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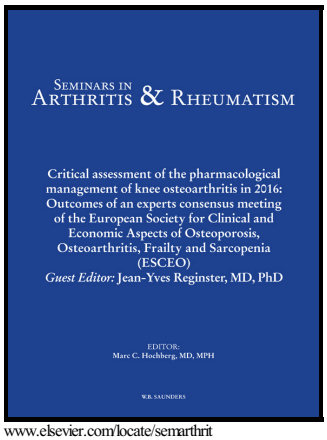

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Title page

Title: Long term outcome of 251 patients with Takayasu Arteritis on combination immunosuppressant therapy: single centre experience from a large tertiary care teaching hospital in southern India

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Abstract:

Introduction: Long term outcome studies in Takayasu arteritis (TA) are few and limited by small sample size. In this study, we analysed the outcome of treatment in a large series of TA patients with a minimum follow up period of ≥ 12 months by objective instruments.

Materials and Methods: Patients with TA satisfying the 1990 ACR, Ishikawa's, Sharma's or EULAR/PRESS criteria were recruited from our clinics between 1998 and 2016. Only patients with a minimum follow up of 12 months were studied. Data related to clinical presentation, disease extent [DEI.Tak score], activity [Indian Takayasu arteritis clinical activity score i.e. ITAS-A (CRP)] and damage score [Takayasu Arteritis Damage Score i.e. (TADS)], angiography and treatment were collected for all patients. Response to treatment was categorised as complete response (CR), partial response (PR) or refractory disease. Patients with sustained CR on prednisolone dose of ≤ 5mg/day were classified as having sustained inactive disease. Appropriate statistical tests were used for parametric and non-parametric data. Relapse free survival was projected by Kaplan Meir curve. Cox proportional hazards regression plot was used to compare the efficacy of medications. Predictors of sustained response were identified by logistic regression and a prediction model was constructed.

Results: Among 503 TA patients examined during study period, 251 had follow-up of ≥ 12 months and were included in this study. Median follow up duration was 42 months (IQR: 24-81, maximum 240 months). Patients (81.7% females, mean age of 29.2 ± 11.8 years, symptom duration of 24 (6-70) months) were treated by a uniform protocol that included high dose steroids (n=239) plus concurrent steroid-sparing immunosuppressant (n=235) with mycophenolate in majority. Biological agents (n= 44 patients) and revascularisation procedures were used in symptomatic patients after control of disease activity. At 1st follow up, CR (ITAS2010 =0, CRP <6mg/L and non-progressive disease on angiography) was observed in 173 (68.9%), partial response (PR) in 42 (16.7%) and no response was seen in only 36 (14%) patients. CR was sustained till the last follow up in 116 (65.9%) of 173 patients with initial CR, while **87** (49.4%) of them achieved **sustained inactive disease**. Disease activity relapsed at a median duration of 37 (29.9- 44.1) months in 56 patients. Cumulative relapse free survival was 93%, 73%, 66% and 52% at 1, 3, 5 and 10 years

respectively. Baseline CRP <6.2, DEI.Tak <9 and angiographic type 4 disease predicted sustained inactive disease and a model comprising these parameters showed sensitivity and specificity of 70% and 61.1%. Two fatalities were observed. New vascular lesions during follow up were observed in 50 (19.9%) patients. Overall, 92.8% had at least one period of CR or PR while 7.2% were refractory to treatment till the last follow up. Damage progression (ΔTADS >1) was arrested in 68% of patients and was lower in patients with sustained inactive disease [0 (0-1)] as compared to the rest [1 (0-2.75)], p=0.000. Both early response as well as cumulative hazard for relapse was similar between patients initiated on 0.5mg/kg/d and 1mg/kg/d steroids.

Conclusions: Our strategy of upfront combination immunosuppressant therapy stabilised disease activity in 92.8% of patients while 7.2% had true refractory disease. Relapse free survival was 66% at 5 years and 52% at 10 years. Damage progression was arrested in 68% and only 2 fatalities were observed. Initial steroid dose of 0.5mg/kg/day had similar efficacy as 1mg/kg/day dose.

Keywords:

Takayasu arteritis, India, ITAS-A, TADS, outcome, predictors

Abbreviations:

TA – Takayasu arteritis, ITAS 2010- Indian Takayasu activity score 2010, EMR- Electronic Medical Records, ACR- American College of Rheumatology, TADS- Takayasu Arteritis Damage Score, DEI.Tak- Disease Extent Index- Takayasu arteritis, CR- Complete response PR- Partial response, TCZ- Tocilizumab, MMF- mycophenolate, AZA- Azathioprine, MTX- Methotrexate, AUC- Area under curve, OR- Odds Ratio, CCF- Cleveland clinic foundation,

Introduction:

