Arteritis.
- Non-invasive and non-irradiating imaging techniques, such as MR angiography, should be preferred for diagnosis and follow-up evaluation of affected children.
- International collaborative efforts are required to improve assessment tools for disease activity in childhood Takayasu Arteritis and to better define the therapeutic management and long-term outcomes.

The genetic contribution to disease pathogenesis is supported by the identification of multiple susceptibility loci in various studies. Both HLA classes I and II have been associated with TAK, and most notably, the HLA-B52 allele has been reported across multiple ethnicities (22, 33, 34). Saruhan-Direskeneli et al. (35) identified *HLA-B/MICA, HLA-DQB1/HLA-DRB1, and FCGR2A/FCGR3A* as susceptibility loci in TAK patients from Turkey and North America. Variants in *IL12B* were identified as a risk factor for TAK in a GWAS study from Japan (33). TAK was also associated with *IL6, RPS9/LILRB3,* and an intergenic locus on chromosome 21q22 (36).

In addition, an association between TAK and tuberculosis infection has been recognized for several decades (37). Both tuberculosis and TAK manifest with granulomatous lesions as one of the symptoms (38). A positive tuberculin skin test has been observed in up to 90% of children with TAK (39), with active tuberculosis in up to 20% of TAK patients (38), especially in regions where the prevalence of tuberculosis is high. Molecular cross-reactivity against vascular peptides that mimic mycobacterial antigens has been suggested (40). Furthermore, gene sequences of Mycobacterium tuberculosis were detected in 23 of 33 (70%) aortic tissue samples of TAK patients (41). Finally, the genetic susceptibility may contribute to the disease burden, as variants in *FCGR2A/FCGR3A* may possibly alter the immune response against infectious agents that may be involved in the pathogenesis of TAK (35). Evidence implicating tuberculosis in disease pathogenesis has accumulated, but its definitive role remains to be elucidated.

Classification

In 1990, the American College of Rheumatology (ACR) developed some classification criteria for TAK based on data from mostly adult TAK patients (42). The new classification criteria for pediatric vasculitis, including TAK, were proposed in 2005 by the vasculitis working group of the Pediatric Rheumatology European Society (PReS) and were endorsed by the European League Against Rheumatism (EULAR) (43). These criteria incorporated items of the 1990 ACR classification, and required that angiographic abnormalities be included as a mandatory criterion. The criteria were further updated to include not only conventional angiography, but also CT or MRI. Finally, hypertension was added as a new criterion. These classification criteria were eventually validated at the 2008 Ankara consensus conference by the EULAR/PReS and Pediatric Rheumatology International Trials Organization (PRINTO) (44). The only modification to the 2005 EULAR/PReS criteria was the addition of increased acute phase reactants as an extra criterion to emphasize on differentiating TAK from non-inflammatory conditions. The currently used EULAR/PRINTO/PReS classification criteria for cTAK are presented in Table 1, and they demonstrate a sensitivity and specificity of 100% and 99.9%, respectively (44).

Clinical features

The clinical spectrum varies greatly according to the localization and extent of the vascular

Table 1. Final EULAR/PRINTO/PRES childhood TAK classification criteria.

Criterion	Glossary
Angiographic abnormality (mandatory criterion)	Angiography (conventional, CT, or MRI) of the aorta or its main branches and pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion, or thickening of the arterial wall not due to fibromuscular dysplasia or similar causes; changes usually focal or segmental
1. Pulse deficit or claudication	Lost/decreased/unequal peripheral artery pulse(s) Claudication: focal muscle pain induced by physical activity
2. Blood pressure (BP) discrepancy	Discrepancy of four limb systolic BP having a >10 mm Hg difference in any limb
3. Bruits	Audible murmurs or palpable thrills over large arteries
4. Hypertension	Systolic/diastolic BP greater than 95th centile for height
5. Acute phase reactant	Erythrocyte sedimentation rate >20 mm per first hour or CRP any value above normal (according to the local laboratory)

CT: Computer Tomography; CRP: C-reactive protein; EULAR: European League Against Rheumatism; MRI: Magnetic Resonance Imaging; PRES: Pediatric Rheumatology European Society; PRINTO: Pediatric Rheumatology International Trials Organization.

