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Tocilizumab treatment in childhood Takayasu arteritis: Case series of four patients and systematic review of the literature

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ABSTRACT

Objective: Our aim was to describe our experience with tocilizumab (interleukin 6 receptor antagonist) treatment in children with Takayasu arteritis and to review previous studies regarding tocilizumab use in Takayasu arteritis patients.

Patients and methods: We reviewed the charts of all pediatric Takayasu arteritis patients followed up between 2000 and 2015 in Department of Pediatric Rheumatology in Hacettepe University, Ankara, Turkey, and we present the patients who were treated with tocilizumab. We screened PubMed and MEDLINE for articles involving Takayasu arteritis patients treated with tocilizumab.

Results: We have followed four pediatric Takayasu arteritis patients who received tocilizumab. The median duration of immunosuppressive treatment before tocilizumab onset was 16 (1–60) months. The median duration of tocilizumab treatment was 9.5 (7–13) months. One of our patients received tocilizumab as a first line immunosuppressive treatment directly after methylprednisolone. Others were resistant to their initial immunosuppressive treatment (cyclophosphamide, methotrexate, or azathioprine). All achieved complete response to tocilizumab at the third month of treatment. None of the patients reported any adverse events during the follow-up. In literature review, we identified 19 articles describing 75 Takayasu arteritis patients treated with tocilizumab. Eight of these received tocilizumab before the age of 18 years. Tocilizumab was the first line immunosuppressive treatment in six patients (five adults and one child).

Conclusion: Our small series suggests that tocilizumab may be a promising alternative for Takayasu arteritis treatment. Long-term controlled studies are warranted to provide better evidence for tocilizumab treatment in childhood Takayasu arteritis.

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Introduction

Takayasu arteritis (TAK) is a rare, granulomatous chronic vasculitis mainly affecting aorta and its main branches [1]. It has an incidence of 1.2–2.6/million per year in Caucasians, but the incidence is almost 100 times higher in East Asians [2,3]. It

primarily affects young women [4,5]. It is rare in children; however, it may be seen even in infants [6]. TAK constitutes 1.5% of pediatric primary vasculitis cases in Turkey [7].

After the diagnosis of TAK, the evaluation of outcome remains challenging. Acute phase reactants (APRs) are not always reliable and we mainly depend on non-invasive imaging techniques such as ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT), computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) [8]. Previously, Kerr et al. [5] defined the National Institutes of Health (NIH) criteria for disease activity (Supplementary Table S1). However, according to these criteria, the disease could only be evaluated as active or inactive. Recently, Misra et al. [9] proposed a novel method for evaluating TAK disease activity called the Indian Takayasu Clinical Activity Score (ITAS2010) to evaluate disease activity in TAK patients (Supplementary Figure S1).

Abbreviations: APRs, acute phase reactants; CRP, C-reactive protein; CTA, computed tomographic angiography; ESR, erythrocyte sedimentation rate; ITAS2010, Indian Takayasu Clinical Activity Score 2010; IL 6, interleukin 6; MRA, magnetic resonance angiography; NIH, National Institutes of Health; PET-CT, positron emission tomography-computed tomography; RANTES, regulated on activation, normal T cell expressed and secreted; TAK, Takayasu arteritis; TNF α , tumor necrosis factor alpha.

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Table 1
Disease activity parameters of Takayasu cases studied before and during tocilizumab treatment