Takayasu arteritis (TA) is a prototypic large vessel vasculitis characterised by granulomatous inflammation of the aorta, its main branches and pulmonary arteries. Untreated inflammation often leads to stenosis and / or occlusion of involved arteries; less frequently, dilatation or aneurysm formations are the sequelae [1,2]. The disease is rare but somewhat more common in Asians. Over the past 16 years, we have created a database of 503 patients with TA in our tertiary care, teaching hospital. Several clinical series from various parts of the world have highlighted different clinical aspects of this disease; most of these studies are retrospective in nature except one from the NIH and a small Indian series [3,4]. Arnaud et al, in their multicentre retrospective study from France have looked at the influence of ethnic background on clinical phenotypes of TA, while Yang et al addressed the predictors of survival in Chinese patients. On the other hand, the two recent Japanese studies analysed changes in the profile of TA in the current decade as compared to those diagnosed in the past, as well as the effects of gender and age on clinical manifestations [5–8]. Even though many case series from various centres across the world have been published, data on long term outcome is negligible and only small series of patients exist with ≥ 1year follow up. Schmidt et al from Mayo clinic described 126 patients with TA, but the outcome data was available only for 79 of them [9]. There is no long term study even from South Asia including India, one of the largest reservoirs of TA. We report here the outcome data of 251 patients from our single centre cohort of TA, restricted to patients with follow up duration of at least 12 months.

In this study, we analysed both retrospectively and prospectively, the outcome of treatment in TA by objective instruments.

Materials and Methods:

2.1 Data extraction: The data for this study has been collected in retrospective manner from our institute's electronic medical records (EMR) for 179 patients and prospectively for the rest of the cohort (n=72). EMR include the records of all discharge summaries, outpatient

medical reports and investigation reports in an electronic workstation by our institute and it is in existence since the year 2002. In addition, doctors' notes and inpatient case records are also saved as hard copies. Scanned documents are also preserved as soft copies for all patients attending this hospital since 2012; these can be retrieved and made available for clinical research after approval from the institute research and ethics committee, Thus, the data in these records has been prospectively entered and saved, but have been extracted for this study in a retrospective manner.

2.2 Patients:

A total of 503 patients with TA, attending our outpatient and in-patient services during the period from January, 1998 to April, 2016 and satisfying the 1990 ACR criteria, Ishikawa criteria or Sharma's modification of Ishikawa criteria or EULAR/PRESS criteria for childhood TA were studied [10–12]. Of these, 251 consecutive patients had complete records of clinical details with a follow up duration of at least 12 months and therefore, were eligible to be included in this study. Details of demography, clinical as well as angiographic features, extent of clinical disease assessed by DEI.Tak, cumulative damage assessed by TADS (Takayasu arteritis damage score), disease activity assessed by ITAS2010 (Indian Takayasu activity score, 2010) along with laboratory parameters i.e. C-Reactive Protein (CRP) and Erythrocyte sedimentation rate (ESR) were noted for each visit till the last recorded follow up.

2.3 Disease assessment:

The disease was categorised into 5 subtypes according to Hata's classification criteria based on angiographic findings [13]. The baseline extent of disease was assessed by **DEI.Tak score** [14,15].

During the follow up visits, we defined disease activity by a hybrid composite score namely, ITAS-A(CRP) which incorporates both clinical assessment by ITAS-2010 and CRP as biomarker [16].

Study definitions:

Juvenile onset TA was defined as TA patients with onset of 1st symptom at or prior to the age of 16 years, while those with age of onset beyond 16 years of age were labelled as adult onset TA.

Disease activity at each visit was defined as

1. **Clinical activity**: by presence of any one of the following:

1a. ITAS 2010 ≥ 2 (not attributable by in-stent restenosis)

1b. ITAS-A (CRP) ≥ 3, at least one point should be contributed by clinical criteria as in ITAS proforma (16)

2. **Imaging activity**: if there was presence of de-novo lesion on follow up angiography or stenosis of the same vessel extending beyond stent margins

3. **Biomarker activity**: defined by persistently raised CRP as well as ESR on 2 consecutive visits without any alternative explanation like infection.

Response to Treatment was classified as

A. *Complete response (CR):* absence of all of these criteria of disease activity as mentioned above

When the patient maintained complete response throughout the follow up period, the outcome was called *persistent complete response*.

The subset of patients with persistent CR during the entire follow up period, who were able to reduce daily steroid dose to ≤ 5mg, were classified as having *sustained inactive disease*.

B. Partial response (PR) was defined as ITAS-A (CRP) value of 1 or 2 along with any improvement in disease activity by any of the 3 categories of criteria as above, not amounting to complete normalisation. This included downward trend from baseline activity by clinical, imaging or laboratory criteria.

If a patient attained CR or PR anytime during study period, whether early or late, they were considered as treatment ***responders***.