Table 2. Clinical and laboratory characteristics of children with TAK.

Author (REF)	Zhu (9)	Jales-Neto (11)	Szugye (8)	Goel (6)	Clemente (2)	Misra (7)	Elefthe-riou (3)	Feng (5)	Aeschli-mann (1)	Sahin (10)	Fan (4)	Summary (1-11)	Brunner (12)
Country	China	Brazil	USA	India	Brazil	India	UK	China	Canada	Turkey	China		
Year of publication	2010	2010	2014	2014	2016	2015	2015	2017	2017	2019	2019	2010-2019	2010
Patients (n)	14	17	21	40	71	29	11	11	27	16	101	358	241
Sex F : M	3.7 : 1	1.8 : 1	2.5 : 1	1.9 : 1	2.6 : 1	1.9 : 1	1.8 : 1	1.8 : 1	2.8 : 1	3 : 1	3.2 : 1	2.5 : 1	3.0 : 1
Age at onset, mean (range), years, *median	10.2 (7-16)	16* (1-18)	11.5 (0.1-17)	12.5* (1-16)	9.2 +/- 4.2 SD	13* (IQR 11-15)	11.8 (1-17)	9.4 (1-14)	12.4* (IQR 9.1-14.4) at dx	12.1* (0.5-16.1)	14* (IQR 12-16)	12 (0.1-18)	10 (1-18)
General features, % (summary and Brunner, n (%))													
Fever	29	41	14	45	NRd	55	36	45	19	44	13	82/287 (29)	47/160 (29)
Weight loss	36	59	48	5	NRd	24e	36	NR	30	19	4	53/276 (19)	44/199 (22)
Headache	64	47	14	53	NRd	21	36	27	33	38	1	70/287 (24)	66/210 (31)
Malaise	NR	NR	NR	53	NRd	24e	NR	NR	48	50	9	58/213 (27)	
LAD	NR	NR	NR	NR	NR	NR	NR	NR	11	NR	NR	3/27 (11)	
Arthritis/ arthralgia	43	41	14	3	65	14e	9	NR	NR	44	2	77/320 (24)	33/230 (14)
Carotidynia	NR	18	5	NR	NR	3	NR	NR	NR	NR	4	9/168 (5)	
Dyspnea	21	NR	19	28	54	NR	27	9	15	NR	30	94/296 (32)	49/210 (23)
Hypertension	93	65	57	73	85	76	73	100	56	63	70	262/358 (73)	199/241 (83)
Abdominal pain	NR	29	10	23	NRd	NR	9	36	15	31	4	34/244 (14)	33/199 (17)
Syncope	14	35	5	15	NRd	7	NR	NR	11	19	10	33/265 (12)	4/199 (2)
Skin features	NR	NR	0	8	NR	14	9	9	NR	NR	NR	9/91 (10)	12/230 (5)
Vomiting	64	NR	NR	NR	NRd	NR	NR	45	19	NR	NR	19/52 (37)	40/199 (20)
Cough	NR	NR	NR	NR	NR	NR	NR	9	NR	NR	12	13/112 (12)	15/199 (8)
Palpitations	50	NR	5	NR	NR	NR	NR	9	NR	NR	9	18/147 (12)	29/199 (15)
Organ-specific features, % (summary and Brunner, n (%))													
Decreased pulse	71	59	62	63	86	79	18	27	59	75	38	213/358 (59)	30/230 (13)
Bruits	21	59	57	47	75	48	45	27	56	88	52	200/358 (56)	38/230 (17)
Claudication	NR	59	14	40	37	41	9	NR	22	38	23	103/333 (31)	32/241 (13)
BP discrepancy	NR	65	71	NR	68	55	18	45	67	75	55	183/304 (60)	NR
Stroke	0	18	0	8	NRd	7	18	NR	11	13	6	21/276 (8)	39/230 (17)
Cardiac disease	21a	18b	5	20c	18d	14e	27f	18	NR	6g	25h	63/331 (19)	52/230 (23)
Ocular disease	21	29b	10	18c	21	21e	9	NR	15	13	38	83/347 (24)	12/230 (5)i

BP: Blood pressure; F: Female; IQR; Interquartile range; LAD: Lymphadenopathy; M: Male; NR: Not reported; SD: Standard Deviation.

