Childhood-onset Takayasu Arteritis — Experience from a Tertiary Care Center in South India

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**ABSTRACT.** **Objective.** To study the clinical profile and outcome of Asian Indian children with childhood-onset Takayasu arteritis (c-TA).

**Methods.** Records were studied of patients with c-TA onset prior to age 16. Disease Extent Index-Takayasu (DEI.TAK), Indian Takayasu Arteritis Score 2010, and Takayasu Arteritis Damage Score (TADS) were calculated retrospectively from electronic records. Cumulative incidence of sustained remission was estimated using the Kaplan-Meier curve.

**Results.** There were 40 patients with c-TA, with median age of onset of 12.5 years (range 1–16) and median diagnostic delay of 11.3 months (range 1–60). The most common presenting features were hypertension, headache, malaise, and fever. Pulsless disease was observed in 25 cases (62.5%). The majority (n = 28) had active disease with raised inflammatory markers, high baseline median DEI.TAK score of 10 (range 3–24), and high median TADS of 7 (range 1–14). Of the 34 patients followed for 21.5 months (range 3–192), remission was attained in 30. However, cumulative sustained remission was achieved in only 29% of them at 5 years. Median period of sustained remission was 22.5 months (95% CI 17.1–26.8). New areas of vessel involvement were observed in 13 patients (38%). Disease progression was arrested in the majority (n = 22, 66%) through aggressive medical management and endovascular intervention. All 11 patients with an increment in TADS of ≥ 4 during followup had persistently active or relapsing disease. There was a single fatality.

**Conclusion.** Despite aggressive immunosuppression, damage progressed in one-third of patients with c-TA in association with persistent inflammation, warranting surveillance with clinical instruments and followup imaging. (First Release May 1 2014; J Rheumatol 2014;41:1183–9; doi:10.3899/jrheum.131117)

**Key Indexing Terms:**

PEDIATRIC TAKAYASU ARTERITIS ITAS 2010 INDIA

Takayasu arteritis (TA) is a chronic granulomatous vasculitis of autoimmune etiology, characterized by narrowing of the aorta and its main branches at origin. It typically involves young adult females, but can occur in childhood. Indeed, it is the third most common cause of vasculitis in the pediatric age group. Brunner, et al, in their review have reported only 8 series of childhood-onset Takayasu arteritis (c-TA), including 2 from India. All except 1 series from Korea were limited by small sample size. Longterm survival in c-TA has been steadily improving from 65% in older series to 100% in a recent series, essentially owing to early diagnosis and multidisciplinary treatment. Assessment of extent, activity, and damage of this disease is a difficult task, both in adult and c-TA, because of a paucity of biomarkers and composite indices.

With this background in mind, we aimed to study the clinical profile and outcome of patients with c-TA attending our large tertiary care center in South India using various disease assessment tools including the recently validated Indian Takayasu Arteritis Score (ITAS) as compared to angiographic findings and large cohorts of c-TA from literature.

**MATERIALS AND METHODS**

In this single-center retrospective cohort study, hospital records were screened for all patients fulfilling American College of Rheumatology 1990 criteria for TA and/or European League against Rheumatism/Pediatric Rheumatology International Trials Organisation/Pediatric Rheumatology European Society consensus criteria for c-TA seen at rheumatology and pediatric rheumatology clinics of Christian Medical College, Vellore, India, between 2004 and 2012. Only consecutive patients with age of onset of symptoms suggestive of TA under 16 years were included in the study. Sixteen years of age was chosen as the cutoff because it is the upper age limit for the patients seen by the pediatric department in our institution. Moreover, rheumatic diseases with age of onset below 16 years are conventionally subclassified as juvenile-onset type in rheumatology.
Baseline visit was defined as the first visit of the patient to our clinic. Details of demography, clinical presentation, laboratory results, angiographic procedures, medications, and outcome were noted from records of baseline and subsequent followup visits. Disease duration was calculated as the interval between the onset of first symptom suggestive of TA and the first baseline visit to our center, while delay in diagnosis was defined as the interval between onset of symptom and the diagnosis as TA. The clinical profile included constitutional symptoms such as weight loss, fever, malaise, headache, and symptoms and signs pertaining to specific organ systems. Details of anatomical involvement of blood vessels on angiography were also recorded from electronic medical records, and angiographic subtype was accordingly depicted. In addition, we noted interventions done such as balloon angioplasty, stenting, surgical bypass grafting, or renal autotransplants. Procedure-related outcome and complications were also noted.