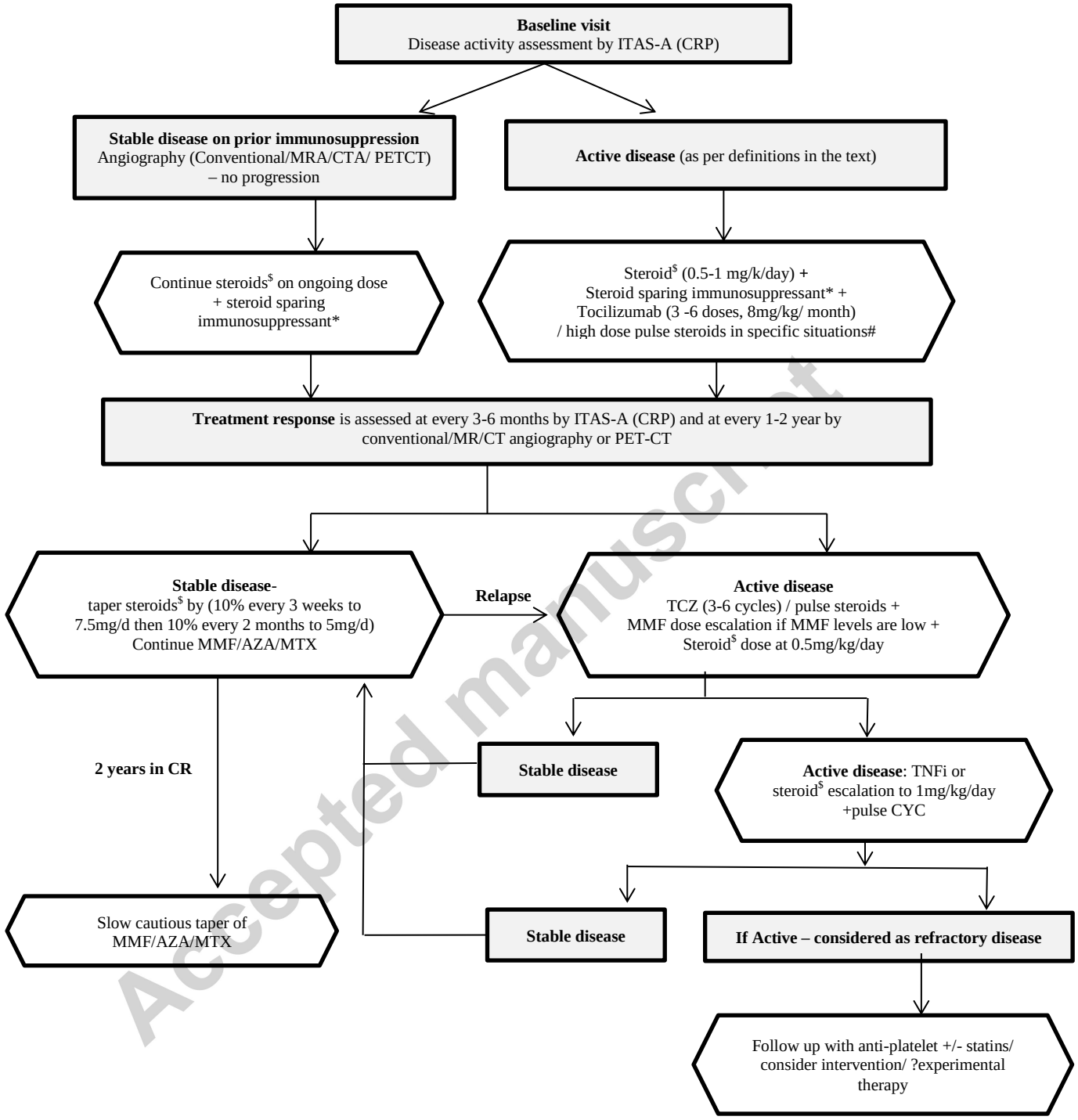
C. *Relapsing-remitting disease*: Patients who had return of disease activity as defined above after having attained complete response.

D. Refractory disease: Inability to achieve CR or PR during the entire follow up period in spite of treatment escalation as per our protocol.

2.4 Medical Therapy protocol: The patients in our study were treated by medical therapy according to protocol adopted by our unit based on clinical, real life efficacy and socio-economic background relevant to our resource limited set up. The treatment protocol is depicted in **figure-1**. Patients with active disease were initiated on high dose steroids (1mg/kg/day of prednisolone or equivalent dose of deflazacort during the period prior to 2009 and 0.5mg/kg/day of the same after 2009) with or without biological agents [mostly interleukin-6 receptor blocker tocilizumab (TCZ) or anti-tumor necrosis alpha agents]. Concurrently, one steroid sparing immunosuppressive agent [mycophenolate (MMF), azathioprine (AZA) or methotrexate (MTX)] were routinely initiated upfront at the 1st visit. Based on our earlier experience (17), MMF has been the first choice steroid sparing immunosuppressant in our clinic. Those who could not afford MMF, azathioprine was the next option. Methotrexate was given only to extremely non-affording patients or in exceptional cases with quiescent disease without any major target organ damage. The dose of MMF was maintained between 2-3 gm/day (majority 2 gm/day) and the dose adjustments were done after assaying the MMF levels by 6 hour AUC. The dosage of AZA and MTX were as mentioned in figure-1. After steroids are slowly tapered down to ≤5mg/day of prednisolone or ≤6mg/day of deflazacort while the treatment response was maintained (ITAS-A =0), further attempt to lower the dose of steroid sparing immunosuppresants were made very cautiously.