[a]Chest pain in n=3 (21%), cardiac murmurs n=5 (36%), congestive heart failure=4 (29%), pericardial effusion and cardiomyopathy n=1 (7%) each. Bruits over subclavian artery and abdominal aorta n=3 (21%) each

[b]Cardiac disease reported as "myocardial infarction" in n=1 (6%) and "heart failure" in n=3 (18%) patients, ocular disease reported as "visual complaints".

[c]Reported as cardiomyopathy and severe aortic regurgitation in n=1 (3%) patient, ocular disease reported as "visual blurring".

[d]"Constitutional symptoms" (fever, asthenia and weight loss) in n=55 (78%) patients, "neurological symptoms" (headache, stroke, syncope) in n=50 (70%), "gastrointestinal symptoms" (abdominal pain, diarrhea, vomiting) in n=41 (58%) patients. Cardiac disease reported as "heart failure".

[e]Malaise and weight loss reported as one item, arthralgia/myalgia reported in n=4 (14%), arthritis in n=1 (3%) patient, "cardiac disease" reported as congestive heart failure, "ocular disease" reported as "blurring of vision"

[f]"Cardiac disease" reported as ischemic cardiac pain in n=2 (18%), as cardiomyopathy in n=3 (27%), as congestive cardiac failure in n=2 (18%), as valvular heart disease in n=1 (9%) and as pericarditis in n=1 (9%) patients.

[g]Reported as "heart failure" and "visual complaints".

[h]"Cardiac disease" was reported as heart failure in n=25 (25%) and myocardial infarction/ischemia in n=3 (3%) patients.

[i]Reported as "uveitis".

inflammation. Accordingly, a diagnosis of cTAK remains a challenge for clinicians and requires a high index of suspicion. Disease onset is characterized by an acute inflammatory phase with non-specific systemic symptoms, which likely contributes to the diagnostic delay. Although the course of the disease may be monophasic, most patients will experience a relapsing-remitting condition. In some cohorts, up to 1/4th of children are diagnosed during the late, inactive, "burnt-out" phase of the disease, which reflects irreversible sequelae to vascular lesions rather than active vasculitis (1, 3, 4).

General features

Hypertension remains the most common presenting feature in cTAK (73% of patients). Children may also present with dyspnea (32%), fever (29%), headaches (24%), weight loss (19%), or abdominal pain (14%). Musculoskeletal symptoms, including arthritis, are overall rather uncommon in children (24%). However, they are more frequently observed in South American children with TAK, a finding that was consistent with previous reports (2, 11, 45). A summary of clinical data is shown Table 2. Severe and life-threatening presentations due to acute hypertensive crisis, heart failure, or arterial dissection have been described (46-49).

Organ-specific features

Organ-specific manifestations reflect ischemia secondary to vascular stenosis. Blood pressure discrepancy (60%), decreased peripheral pulses (59%), and bruits over large arteries (56%) are frequently found; they underscore the necessity of a thorough clinical exam. A third of children present with claudication of extremities, which results from decreased blood supply; abdominal claudication may occur secondary to the involvement of the abdominal aorta or the intestinal vessels. Secondary cardiac involvement, including cardiomyopathy and ischemic heart disease, is reported in 19% of children. Neurologic manifestations such as headache, stroke, or seizures are commonly described (3, 7, 8). Carotidynia (5%) is less frequent in children as compared to adults (16), and this might be related to a reporting bias in the pediatric population. Skin disease is rare in children (10%), but nodules, erythema nodosum, and pyoderma gangrenosum have been described (50-52). Ocular diseases, such as retinal vasculitis, are uncommon (52-54) and lymphadenopathy is rarely reported in children (1).