Disease Extent Index-Takayasu (DEI.TAK)\textsuperscript{13}, ITAS 2010\textsuperscript{9}, and Takayasu Arteritis Damage Score (TADS)\textsuperscript{14,15} were calculated retrospectively at each visit using the detailed clinical information available in the electronic records of the hospital. We also calculated ITAS-A (ITAS-acute-phase reactants) with either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), in accordance with a recent report by Misra, et al\textsuperscript{6}. DEI.TAK is an instrument derived from the Birmingham Vasculitis Activity Score to characterize disease extent in TA\textsuperscript{13,16} (see online supplement, Disease Extent Index, at jrheum.org). It contains 59 items from 11 organ systems, with emphasis on cardiovascular manifestations. Items occurring within the previous 6 months are given a point each and the score is added up. This tool has been validated in 143 adult patients with TA from 2 centers in India\textsuperscript{13}.

ITAS 2010 is a disease activity assessment tool derived from DEI.TAK using disease activity variables alone. It records symptoms newly developed during the previous 3 months. The score incorporates 44 items, with 33 features representing cardiovascular symptoms and signs. Seven items are assigned a score of 2 each, while each of the remaining items are given a maximum score of 1. This instrument has been validated in adult-onset TA. ITAS-A is a sum of ITAS 2010 and scores assigned to ESR (ITAS-A ESR) or CRP (ITAS-A CRP) values\textsuperscript{9}.

TADS, at baseline, was calculated for patients having clinical records for the preceding 6 months from the referring physicians. Briefly, TADS is a damage index devised by the Indian Rheumatology Association Vasculitis Group (IRAVAS), which consists of 42 items classified under 7 headings. The score measures damage and was derived from DEI.TAK. It notes only features persistently present for at least the previous 6 months. There is a strong focus on cardiovascular systems, with 8 of its items included (see online supplement, Takayasu Arteritis Damage Score, at jrheum.org). The score has been published as a conference abstract and has not yet been validated\textsuperscript{14,15}.

Laboratory results noted include inflammatory markers such as ESR and CRP, serum creatinine values, lipid profile, and antiphospholipid antibody tests. An ESR value of $\geq 20$ mm/h and CRP value of $\geq 6$ mg/l were taken as a cut-off for the normal range.

Outcome measures. Active disease was defined as (1) ITAS 2010 of $\geq 2$; (2) raised inflammatory markers, i.e., ESR and CRP in the absence of documented active infection along with an ITAS 2010 of $\geq 1$; and/or (3) angiographic evidence of a new area of vessel involvement or in-stent restenosis of $> 70\%$ or diffuse narrowing in areas beyond stent margins.

Stable disease was defined as the absence of all of the 3 criteria of disease activity mentioned above. Relapse was defined as reappearance of active disease as defined above. Sustained remission was defined as maintenance of a stable disease state until the last followup visit. A bad outcome was defined as an increment in TADS (ATADS) of $\geq 4$ during the last visit as compared to baseline. A good outcome was defined as the absence of disease activity or relapse.

Immediate outcomes of percutaneous intervention (PI). (1) Successful — residual stenosis of $< 50\%$ without any major vascular complications; (2) Suboptimal — residual stenosis of $\geq 50\%$; (3) Failure — lesion could not be crossed and dilated. Sustained success meant maintaining residual stenosis of $< 50\%$ at or beyond 6 months after the last PI.