In addition, symptomatic vascular stenosis with >70% occlusion were subjected to revascularisation procedures, after initial control of disease activity by medical treatment, usually at 1st or 2nd three monthly follow up visit. Endovascular percutaneous trans-luminal angioplasty with or without placement of stent were preferred choices over surgery in our centre. Open surgeries mainly renal auto-transplantation or aneurysmal repair, were opted in small number of cases with lesions not amenable to endovascular intervention.

Figure 1: Treatment protocol for TA patients in the present study#



*The preferred immunosuppressant is mycophenolate (MMF) (2-3 gm/day). For patients with limited finances, azathioprine (AZA) (2mg/kg/day) is used; while methotrexate (MTX) use 15-25mg/week) is restricted only to those patients with mild, non-organ threatening disease and severe financial constraints.

$Steroids were oral prednisolone or equivalent dose of deflazacort

For critical symptomatic vascular narrowing requiring revascularisation after medical control of disease activity / clinically (ITAS-A) or angiographically aggressive disease / young patients requiring rapid taper of steroids / myocardial involvement

Note: All patients are initiated on anti-platelet therapy and additional treatment with statins and anti-hypertensive drugs is given as and when required. Re-vascularisation procedures are performed after controlling disease activity when needed.

2.5 Statistical analysis: Demographic variables are depicted as mean ± S.D. or median (interquartile range or IQR) wherever applicable. Intergroup comparisons were performed using nonparametric test (Mann Witney U test) for continuous variables or $\chi 2$ test for categorical variables. Pearson coefficient was used to determine correlation between two continuous parameters. Logistic regression was performed to ascertain the independent effect of various parameters on different aspects of disease.

Predictors of sustained inactive disease were identified using regression analysis. A prediction model has also been constructed incorporating the parameters which were significant to the precision levels of 10% in regression analysis. Area under curve (AUC) for individual predictors as well as the prediction model were generated by constructing receiver operating curves (ROC) and optimal cut off values were determined. The overall survival and relapse free survival were projected by Kaplan Meir survival curve.

Wherever applicable, Cox proportional hazards regression plot was used to compare the efficacy of medications on disease course. SPSS version 16 was used for all analysis.

Results:

3.1 Baseline demography and disease extent: In total, 251 patients with follow up details of ≥ 1 year were included in this study. Majority (n=205, 81.7%) were females with mean age at 1st visit to our clinics of 29.2 ± 11.8 years and mean age at onset of symptoms of 24 ± 11.0 years. Median duration of disease prior to presentation to us was 24 (6-70) months. At baseline, the most common clinical presentations included pulse loss, claudication, and hypertension which were noted in 60.6%, 59% and 53.4% of patients respectively (**supplementary figure-S1)**. Detailed angiography was done for all but 3 patients; 9 of them had undergone only CT/MR angiogram, while the remaining vast majority had undergone conventional angiography (**supplementary figure-S2**). Type V disease was the commonest type (n=135, 54.2%) followed by type 4 and type 1 (n=45, 18% each). The commonest comorbidity was tuberculosis in 26 patients; diabetes mellitus was present in 6 patients.

Median DEI.Tak was 9 (IQR: 6-13). Median ITAS 2010 score at baseline was 8 (2-12) and ITAS-A scored in 229 patients was 8 (3-14). Raised CRP (≥6mg/L) and ESR (≥ 20 mm/1st hr) at baseline was observed in 135 (58.9%) and 183 (78.2%) patients respectively. Baseline TADS, scored in 248 patients, was 6 (4-10). A modest correlation was observed between the diagnostic delay and TADS score with Pearson correlation coefficient of 0.698 (p=0.027). Altogether, 81 patients (32.3%) had present or prior history of major complications at the time of presentation to our unit; of these, hypertensive emergency including accelerated hypertension, cerebrovascular accident and aortic regurgitation were the most common ones.

3.2 Treatment details: Medical immunosuppressive therapy was initiated for the large majority of patients. Steroids (deflazacort in majority) were started in 239 (95.2%) patients. The initial steroid dose was 1 mg/kg/day for 93 (37%) patients, 0.75 mg/kg/day for 4 patients (1.6%), 0.5mg/kg day for 113 patients (45%), while 29 (11.6%) patients received <0.5mg/kg/day steroids. Steroid sparing immunosuppressive agents were initiated in 235 (93.6%) patients upfront along with steroids from day 1. Mycophenolate was the most frequently used immunosuppressant (160, 63.7% patients) followed by azathioprine (54, 21.5%) and methotrexate (20, 8.0%). Tocilizumab with or without mycophenolate was used in 14 patients (5.6%).