TAK has been associated with inflammatory bowel disease, spondylarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, and sarcoidosis (52, 55-57). A pediatric case of concomitant TAK, pyoderma gangrenosum, and chronic recurrent multifocal osteomyelitis has also been reported (50).

Laboratory features

To date, a specific biomarker for TAK does not exist. In pediatric cohorts, biologic inflammation is commonly reflected by the elevation of acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (3, 6). However, their sensitivity to reflect active disease remains uncertain, and in addition, they lack specificity as well. Anemia and thrombocytosis have been reported secondary to chronic inflammation. Autoantibodies, such as the antinuclear antibody or antineutrophil cytoplasmic antibody, are usually absent.

Research on novel laboratory markers is ongoing. In adult TAK patients, pentraxine-3, a soluble pattern recognition receptor produced at sites of inflammation, has been reported to be significantly higher in patients with vascular inflammation and is detectable on radiographic imaging (58). However, the role of pentraxin-3 as a biomarker for disease activity in TAK remains unclear because contradictory results originated from a Turkish study with 94 adult TAK patients, which did not find any correlation between pentraxine-3 levels and disease activity (59). Further, IL-2, IL-3, IL-4, IL-6, IL-8, TNFa, IFNg, MMPs, TIPM1, VCAM, and RANTES have been associated with increased TAK activity (60). However, none of them have yet been validated or implemented in clinical practice.

Imaging

Vascular imaging is required for the diagnosis and management of cTAK. Imaging modalities include conventional angiography, magnetic resonance angiography (MRA), computer tomography angiography (CTA), Doppler ultrasound (US), and more recently, fluorodeoxyglucose positron emission tomography (PET) (^{18}F-FDG-PET).

Efforts to characterize the distinct angiographic patterns of TAK are ongoing (61-67). In children with TAK, the thoracic and abdominal aorta are the most frequently involved vessels, followed by the renal, subclavian, and carotid arteries (1, 2, 5, 12). Stenosis is the most common vascular lesion, and vessel wall thickening (which is typically concentric), aneurysms, and occlusion may also be seen (2-4, 8). Arterial dissection is a potentially severe complication (46).

Conventional angiography (CA; intra-arterial digital subtraction angiography) remains the gold standard to study the arterial lumen (68). Its strengths include good spatial resolution and visualization of the extent of collateralization. However, CA is invasive and is associated with radiation exposure and potential procedural complications. In addition, there is no visualization of the arterial wall, therefore, other diseases causing vascular narrowing, such as chronic wall fibrosis, are indistinguishable by CA (12). Due to its limitations and the wide availability of MRA, the use of CA is restricted to very few, specific indications in children with TAK (i.e. angiographic imaging prior to revascularization procedures) (69).

MRA has become the most popular imaging modality in cTAK, and the recent EULAR recommendations on the imaging modalities of large-vessel vasculitis propose the use of MRA as the first imaging test for suspected TAK (69). Lack of invasiveness and radiation makes this imaging modality particularly appealing for repeated evaluations in children (68). In addition to the visualization of the arterial lumen, MRA provides valuable information on vessel wall lesions and disease extent in various vascular territories. Generally, T1-weighted imaging demonstrates arterial wall lesions (such as thickening), T2-weighted imaging depicts inflammatory edema and contrast-enhanced T-1 weighted imaging with late-contrast enhancement, which is suggestive of active inflammation in the arterial wall. Although the disease activity on contrast-enhanced MRA has been shown to correlate with clinical findings and acute phase reactants in some patients (70, 71), it remains difficult to differentiate the state of the disease (active or inactive) on MRA, as neither the presence of vessel wall edema nor post-contrast arterial enhancement are specific features of an active disease state (72, 73). Thus, the debate of whether MRA is a useful modality to assess TAK disease activity continues to date.