Pt	Previous tx	Age at dx (yrs)	Time from dx to onset of TOC (mo)	Duration of TOC tx (mo)	ESR (mm/h)/CRP (mg/dL)		ITAS2010-A				Prednisone dose (mg/kg)		Imaging		During TOC (3 mos later)
					Before TOC	During TOC (3 mos later)	At diagnosis	Before TOC	3rd mo of TOC	6th mo of TOC	12th mo of TOC	Before TOC	During TOC (3 mos later)	Before TOC	
1	Pred	16	1	7	40/2.14	11/0.09	12	12	0	0	-	10	5	Thickening of the vessel wall of the arcus aorta, at the origin of LSCA, and abdominal aorta (suprarenal segment). Irregularities, ectasia in aorta	Stable findings
2	Pred, CYC, ETA	16	9	11	35/1.5	8/0.3	10	14	1	1	-	10	5	Graft in ascending aorta Aneurysms in arcus aorta, descending aorta, abdominal aorta (suprarenal segment), BCA, bilateral SCAs, bilateral main CAs Stenoses in distal part of the LCA and at the origin of celiac trunk	Stable findings
3	Pred, CYC, MTX	13	23	13	39/1.9	2/0.3	9	11	0	0	0	10	5	Aneurysms in ascending aorta, arcus aorta, BCA, LCA, LSCA	Stable findings
4	Pred, CYC, MTX, AZA	4	60	8	42/2.5	14/0.5	9	15	1	1	-	10	5	Stenoses in ascending, arcus, descending aorta, distal parts of aorta, BCA, bilateral main CAs	Stable findings

BCA, brachiocephalic artery; CA, carotid artery; CRP, C-reactive protein; CYC, cyclophosphamide; dx, diagnosis; ESR, erythrocyte sedimentation rate; ITAS2010-A, Indian Takayasu's arteritis activity score with acute phase reactants; L, left; MTX, methotrexate; Pred, prednisolone; pt, patient; R, right; SCA, subclavian artery; TOC, tocilizumab; tx, treatment.

The pathogenesis of TAK is still poorly known but several cytokines such as tumor necrosis factor alpha (TNF α) and interleukin 6 (IL-6) have been demonstrated to be effective in the disease pathogenesis [10,11]. IL-6 is a pleiotropic cytokine influencing the function of different cell types which present in TAK arterial lesions [12,13]. It plays a role in T- and B-cell differentiation, T-helper 17 generation, fibroblast proliferation, and hepatic production of APRs such as C reactive protein (CRP) [10,11]. High expression of IL-6 was demonstrated in the vascular lesions of TAK [10]. Furthermore, serum IL-6 level was shown to correlate well with disease activity in TAK [11].

The mainstay of treatment for early, active TAK is high-dose corticosteroids [14,15]. However, the addition of immunosuppressive agents such as methotrexate and cyclophosphamide is usually needed [13]. Our group has reported effective and safe treatment with corticosteroid and cyclophosphamide induction followed by methotrexate in children with TAK [16]. However, gonadal toxicity remains an important concern with cyclophosphamide. Furthermore, the relapses are frequent in TAK even with these treatments. Promising results have been reported with anti-cytokine drugs [13]. Several studies have shown favorable effect and good tolerance of tocilizumab (IL-6 receptor antagonist) treatment in TAK patients [17-19].

In this study, we have described our experience with tocilizumab treatment in four children with TAK. We have also reviewed previous studies regarding tocilizumab use in pediatric TAK patients.

Patient and methods

Patient selection and characteristics

We reviewed the charts of all pediatric TAK patients followed up between 2000 and 2015 in Department of Pediatric Rheumatology in Hacettepe University, Ankara, Turkey, and we present the patients who were treated with tocilizumab. All patients fulfilled the Ankara 2008 criteria for TAK [20]. Tocilizumab was administered intravenously at a dosage of 8 mg/kg every 4 weeks.

We defined complete response as improvement/resolution of symptoms, absence of new arterial lesions/symptoms, normalization of APRs, absence of radiographic activity (no new lesions on angiography and/or no vasculitis activity on PET), and the use of ≤ 7.5 mg or ≤ 0.2 mg/kg (whichever was lower) daily prednisolone.

The disease state was evaluated as active or inactive according to the National Institutes of Health (NIH) criteria (Supplementary Table S1) [5] and for the disease activity score we have calculated ITAS2010-A (Supplementary Figure S1) [9].