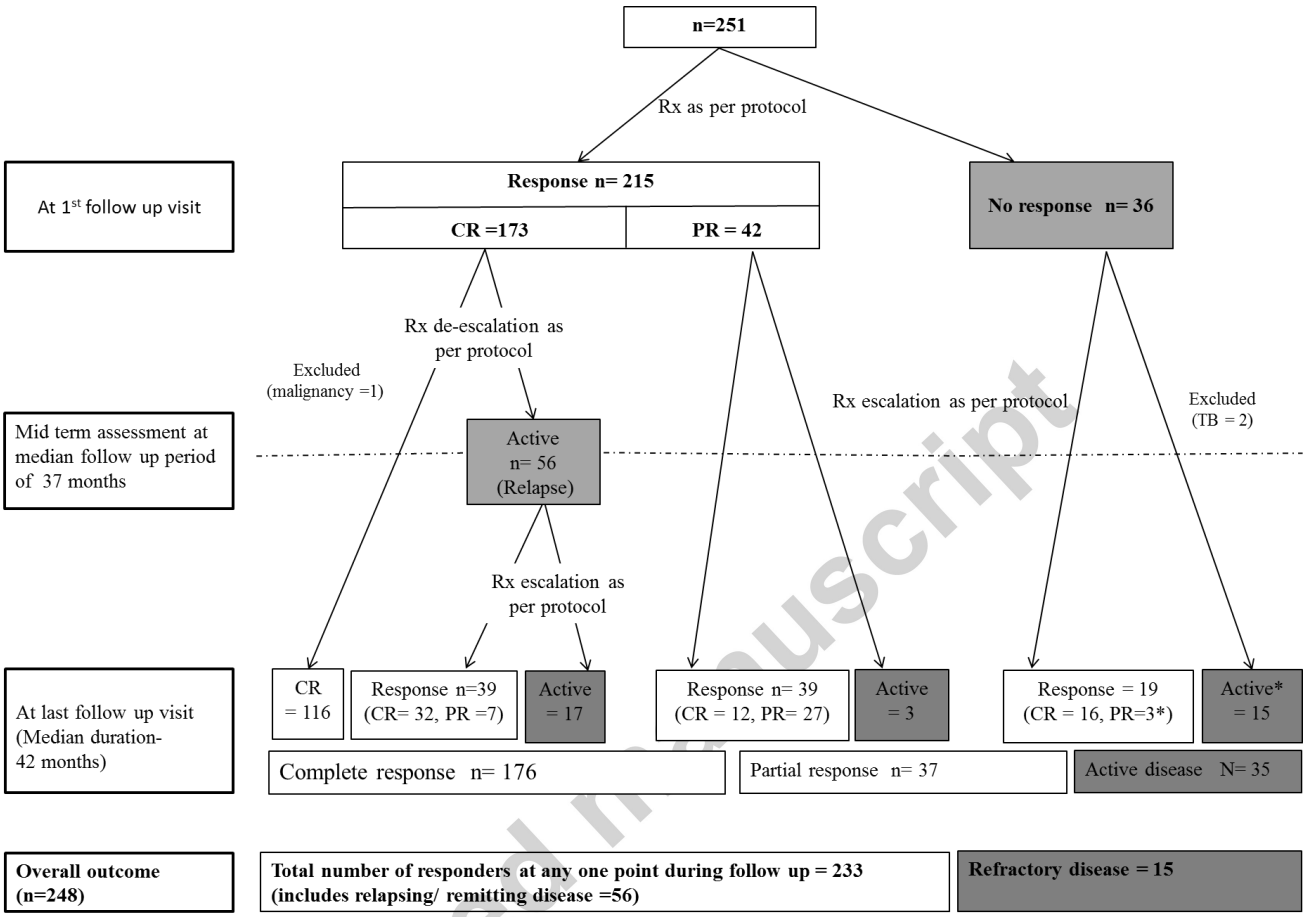
Thirteen patients (5.2%) were not initiated on any steroid and/or steroid sparing immunosuppressant due to various reasons, such as inactive and non-progressive disease prior to 1st consultation with our unit, pregnancy, tuberculosis and other contraindications.

Revascularisation procedures were performed in 180 (71.7%) patients between 3 and 6 months after initiation of medical therapy, provided the disease activity was under control. The majority (n=174; 96.7%) were endovascular interventions, while 14 patients (3.3%) underwent open surgeries as mentioned in methods above.

3.3 Disease outcome during follow up (figure 2, 3A and 3B): Median follow up duration was 42 months (IQR: 24-81, maximum 240 months) with 192 of the total cohort of patients (76%) following up for ≥24 months, while 88 (35%) were followed up for ≥ 5 years. Good compliance to treatment was observed in 80.5% of patients; although 16% defaulted for a short period in between, only 13.1% of patients were non-compliant to medical treatment throughout the follow up period.