Statistical analysis. Demographic data was reported as median with interquartile range (IQR). Logistic regression was used for estimating predictors of disease outcome. Kaplan-Meier survival curve was constructed for estimating median relapse-free disease duration. Variables between groups were compared using the chi-square test. A p value of $< 0.05$ was considered significant for all analysis. K statistics were used to assess agreement of clinical scores or inflammatory measures with angiography findings. Generalized estimating equations were used to analyze correlation between ITAS 2010 and inflammatory markers over various timepoints. For all analysis, ITAS 2010 $\geq 2$ or ITAS-A $\geq 5$ were categorized as active disease. SPSS version 16 was used.

RESULTS

Among 268 patients with TA seen at our center during this period, 40 were classified as c-TA and were included in this study. The diagnosis of TA was confirmed by conventional angiography in 38 patients and MR angiography in the remaining 2 patients. Thirty-nine patients had their first visit to our clinics during the study period of 9 years. Only 1 patient had consulted us after a gap of 14 years from baseline visit.

Demography and presenting features at baseline visit. Median age at disease onset was 12.5 years (range 1–16; IQR 10–15) with female:male ratio 26:14. Median age at presentation to a local physician was 13.5 years (range 2–18, IQR 11–15).

Patients had been diagnosed with TA after a median delay of 11.3 months (1–60). Prior to being diagnosed with TA, 18 out of 40 patients had been treated for alternatively diagnosed conditions because of mimicking clinical features, as follows: suspected tuberculosis (n = 3), pyrexia of unknown origin (n = 4), meningitis (n = 3), cerebrovascular accident (n = 2), hypertensive encephalopathy (n = 2), cerebral edema (n = 1), systemic-onset juvenile idiopathic arthritis (n = 1), poststreptococcal reactive arthritis (n = 1), and coexisting biopsy-proven ulcerative colitis (n = 1). Details of clinical features at time of baseline visit are presented in Table 1.

Hypertension (HTN) was the most common presenting feature (73%) followed by headache (53%) and constitutional symptoms, i.e., malaise (53%) and fever (45%). Dilated cardiomyopathy was observed in 8 patients, with concomitant HTN in 5 of them.

Digital gangrene, multiple pyogenic abscesses, and gluteal ulcer were the presenting manifestations in 1 patient each. Baseline DEI.TAK score at presentation was 10 (range 3–24), which reflected the extensive nature of the disease.

The angiographic type seen in the majority of children (53%) was type 5 disease followed by type 4 (25%), type 1 (10%), type 3 (8%), and type 2 (5%). Thus, altogether 78% of this cohort had involvement of subdiaphragmatic aorta. Renal arteries were the most commonly involved arteries on angiography (21%), followed by subclavians (16%), and...
abdominal aorta (14%; Figure 1). Thirty-nine patients had stenotic lesions, with complete occlusion of a vessel in 20 and aneurysmal disease in 3 of them.

At presentation, clinically active disease with median ITAS 2010 of 11 (4–27) was present in 39/40 children (98%). ESR and CRP values were available for 38 patients at their baseline visit. Raised ESR (> 20 mm/h) was observed in 25/38 (65.7%) and raised CRP (≥ 6 mg/l) in 15 out of 35 patients in whom it was measured (42.8%). Overall, 28/40 (70%) had raised acute-phase reactants by either or both markers. Baseline mean ESR and CRP were 33 ± 29.4 mm/h and 4.0 ± 25.6 mg/l, respectively.

At presentation, a majority of patients (n = 28) had unequivocal evidence of active disease, with both raised ITAS 2010 and elevated levels of inflammatory markers. Damage by TADS score could be assessed at presentation for 35 patients. Median baseline TADS score was 7 (range: 1–14). Diagnostic delay of more than 1 year did not make a difference in TADS when compared with those without this delay. Peripheral vascular system involvement (pulse loss and bruit) in a significantly higher proportion of patients with high TADS (> 4), as compared to those with low TADS (≤ 4), was the only notable correlation of TADS at baseline (96% vs 55.6%; p = 0.01; see online supplementary Figure 1 at jrheum.org).