Systematic review of the literature

We screened PubMed and MEDLINE by entering these keywords; "Takayasu," "Takayasu arteritis," "anti-IL 6," "tocilizumab," "actemra," "child." We searched the English literature from inception to January 2016. We included randomized and nonrandomized controlled trials, observational studies (case-control, cohort studies, and case series) and single case reports involving TAK patients treated with tocilizumab. Two reviewers (E.D.B. and H.E.S.) independently screened titles, abstracts, and full texts of all relevant articles.

We analyzed the following parameters from these studies: gender, age at diagnosis, age at tocilizumab initiation, disease duration before tocilizumab, previous immunosuppressive agents, prednisolone dose before and after tocilizumab, co-treatments, ITAS2010-A before and after tocilizumab, duration of tocilizumab

treatment, response to tocilizumab treatment, vascular improvement on imaging, relapses, duration of follow-up, and adverse events.

Results

Patient characteristics

We have followed up 11 pediatric TAK patients between 2000 and 2015. Four (36.3%) of them received tocilizumab. All four patients were female. The characteristics of these patients were summarized in Table 1. The median (minimum–maximum) age at diagnosis was 14.5 (4–16) years and the median duration of disease was 30 (7–68) months. The median duration of immunosuppressive treatment before tocilizumab onset was 16 (1–60) months. The median duration of tocilizumab treatment and the median duration of follow-up after the first dose of tocilizumab both were 9.5 (7–13) months since all four patients continue to receive tocilizumab.

One of our patients received tocilizumab as a first line immunosuppressive treatment directly after one dose of pulse methylprednisolone because the family refused cyclophosphamide. Others were resistant to their initial immunosuppressive treatment. Prior to tocilizumab administration, three patients received IV cyclophosphamide, two received methotrexate, and one azathioprine. Patient 2 received monthly doses of cyclophosphamide and pulse methylprednisolone for 6 months. APRs were high and the lesions progressed under this treatment. Thus, etanercept was initiated. APRs remained high with etanercept, as well and her ITAS2010-A was 14. At the third month of etanercept treatment, tocilizumab was initiated and etanercept was discontinued. Patient 3 also received monthly doses of cyclophosphamide and pulse methylprednisolone for 6 months, after the diagnosis. After this treatment, APRs were still slightly elevated and the lesions remained active on PET. Methotrexate was initiated; however, the lesions progressed further under this treatment and her ITAS2010-A was 11. Thus, tocilizumab was commenced and methotrexate was discontinued. Patient 4 received methotrexate and oral corticosteroid treatment for 1 year after the diagnosis. Since MRA revealed disease progression and the APRs were high, monthly doses of cyclophosphamide and pulse methylprednisolone was given for 3 months. Then azathioprine was given for maintenance. However, at the sixth month of treatment with azathioprine, MRA revealed progression in the lesions of aorta. Thus, tocilizumab was initiated and azathioprine was discontinued.

Clinical effectiveness

All four of our patients achieved complete response to tocilizumab after 3 months of treatment. Repeated MRAs showed no new vascular lesions in our patients. ITAS2010-A values were decreased from a median of 11.5 (1–15) to 0.5 (0–1) after 3 months of treatment with tocilizumab. According to the NIH criteria, all patients had active disease at the initiation of tocilizumab treatment and after 3 months of treatment with tocilizumab, the disease state was inactive.

Safety

Tocilizumab treatment was well tolerated in our patients and none of the patients reported any adverse events during follow-up.