Short term outcome (response at 1st follow up visit): Overall, 215 patients (85.6%) responded to treatment at 1st follow up visit; 173 of them (68.9%) achieved complete response (ITAS 2010 =0, CRP <6mg/L and non-progressive disease on angiography), while 42 (16.7%) patients had partial response. Only 36 patients (14%) did not show any initial response to treatment (**Figure-2**). Since majority (95%) of patients were on steroids plus second line immunosuppressant combination, we did not compare their outcome with that of a negligible number of patients (n=4) on steroids alone.

Figure-2: Outcome of 251 TA patients with a follow up of ≥ 12 months in this series



***includes 1 fatality each**

Long term outcome (median follow up 42 months): During further follow up at 42 (IQR: 24-81) months, 116 patients (65.9%) amongst the 173 initial complete responders maintained their CR status till their last follow up visit. Steroid dose could be tapered to ≤ 5mg/day of prednisolone or ≤ 6mg/day of deflazacort by last follow up visit in 87 (49.4%) patients, who also maintained the initial complete response. They were, therefore, classified as having **sustained inactive disease**. However, only 13 (14.9%) of the 87, could be completely taken off 2nd line immunosuppressive agents at the last visit (15 continued on azathioprine, 56 on mycophenolate and 3 on methotrexate). Discontinuation of both steroids and immunosuppressive agents could only be achieved in 11 patients.

Relapse of disease activity, after an initial complete response, was observed in 56 patients (32.4% of 173 patients with initial CR i.e. 22.3% of total cohort of 251 patients) with median time to relapse of 37 (29.9- 44.1) months. Later during further follow up till the last visit, treatment escalations led to a complete or partial response in 32 and 7 of these 56 relapsed patients, respectively. Only 17 of them (30.4% of 56 relapsed patients i.e. 6.8% of total cohort) did not regain CR or PR till the last follow up visit.

Only two fatalities were observed in the whole cohort during the study period; one patient expired due to sepsis following a osteoporotic vertebral fracture and another patient with underlying dilated cardiomyopathy had succumbed to acute pulmonary edema.

One patient had developed acute myeloid leukemia (at 50 years of age) during 48th month of follow up and was excluded from analysis, though the patient was alive till the last follow up visit.

Among the initial non-responders, 19 patients eventually responded (CR in 16, PR=in 3) after escalating steroid dose with or without addition of biological agent TCZ (n=9). Thus, of the entire cohort, only 15 patients (6%) did not attain complete or partial response anytime during follow up, in-spite of treatment escalation.

The Kaplan Meir curve showed cumulative relapse free survival to be 93%, 73%, 66% and 52% at 1 year, 3 years 5 years and 10 years respectively (**figure-3A**). During any follow up interval period, initial high overall response rate (CR+PR) was noted to persist consistently (**figure 3B**). Even the lowest overall response rate was 68.2% during 8-24 months follow up period; beyond 2 years this figure peaked to ≈ 80% till the last follow up.

Figure 3A: Cumulative relapse free survival in patients with TA

Follow up is censored at 150 months as very few of our patients followed up beyond this time point and the last relapse was observed at 144 months.