CTA provides information similar to what is obtained from the MRA; it depicts the anatomy of the vascular lumen and wall, and assesses the post-contrast enhancement and extent of vessel involvement (74, 75). In addition, CTA may better visualize the coronary artery involvement in very young children with rapid heart rates (76). In children, MRA is preferred over CT, since CTA is associated with non-negligible radiation exposure.

Doppler US is inexpensive, non-invasive, and lacks radiation exposure. It is useful for the visualization of the arterial wall, measurement of intima-media thickness, and for the anatomic study of vascular stenosis or aneurysms (77, 78). Furthermore, it may help in the detection of TAK in a pre-stenotic phase (78). Its limita-

tions include the investigator-dependent quality of the exam and the fact that only certain vessels are accessible for US assessment.

^{18}F-FDG-PET has a limited role in the management of cTAK, mainly because of its significant radiation exposure if it is combined with CT and the high costs of the scan. In adults, ^{18}F-FDG-PET has been widely used and shown to accurately assess disease activity in the vascular wall (^{18}F-FDG uptake by metabolically active cells) and visualize anatomic abnormalities (68, 79). However, a poor correlation between ^{18}F-FDG uptake and disease activity markers has also been described (80). Accordingly, the definite role of ^{18}F-FDG-PET in the management of TAK has yet to be determined. The utility of novel imaging modalities, such as MR-PET or diffusion-weighted whole-body imaging with background body signal suppression (DWIBS), has yet to be validated (68, 81).

Differential diagnosis

Given the rarity of the disease and the wide spectrum of non-specific symptoms, various other disorders have to be considered in the differential diagnosis of a child with suspected TAK. Infections, such as tuberculosis and syphilis, may cause aortitis and in children with a more acute clinical presentation, microorganisms such as staphylococcus aureus, streptococcus, and salmonella may be found (82-84).

Other primary vasculitides (Behçet's disease, Kawasaki disease, and panarteritis nodosa) and vasculitides secondary to SLE, spondylarthritis, or sarcoidosis may mimic the features of TAK. The differential diagnosis also includes non-inflammatory disorders, such as aortic coarctation, Williams syndrome, Marfan's or Ehlers-Danlos syndrome, and fibromuscular dysplasia (FMD). FMD is not an inflammatory disease, however, differentiating TAK from FMD in the chronic non-inflammatory phase may be challenging because, in contrast to adults, the characteristic angiographic 'string of beads' pattern is rarely seen in childhood-onset FMD (85).

Treatment

Immunosuppressive therapy

The majority of children with TAK suffer from a progressive or relapsing type of disease and require immunosuppressive therapy to control vascular inflammation. The diagnostic delay, which is often significant in children, remains a major challenge, as irreversible vascular damage and secondary organ dysfunction may occur in the pre-diagnostic phase of the illness. Furthermore, therapeutic management is challenging, because biomarkers for disease activity have not yet been identified. Finally, the disease may progress on repeat imaging due to sub-clinical disease activity (86).

High-level evidence, including randomized controlled trials, to guide the treatment of cTAK is lacking, and treatment recommendations are often extrapolated from adult TAK studies. Corticosteroids remain the mainstay for the induction of remission (87, 88). However, relapses are high if patients are treated with corticosteroids alone (89), and the side effects of long-term high-dose corticosteroids may be devastating and amplified in children. Therefore, the use of corticosteroid-sparing agents upfront has been recommended (87, 88, 90). Among second-line agents, conventional DMARDs, such as methotrexate (MTX), azathioprine (AZA), mycofenolate mofetil (MMF), and cyclophosphamide (CYC) have been used with success for inducing remission and facilitating the maintenance-phase treatment (88, 90). CYC is traditionally initiated in children with extensive or life-threatening disease or those with critical organ perfusion, while MTX, AZA, and MMF are used in less severe cases.