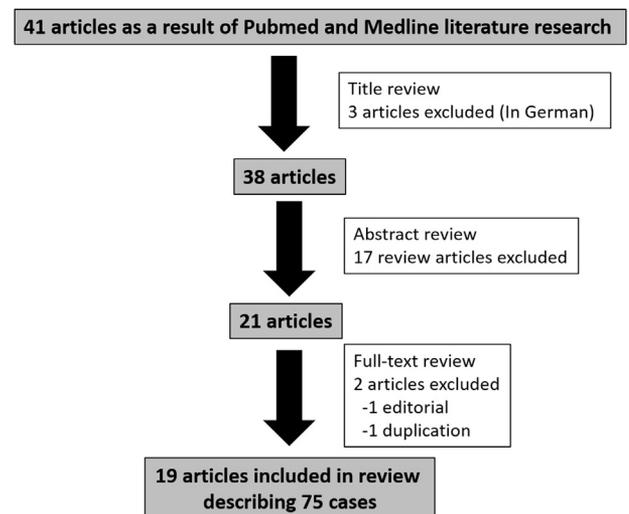


Fig. Schematic overview of the studies included in literature research.

TAK patients treated with tocilizumab in the literature

The schematic overview of the studies included in this review was shown in the Figure. We identified 19 articles describing 75 TAK patients treated with tocilizumab during our literature search [15,17–19,21–35]. The characteristics of these patients were summarized in Table 2. Of these patients, 11 experienced relapse during tocilizumab treatment [15,17,22,23,25,32,34], while eight flared 2–14 months later than the withdrawal of tocilizumab [18,25].

Overall, 12 patients received tocilizumab before age of 18 years including ours [21,25–27]. The characteristics of pediatric patients were summarized in Table 3. Tocilizumab was given as the first line immunosuppressive treatment in seven patients [23,27,29,33] including two children; one patient (Patient 1) from our series and another one reported by Canas et al. [23].

Discussion

In this study, we have described four pediatric TAK cases with good clinical and laboratory responses to tocilizumab treatment. Our literature search revealed eight more pediatric TAK patients treated with tocilizumab before the age of 18 years [21,25–27]. One of our patients (Patient 1) was the second pediatric patient receiving tocilizumab as a first line immunosuppressive agent in the literature.

Corticosteroids are the mainstay of TAK treatment [15]; however, the addition of immunosuppressive agents such as methotrexate, azathioprine, or mycophenolate mofetil allows better disease control and corticosteroid dose reduction [13]. In our previous study, we had suggested that cyclophosphamide induction and corticosteroids followed by methotrexate was an effective and safe treatment for childhood TAK if the disease involved aorta on both sides of the diaphragm [16].

Refractory patients may benefit from biologic drugs. The most widely used biologics are TNF inhibitors in TAK. In a literature review by Cliffold and Hoffman [36] they found that 90% of the patients responded to anti-TNF agents while 40% of these relapsed. In 2014, Osman et al. [37] performed a systematic review and meta-analysis about the role of biologic agents in the management of large vessel vasculitis and they demonstrated weak evidence to assess the effectiveness of biologic treatment in large vessel vasculitis. They included three randomized controlled trials all of

Table 2
Reported series and case reports of Takayasu arteritis patients who received tocilizumab^a