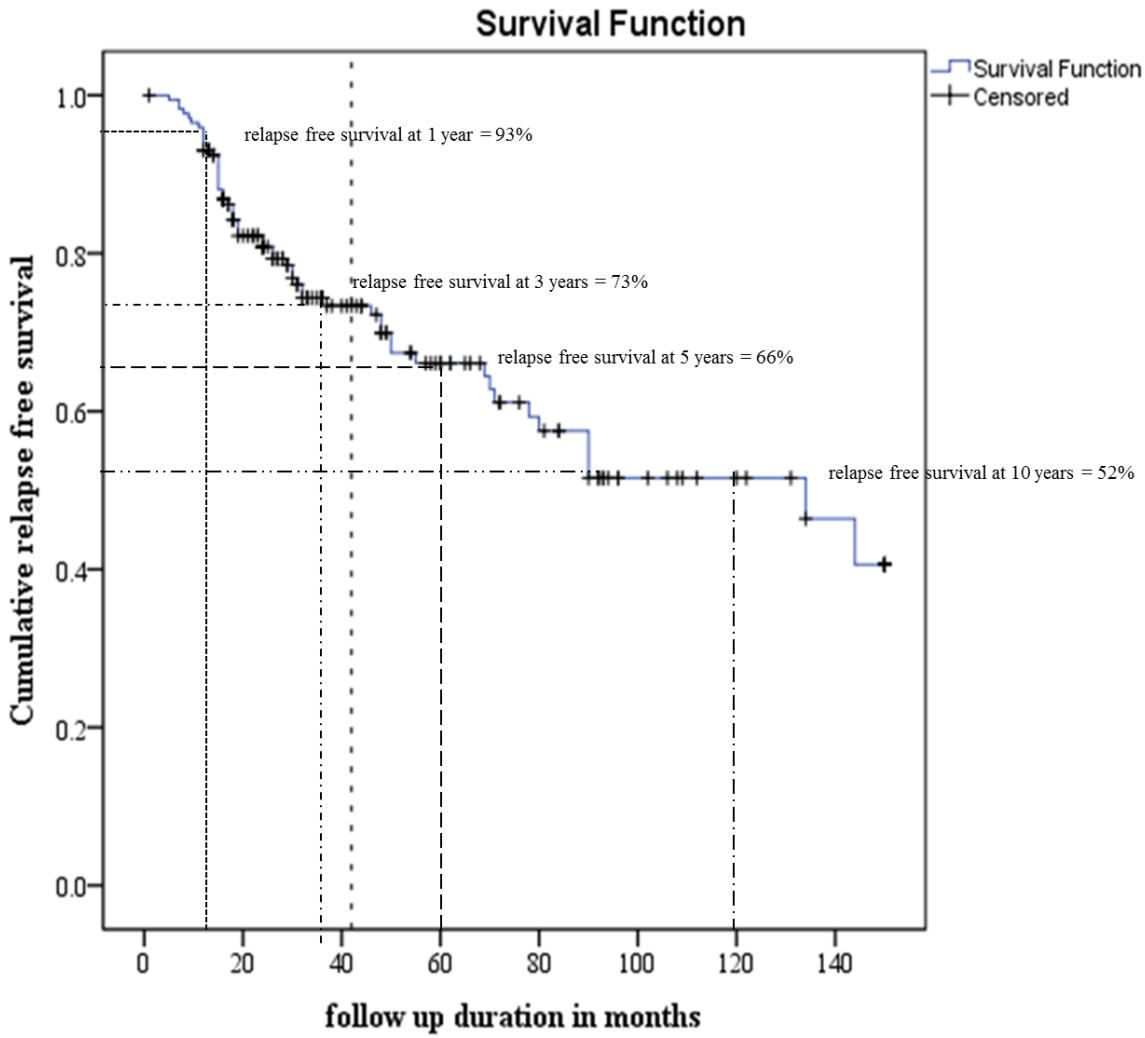
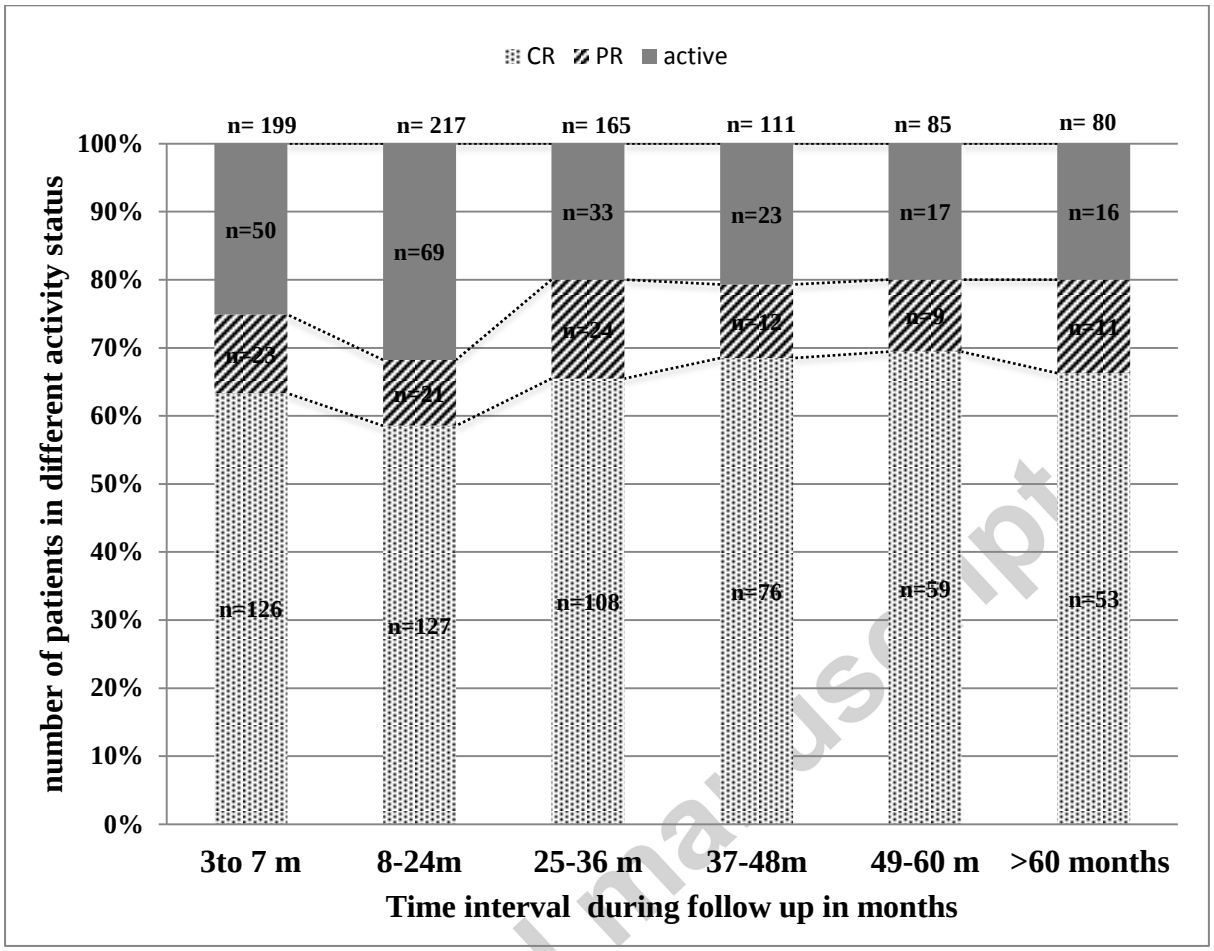