A majority (34/40; 85%) were prescribed steroids and second-line immunosuppressant [mycophenolate mofetil (MMF) in 19, azathioprine (AZA) in 10, methotrexate (MTX) in 5 patients] at the first or subsequent visits. Thirty-six patients (90%) underwent PI. Unilateral hemi-

**Table 1.** Clinical and laboratory features of 40 patients at diagnosis.

<table>
<thead>
<tr>
<th>Symptoms/signs</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>General systemic</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>21 (53)</td>
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<tr>
<td>Malaise</td>
<td>21 (53)</td>
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<tr>
<td>Fever</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2 (5)</td>
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<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Absent pulses</td>
<td>25 (63)</td>
</tr>
<tr>
<td>Bruit</td>
<td>19 (47)</td>
</tr>
<tr>
<td>Claudication</td>
<td>16 (40)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Severe aortic regurgitation</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4 (10)</td>
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<tr>
<td>Neurological/visual</td>
<td></td>
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<tr>
<td>Visual blurring</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>29 (73)</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>13 (33)</td>
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<tr>
<td>Abdominal pain</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Disease markers</td>
<td>Blood levels / score</td>
</tr>
<tr>
<td>Mean ESR, mm/first h</td>
<td>33.0 ± 29.4</td>
</tr>
<tr>
<td>Mean CRP, mg/l</td>
<td>4.0 ± 25.6</td>
</tr>
<tr>
<td>Median DEI.TAK score (range)</td>
<td>10 (3–24)</td>
</tr>
<tr>
<td>Median ITAS 2010 (range)</td>
<td>11 (4–27)</td>
</tr>
<tr>
<td>Median TADS (range: calculated in 35 cases)</td>
<td>7 (1–14)</td>
</tr>
</tbody>
</table>

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DEI.TAK: Disease Extent Index-Takayasu; ITAS: Indian Takayasu Arteritis Score; TADS: Takayasu Arteritis Damage Score.
Nephrectomy was done in 1 and successful renal autotransplantation in 2 patients.

**Followup visits.** Thirty-four children (85%) had at least 1 followup visit at ≥ 3 months interval, with median followup duration of 21.5 months (IQR 8.7–37.2, range 3–192). Thirty of these 34 patients (88%) had attained stable disease state with treatment for a median period of 5.5 months (IQR 3–9.2, range 1–192). However, only 15 of them (50%) could maintain this state of inactivity until the last followup. The remaining 15 patients relapsed within a median period of 16.5 months (IQR 9.5–22.5, range 6.5–47). The median dose of steroids at relapse was 5 mg/day (IQR 0–15, range 0–40). A Kaplan-Meier survival plot showed cumulative incidence of sustained remission of 79%, 45%, 39%, and 29% at 1, 2, 3, and 5 years, respectively, with a median sustained remission period of 22.5 months (95% CI 17.1–26.8; Figure 2).

**Angiographic followup.** Repeat angiography was performed in 28 patients, mainly to assess the patency of previously treated vascular lesions or to perform new PI procedures. New areas of vessel involvement were observed in 13 out of 16 patients who relapsed. Of these, 3 had clinically stable disease (ITAS = 0), with inflammatory markers within normal limits. The remaining 2 had ITAS 2010 of 0, but had raised inflammatory markers.

**ITAS-A as a measure of disease activity.** Angiographic data along with concomitant ITAS 2010, ITAS-A by ESR, and ITAS-A by CRP were available for 60, 56, and 57 occasions, respectively, in 28 patients. Of these, ITAS-A CRP or ITAS-ESR, with a cutoff value of 4, seem to have correctly detected presence or absence of new areas of vessel involvement at 47/57 (κ = 0.441) and 45/56 (κ = 0.36) occasions, respectively, as compared to inflammatory markers alone, i.e., ESR > 20 mm/h (κ = 0.28) and CRP ≥ 6 mg/l (κ = 0.341). ITAS-CRP, therefore, fared somewhat better than inflammatory markers alone. In-stent restenosis was more likely when concurrent ITAS 2010 was ≥ 2 as compared to ITAS 2010 < 2 (14/16 vs 11/27; p = 0.004). Correlation of rising ITAS 2010 over time with increasing inflammatory marker levels showed only a nonsignificant trend (p = 0.422).