Study	Number of TA pts who received TOC	Age at dx (yrs)	Age at TOC initiation (yrs)	Disease duration before TOC initiation	IS agents prior TOC	Prednisone before TOC (mg/day)	Prednisone after TOC (mg/day)	Co-tx	Remission/no response	Relapse	Vascular improvement on imaging	Follow-up	ITAS before TOC	ITAS after TOC	Side effects
Nishimoto et al. [28]	1	15	20	5 yrs	CSA, CYC, AZA, MMF, MTX	30	7.5	No	Yes	No	Yes	180 wks	NA	NA	No
Seitz et al. [32]	2	27–40	NA	3.5–6 yrs	MTX, AZA, INF	35–40	2.5–10	No	2/0	1 pt	Yes	4–8 mos	NA	NA	No
Bravo Manchero et al. [21]	1	3	6	3 yrs	MTX, ETA, INF, CYC, MMF	30	0	MMF Antiplatelet drug	Yes	No	Yes	2 yrs	NA	NA	No
Bredemeier et al. [22]	1	22	28	6 yrs	MTX, CYC, MMF, AZA, INF, ADA	30	5	MTX	Yes	Yes	No	1 yr	NA	NA	Elevated transaminases
de Kruif et al. [24]	1	60	63	3 yrs 5 mos	MTX, AZA, INF	3.75	3.5	AZA	NA	NA	Yes	6 mos	NA	NA	Streptococcal lung abscesses
Salvarani et al. [30]	1	25	28	3 yrs	MTX, INF, ADA, MMF	10	5	MMF	Yes	No	Yes	6 mos	3	0	No
Salvarani et al. [29]	2	21–40	22–40	3 mos–1 yr	MTX	12.5	0	No	2/0	No	Yes	7–10 mos	4 (n = 1), 3 (n = 2)	0	No
Unizony et al. [33]	2	41	NA	20 mos	IFN	0–5	0	No	2/0	No	Yes in 1 pt	9.5 mos	NA	NA	No
Xenitidi et al. [34]	2	21–45	33	1.5–10 yrs	MTX, AZA, CYC, INF, ADA	10 in 1 pt; NA for other	10 in 1 pt; NA for other	NA	No	NA	No/MRI	8 mos	NA	NA	Severe RTI (n = 1)
Abisror et al. [17]	5	46–65	NA	NA	MTX, AZA, INF, CYC	0–75	0	MTX, AZA	3/2	2 pts	Yes in 3 pts	6–24 mos	NA	NA	Neutropenia (n = 1)
Nakaoka et al. [18]	4	NA	NA	3.8 years (1–10)	CYC, CSA, MTX, AZA, MMF	21.3 (12.5–35)	1.5 (0–4)	MTX	4/0	1 pt	Yes in 2 pts, stable in 2 pts	NA	NA	NA	No
Tombetti et al. [15]	7	24 (23–30)	NA	66 mos (17–82)	MTX, AZA, CSA, CYC, MMF, ADA, INF, RTX, ANA, sirolimus	10 (7.5–15)	6.2 (3.7–10)	IS tx	4/0	NA	Yes or stable in 3 pts	14 mos (10–33)	NA	NA	Severe rash (n = 1) increase in transaminases (n = ?) recurrent RTI (n = 2)
Goel et al. [25]	10	24.5 (13–53)	NA	25.5 mos (1.5–60)	MMF, AZA	24 ± 15	5.4 ± 4.9	NA	10/0	3 pts	Stable in 6 pts	NA	4.5 (0–3)	0	Rash (n = 1) Transaminitis (n = 1) Uncx inf (n = 2)
Canas et al. [23]	8	NA	NA	4.5 yrs (1–31)	MTX, CSA, AZA, INF	50 (30–60)	6.25 (2.5–10)	MTX, AZA	8/0	1 pt	Yes in 4 pts	18 mos (9–36)	NA	NA	No
Loricera et al. [26]	7	NA	7–57	–	MTX, CYC, AZA, MMF, CSA, anti-TNF	25–50	0–10	NA	7/0	NA	Improvement in 6 pts	3–24 mos	NA	NA	Thrombocytopenia (n = 1)
Youngstein et al. [35]	3	16–26	NA	5 yrs	MTX, INF, ADA, MMF, AZA	5–40	0–5	MTX	2/0	No	Yes in 1 pt	18.5 mos	5 (n = 1), 2 (n = 2)	0	Pancreatitis (n = 3)
Schiavon et al. [31]	1	18	20	2 yrs	MTX	25	5	MTX	Yes	No	Yes	21 mos	NA	NA	No
Mekinian et al. [27]	14	NA	NA	NA	DMARD	12.5 (4–75)	4.5 (1–14)	DMARD	9/1	NA	NA	24 mos (2–95)	NA	NA	Severe infection (n = 4) Breast cancer (n = 1)
Osman et al. [19]	3	18–35	–	3–40 mos	MTX, AZA, RTX	20–80	0–35	AZA	3/0	No	Yes in 3 pts	6 mos (7–24)	NA	NA	Persistent neutropenia (n = 1) Increase in liver enzymes (n = 2)