Increased knowledge of the disease pathophysiology has resulted in the identification of key inflammatory mediators and the use of cytokine-targeting agents, such as TNF or IL-6 inhibitors (31, 32). Several studies have reported beneficial effects of biologic agents on the clinical and laboratory response in children with TAK (91, 92), and their use was included in the recent European consensus-based recommendations for the treatment of childhood vasculitis (88). When considering the toxicity profile, biologic agents may be favored over CYC in children.

In his study, Filocamo reported four children with TAK, who were treated with anti-TNF agents for refractory disease or as the first-line agents for two patients in remission and to elicit a partial response in two others (92). In a retrospective case series from Canada, children treated with biologic agents (TNF-inhibitors and tocilizumab) had higher flare-free survival rates and were more likely to exhibit an inactive disease state at the last follow-up, than those treated with conventional DMARDs (1). Mekinian et al. (93) documented equivalent efficacy and safety of TNF-inhibitors and tocilizumab (TCZ) in 49 adult TAK patients who were refractory to non-biologic therapies. In summary, the data on TNF-inhibition in TAK are encouraging and anti-TNF agents seem to be an effective therapeutic strategy in some patients, but high-quality evidence for the same is lacking. Reports originate from retrospective case series that combine anti-TNF agents with various mechanisms and other classes of therapeutic agents. Furthermore, controversy emerges from reports of patients who developed TAK while they were being treated with an anti-TNF agent for inflammatory bowel disease (1).

Good efficacy and safety profiles of IL-6 inhibitors have been reported in several pediatric and adult retrospective case series of patients with TAK (91, 94-99). Batu et al. (91) described four children with TAK (three of the four with disease refractory to DMARDs) who showed a good response to TCZ and experienced no adverse events. A randomized, placebo-controlled trial of TAK patients who had recently relapsed did not find a statistically significant difference between patients receiving TCZ and those on placebo, although patients receiving TCZ trended toward showing a reduction in the time to relapse (100). Among the 36 enrolled patients, six children older than 12 years were included (four receiving TCZ, two placebo) and there were no new safety concerns (100). In a recent retrospective study of 46 mostly DMARD-refractory adult TAK patients, event-free survival was significantly better with TCZ as compared to conventional DMARDs (99). Although results in TAK patients treated with TCZ seem promising, not all TAK patients have been found to respond to TCZ and the disease progression during the treatment has been described (101-103). In addition, the assessment of disease activity is even more challenging in TAK patients treated with TCZ, as biologic inflammation may be suppressed and disease activity scores that include acute phase reactants may not be sensitive enough for accurate detection (104, 105).

Various other biologic agents have been used with limited success in adult TAK patients. Increased evidence of a pathogenic role of B cells in TAK provided a rationale for the use of Rituximab as a therapeutic agent (29). In adults, retrospective case reports have demonstrated the potential effect of Rituximab in refractory TAK patients (29, 106). Data on pediatric cases are lacking, although its use has been described previously (3). Genome-wide association studies have determined *IL12B* as a susceptibility gene for TAK (33). Based on these findings, Ustekinumab, a monoclonal antibody against IL-12/IL-23, has been used in few refractory TAK patients with good clinical and laboratory response, although imaging evidence did not support any improvement (107). Finally, the T-cell co-stimulation inhibitor, abatacept, failed to reduce relapse rate at the 12-month

follow-up in a randomized, placebo-controlled trial in adult TAK patients (108).

Overall, recent data support the use of biologic pathway-targeting agents, such as TNF or IL-6 inhibitors, for children with critical organ perfusion or end-organ damage at diagnosis and for those showing severe, refractory disease.

Vascular interventions

Endovascular interventions or vascular surgery is often required to treat symptomatic organ ischemia or life-threatening vascular lesions, such as aneurysms or dissection (23, 46, 109, 110). Ideally, they should be performed during the inactive phase of the disease (23). In children, revascularization procedures (percutaneous transluminal renal angioplasty, kidney auto-transplant, and arterial bypass surgery) are performed mainly for TAK-associated renal artery stenosis; a beneficial outcome has been reported in about half of the patients, and the length of the vascular lesion seems to correlate with the clinical success (109, 110). In adult TAK patients, the most common indications for surgery are renal artery stenosis, aortic disease (coarctation, ascending aortic dilatation, and aortic valve regurgitation), ischemic heart disease, supra-aortic vessel involvement with cerebral ischemia, mesenteric ischemia, severe limb claudication, and aneurysm repair (23).