**Percutaneous interventions.** Thirty-six (90%) of the 40 children underwent a total of 170 PI procedures to treat 100 obstructive lesions (25 occlusions, 75 stenosis). PI per lesion ranged from 1 to 5 (average 1.7) and involved the following vessels: renal 32, subclavian 27, aorta 16, carotid 10, iliac 6, celiac 3, vertebral 3, and superior mesenteric 3. Stents were deployed in 84 lesions (84%). Eighteen lesions were resistant and required high-pressure (≥ 20 atm) dilation using noncompliant balloons. The immediate result after the first PI (PI-1) on the 100 lesions was success 78, suboptimal 19, and failure 3. Followup data at ≥ 6 months post-PI was obtained for 70 of 97 lesions with no failure as the PI-1 outcome; these 70 lesions included sustained success in 28 lesions (40%) and restenosis or continued suboptimal outcome in 42 (60%). One or more repeat PI were performed in 38 of the 42 lesions in the latter group, yielding an additional 19 sustained successes. Final outcome achieved in these 100 lesions, therefore, include sustained success in a total of 47 lesions, suboptimal.
outcome in 4, and failure in 4; followup data of 45 performed PI (successful immediate outcome in 39, sub-optimal in 6) is still awaited. Complications encountered were dissection (11), stent thrombosis (8), access site thrombosis (2), and stent displacement (2); these were managed satisfactorily by percutaneous methods. There was no procedure-related mortality, neurological complication, or free arterial rupture.

**Immunosuppression during followup.** Second-line agents were switched to another agent in 9 of the 16 patients who had relapsed. Three patients each taking MTX or AZA were switched to MMF, while 3 others taking MMF required addition of tocilizumab (TCZ) because of persistently active disease. Of the 3 patients treated with TCZ as add-on therapy, 2 continued to do well until their last review, while 1 of them still has active disease.

**Mortality and damage.** The single fatality was due to septicemia following immunosuppression rather than to disease. Overall damage accrued, however, was very high, with a median TADS score of 8 (3–23) at the last followup. But baseline high TADS did not predict relapse in our cohort. Relapsing or persistently active disease was observed in 50% of patients with baseline TADS ≤ 4 (4 out of 8 patients), in 38% of those with TADS between 5 and 9 (5 out of 13 patients), and in 70% of those with TADS ≥ 10 (10 out of 14 patients).

Change in TADS between baseline and last visit (ΔTADS) could be calculated for 33 patients. There was no progression of damage in 13/33 children (39.4%) as reflected by ΔTADS = 0, whereas 9/33 (27.3%) had minimal disease progression with ΔTADS between 1 and 3, and 11/33 (33.3%) had higher progression of damage with ΔTADS ≥ 4 (range 4–16). All 11 patients with high progression (ΔTADS ≥ 4) had active or grumbling disease at some time during the followup period, i.e., they could not maintain a stable disease state during the followup period.

**DISCUSSION**

We have studied the clinical profile and outcome of our patients with c-TA. We have also defined the disease extent, activity, and damage using composite clinical indices (DEI.TAK, ITAS 2010, and TADS). To our knowledge, this is the first study to use objective instruments to evaluate disease activity and damage in c-TA. ITAS 2010 has already been validated for use in adult-onset TA by the Indian Rheumatology Association Vasculitis Study Group in Indian patients; the authors suggested a cutoff point of ITAS 2010 ≥ 2 and ITAS-A ≥ 5 for defining active disease. However, certain items in DEI.TAK and ITAS 2010 such as weight loss of 2 kg and HTN defined according to criteria used for adults may limit its sensitivity in identifying disease activity or minor relapse in c-TA and requires modification tailored to children with this disease. Nonetheless, using these tools, we could demonstrate that persistent disease activity and thereby continued inflammation as reflected by high ITAS 2010 during followup leads to progression of damage with an increment in TADS of ≥ 4.