ADA, adalimumab; ANA, anakinra; AZA, azathioprine; CSA, cyclosporine; CYC, cyclophosphamide; DMARD, disease modifying antirheumatic drugs; dx, diagnosis; ETA, etanercept; INF, infliximab; IS, immunosuppressant agents; ITAS, Indian Takayasu activity score; MTX, methotrexate; MMF, mycophenolate mofetil; NA, not available; pts, patients; RTI, respiratory tract infection; RTX, rituximab; TA, Takayasu arteritis; TOC, tocilizumab; tx, treatment; uncx inf, uncomplicated infection.

^a Tocilizumab was administered IV at 4 mg/kg/dose per week for 6 weeks; then 4 mg/kg/dose per 2 weeks for 40 weeks; then 8 mg/kg/dose per 3 weeks in the study by Nishimoto et al. The dose was 4–8 mg/kg per 4 weeks in the study by Bredemeier et al. In all other studies, tocilizumab was administered at a dose of 8 mg/kg per 4 weeks.

Table 3
Reported pediatric Takayasu arteritis patients who received tocilizumab before 18 years of age*

Study	Number of TA pts who received TOC	Age at dx, yrs	Age at TOC initiation, yrs	Disease duration before TOC initiation	IS agents prior TOC	Prednisone before TOC (mg/day)	Prednisone while on TOC (mg/day)	Co-tx	Remission/no response	Relapse	Vascular improvement on imaging	Follow-up mos	ITAS before TOC	ITAS while on TOC
Our series	4	14.5 (4–16)	15.5 (9–17)	16 (1–60) mos	MTX, CYC, AZA	10	5	None	4/0	No	No, stable	9.5 (7–13) mos	11.5 (1–15)	0.5 (0–1)
Bravo Manchero et al. [21]	1	3	6	3 yrs	MTX, ETA, INF, CYC, MMF	30	0	MMF	Yes	No	Yes	2 yrs	NA	NA
Goel et al. [25]	2	NA	13–15	5–10 mos	MMF	25–50	NA	Antiplatelet drug	2/0	NA	NA	NA	4	0
Loricera et al. [26]	2	7–16	NA	NA	ADA, MTX, CYC, MMF, ETA, INF	30–50	0–7.5	NA	2/0	NA	NA	12–24 mos	NA	NA
Canas et al. [23]	3	12–17	NA	1.5–3 yrs	MTX	30–60	5–10	MTX, AZA	3/0	No	Yes in 2 pts	12–18 mos	NA	NA

ADA, adalimumab; AZA, azathioprine; CYC, cyclophosphamide; dx, diagnosis; ETA, etanercept; INF, infliximab; IS, immunosuppressant agents; ITAS, Indian Takayasu activity score; MTX, methotrexate; MMF, mycophenolate mofetil; NA, not available; pts, patients; TA, Takayasu arteritis; TOC, tocilizumab; tx, treatment.

* All patients were female and all received tocilizumab at a dose of 8 mg/kg per 4 weeks. No side effects were reported except in the study by Goel et al. (one patient each had transient skin rash, transient transaminitis, uncomplicated urinary tract infection, and upper respiratory infection; however, it is not stated that which ones were pediatric patients).

which were about the use of anti-TNF agents in giant cell arteritis and these studies did not suggest a benefit. There was no randomized controlled trial on tocilizumab use in large vessel vasculitis. Overall, the evidence from this analysis suggested that etanercept and adalimumab were not effective for remission or reduction of corticosteroid use while tocilizumab and infliximab may be effective in the management of large vessel vasculitis.