Disease activity and disease damage

Assessment of disease activity and outcome is challenging in TAK, especially in the pediatric population, and the current tools insufficiently reflect disease activity and management decisions (111). The Pediatric Vasculitis Activity Score (PVAS) is a disease activity measurement tool based on the modifications of the Birmingham Vasculitis Activity Score; it captures clinical manifestations resulting from active vasculitis (112). Although it has been validated in childhood vasculitis, only six out of 63 children with systemic vasculitis suffered from TAK, and the PVAS may not be the optimal disease activity measurement tool for large-vessel vasculitis (112). The Indian TAK Clinical Activity Score (ITAS 2010 and ITAS-A, which includes acute phase reactants) has specifically been developed to assess disease activity in TAK, however, has been validated only in adult TAK patients of Indian origin (113). Both the disease activity scores measured disease activity, including signs and symptoms that had newly occurred, had worsened over the past 4 weeks, or had persisted for less than 3 months (112, 113). The Disease Extent Index in TAK (DEI.TAK) is a clinical scoring tool used to assess the disease activity and progression in TAK (114), but it has not been validated for use in children.

The most commonly used criteria to define active disease in TAK were initially proposed and used in a study from the US National Institute of Health (NIH) (86, 115). According to these criteria, a patient shows an active disease state in the presence of constitutional symptoms, new bruits, elevated acute phase reactants, or new angiographic findings (86).

To date, a validated tool for assessment of disease damage in children with TAK does not exist. The Pediatric Vasculitis Damage Index has been modified from the adult Vasculitis Damage Index and has been made to incorporate features present for more than 3 months (116). The Takayasu Arteritis Damage Score (TADS) has been developed specifically for TAK and considers features present for more than 6 months (117). Although TADS has been used for study purposes, it has not yet been validated for clinical use (117). Damage scores may help to assess cumulative damage over time, however, discriminating between disease- and treatment-related damage is difficult (111).

Outcome

Recent advances in early recognition and in therapeutic strategies have shown a decreased rate of morbidity and mortality in cTAK (1, 3). In a retrospective case series from Canada, children being treated with biologic agents had a significantly higher 2-year flare-free survival and higher rates of inactive disease at the last follow-up as compared to children who were treated with non-biologic therapies (1). However, the disease burden remains high and children often accrue significant damage over time, both from the progressing disease and the treatment-related adverse effects (1, 3, 6). Stroke, high CRP at disease onset, lower BMI, and younger age at admission have been associated with poor outcomes (4). In addition, the young age at onset and high scoring of permanent damage have been identified as independent risk factors of mortality in cTAK (3). The mortality rate varied between 0% and 27% in a recent pediatric case series (1-11). This variability might be explained by factors such as study region, recruitment bias, era effect, and access to medication, among others.

Conclusion

Childhood-onset TAK is a rare, severe, and potentially life-threatening disease that is associated with significant morbidity and mortality. The etiology of TAK remains poorly understood, but both the innate and adaptive immune systems play a role in the disease pathogenesis. Recent data on cTAK have helped in better defining the clinical features of this rare disease. Treatment recommendations are mostly at evidence level 3 and are based on descriptive adult studies. While corticosteroids remain the mainstay of the induction regimen, biologic agents such as TNF- or IL-6 inhibitors are increasingly being used, especially for severe and refractory cases. Large international collaborative efforts are required to conduct multicenter pediatric clinical trials to determine the efficacy of the current treatment regimens, to provide disease assessment tools that address the multiple facets of cTAK, and to better define the long-term outcomes of pediatric TAK.

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