This is also the first data used to analyze relapse-free survival at various timepoints in c-TA. The cumulative incidence of sustained remission was 79% at 1 year, which dropped to 29% at 5 years in our cohort (Figure 2). This reinforces the need for continuous surveillance and longterm immunosuppression in these children.

Our study revealed that delay in diagnosis is a major problem, resulting in disease progression toward pulseless phase in 66% of patients and major damage (TADS ≥ 4) at presentation. One of the reasons for this delay could be clinical features of TA mimicking other conditions. This finding was similar to the data from an earlier Indian series reporting a diagnostic delay of 4 ± 1.5 months. Detailed clinical profiling of our cohort revealed HTN (72.5%) to be the most common presentation, similar to that reported in previously published papers on c-TA. Complications such as cerebrovascular accidents were less common in the present series (7.5% vs 16.9%), which could be due to early endovascular revascularization procedures in our cohort (Table 2).

Both sides of the diaphragm were involved in 53% of our children, less than the 63% and 72% previously described in 2 other series from India. Arresting progression of damage with ΔTADS of < 4 in two-thirds of our patients is noteworthy. This encouraging result could be due to the presence of active disease at presentation in a majority (70%), making them amenable to immunosuppression. In our series, PI were associated with fairly good immediate success (78%), but the sustained success rate was only 40% at ≥ 6 months following the procedure, mainly because of restenosis; this result matches the 40% (6/15) success previously reported from India. However, repeated PI in restenotic lesions resulted in more sustained successes in our cohort, yielding a cumulative sustained success rate of 85% (47 of 55 lesions completing ≥ 6 months followup after the last performed PI).

We anticipate a similar trend for the remaining 45 lesions with awaited followup, because repeat PI done by the same expert usually involves a simpler, safer, and cheaper balloon dilation of the previously deployed stent using the same percutaneous vascular access, unlike the complex PI-1.

In contrast to earlier studies of c-TA reporting mortality figures as high as 35%, there was only a single fatality in our series, due to infection-related complication. This could have been caused by use of aggressive immunosuppression and interventions in the majority (90%). Despite this fatality, the benefit of aggressive immunosuppression and timely interventional procedures in our patients is high-lighted by several favorable outcomes in this cohort.

Because of the small sample size in each group, we could not compare the efficacy of various second-line agents in...
c-TA. In a Turkish retrospective study of 6 children with TA, the authors have proposed cyclophosphamide and corticosteroids in the induction phase, followed by MTX maintenance\textsuperscript{18}. However, in our series, we have used MMF in the majority (n = 19) of patients. The efficacy of MMF in c-TA was clearly demonstrated in our series by the fact that only 3 patients taking it required additional TCZ because of persistent disease activity. Earlier series on adult-onset TA also have shown a similar good response to MMF\textsuperscript{19,20}. Two of 3 children with refractory disease while taking MMF in the present series could achieve stable disease status after adding TCZ therapy. These results were encouraging and in concordance with experience in adult patients with TA and in 1 case report in pediatric TA\textsuperscript{21,22}.

Repeat angiography data were available for 28 out of 34 patients with available followup data, and this gave us a clearer idea of disease progression. We were also able to correlate the change in ITAS 2010 and TADS with angiographic progression of disease, which was not attempted earlier in any other series.

We were, however, limited by a small sample size and lack of a validation process for DEI.TAK and TADS. Our data may lay the path toward preliminary validation much needed before their use in clinical trials on c-TA.

TA in children is diagnosed late because of nonspecific features mimicking other illnesses. This leads to persistent disease activity and progression of damage. Aggressive immunosuppression and timely endovascular interventions could arrest disease progression, reducing the need for surgical procedures and mortality. Tools assessing clinical disease activity and damage along with inflammatory markers and imaging may help in better followup evaluation of disease to guide therapy in c-TA.

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ONLINE SUPPLEMENT
Supplementary data for this article are available online at jrheum.org

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