Up to date, 75 TAK patients were reported to be treated with tocilizumab in the literature (Table 2). Most of them responded to the treatment; however, there could be publication bias since favorable results are more likely to be reported. With the addition of our four cases, tocilizumab was used in 12 pediatric TAK cases with favorable results [21,25–27]. All pediatric patients were continuing on tocilizumab and the reported duration of tocilizumab treatment ranged between 6 and 24 months. None of these patients relapsed. However, there are no randomized controlled trials and no clear evidence in the literature for the optimum duration of tocilizumab treatment in TAK. For our patients, we have planned to continue tocilizumab treatment for at least 1 year after a stable imaging and clearance of clinical symptoms.

Seven patients received tocilizumab as the first line immunosuppressive treatment [23,27,29,33], two of them were children (including one of our patients and one patient by Canas et al. [23]).

Flares are common after cessation of tocilizumab treatment in TAK. In the study by Goel et al. [25], they followed up nine TAK patients for a median of 8 (3–14) months after cessation of tocilizumab and stable disease maintained in only two of them. They have concluded that the benefit of tocilizumab was not sustained after its withdrawal. However, the duration of tocilizumab treatment was short (6 months) in these patients. Arita et al. [38] have shown that a flare-up with a cytokine storm could occur in the patients with TAK after acute cessation of tocilizumab even when the disease activity seemed to be under control according to the serum IL-6 levels. Thus, addition of drugs such as methotrexate might be useful during the cessation of anti-IL-6 treatment.

There are no accurate markers of disease activity in TAK. The activity definition is based on composite measures integrating clinical, laboratory, and radiological data [13]. Inflammation-related markers such as erythrocyte sedimentation rate (ESR) and CRP are often used in daily practice; however, previous studies demonstrated progression in vascular lesions without elevation of APRs in TAK patients receiving tocilizumab treatment [15,22,33,34]. Especially in patients receiving tocilizumab treatment, CRP is no longer a biomarker reflecting disease activity in most cases. Silent progression in vascular lesions may depend on re-modelling and local vessel inflammation through locally produced inflammatory molecules such as pentraxin-3 independent of IL-6 [15,39]. Biomarkers other than ESR and CRP such as IL-6, matrix metalloproteinases, vascular cell adhesion molecules, RANTES (regulated on activation, normal T-cell expressed and secreted), and pentraxin-3 have been reported to be associated with TAK disease activity [39–42] but none of them is a validated outcome predictor in TAK.

ITAS2010 is a disease activity score mainly evaluating the clinical features of the vascular disease assessed by the physician [9]. APRs were also incorporated into the score (ITAS2010-A) to increase the extent of evaluation [9]. However, new vascular lesions in vascular imaging also reflect active disease and these might not cause increase in APRs and clinical findings. Imaging is also very important in diagnosis and evaluation of outcome in TAK. However, how to measure the degree of inflammation and disease activity by MRA or PET-CT remains controversial [43]. Recent outcome measures are not sufficiently validated in TAK; however, large-scale, longitudinal studies may help determining and validating better composite measures for follow-up of TAK patients.

The limitations of our study are mainly its retrospective design and small number of patients. In addition, it is difficult to evaluate disease activity with APRs after tocilizumab treatment since CRP remains normal during this treatment.

Conclusion

The optimal management and treatment of TAK is still a challenge for the physician. This is probably due to the rarity of the disease, inadequate tools for assessing ongoing vessel inflammation, and the longer follow-up required because of the evolution of this peculiar vasculitis. The disease seems to have a more severe course in young children [44–48]. This had led us to use aggressive treatments such as cyclophosphamide to escape from severe damage for children who have a long life expectancy ahead of them. The presented small series and the literature review suggest that tocilizumab may be a well-tolerated promising alternative for this purpose. We hope that long-term controlled studies will offer us better evidence for the place of tocilizumab in childhood TAK.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.semarthrit.2016.07.012>.

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