Figure 3B: Disease activity status at various time intervals of follow up (months)



Angiographic progression: Among the patients with active disease at any one time point during follow up, repeat angiography showed new vascular lesions in 50 (19.9%) patients, 11 of whom had isolated angiographic progression without clinical and laboratory criteria. Others had isolated biomarker activity (n= 32), clinical and biomarker activity (n= 19), only clinical activity (n= 12), while the disease was active by all three criteria in 19 patients.

Disease outcome and damage at last visit: On cross sectional analysis at their last recorded visit, 176 patients (70.5%) had stable disease (i.e. complete response) with 127 (72.2%) of them maintaining stable disease status on ≤ 5mg/day of prednisolone or ≤ 6mg/day of deflazacort. Partial response was observed in 37 (14.7%) patients, while 35 patients (14.3%) had active disease state. Activity of TA could not be clearly ascertained in 3 patients due to malignancy in 1 and active TB infection in 2 patients. These 3 patients are not included in

final analysis of outcome. Overall, median ITAS-A CRP score at the last follow up visit (calculated in 248 patients) was 0 (IQR: 0-2).

Median dose of steroids at last visit was 5 (2.5-10; range 0-70) mg/day of prednisolone or equivalent dose of deflazacort. Steroids had been discontinued in 37 patients (14.7%) and tapered to≤ 7.5mg of prednisolone or equivalent dose of deflazacort in 175 patients (70%) by the last visit. Majority of patients (n=226, 90%) were on steroid sparing immunosuppressive agents at the last visit.

Damage progression: Median TADS at last follow up visit was 8 (4.25-11, range: 0-24). Increment in TADS from 1st visit to the last visit (Δ TADS calculated for 244 of these patients) was 1.0 (IQR: 0-2, range 0-10). Majority (68%) had no or minimal progression of damage (delta TADS score of 0 and 1 in 103 and 63 patients respectively). Median delta TADS was significantly lower in patients with sustained inactive disease [0 (0-1)] as compared to rest of the cohort [1 (0-2.75)], p=0.000.The increment in TADS score in patients with different disease courses is shown in **table-1**.

Table-1: Increment in TADS score (ΔTADS) in patients with different disease courses

Parameter	Persistently stable (any steroid dose)	Partial response	Relapsing/ Remitting	Delayed response	Persistently active	p1*	p2*	p3*
No. of patients with ΔTADS calculated	112	41	54	7	28			
Median ΔTADS	0 (0-1, range 0-9)	1 (0-2, range: 0-8)	1 (0-3, range 0-9)	2 (0=3, range 0-3)	2 (0.25-3, range 0-10)	0.000	0.000	0.85

p1 - persistently stable vs persistently active group
p2 – persistently stable vs relapsing disease
p3 – relapsing vs persistently active disease

3.4 Predictors of outcome: Our second objective was to construct a prediction model for the subset of 87 patients with less aggressive disease i.e. those with sustained inactive disease (persistent complete response with prednisolone dose of ≤ 5mg/day or equivalent at last visit). Univariate analysis for clinical associates of sustained inactive disease showed significantly lower baseline ESR, CRP, and DEI.Tak values in these patients as compared to other patients (p= 0.000). Angiographic type 4 disease was the most frequent subset in patients with sustained inactive disease as compared to rest of the patients (p=0.002). The scenario was diametrically opposite for type 5 disease (p= 0.019) (**supplementary table S3**).

The optimal cut-off values which differentiated patients with sustained inactive disease from rest of the cohort included baseline CRP < 6.2 mg/L, ESR <32 mm/1st hr, DEI.Tak < 9 with an ROC curve AUC of 66.2%, 63.1% and 60.7% respectively. Baseline ITAS-2010 did not significantly predict sustained inactive disease.

Multivariate analysis showed baseline CRP < 6.2 mg/L and type 4 disease to be independent predictors of sustained inactive disease with an adjusted OR of 2.65 (1.38- 5.08, p= 0.003) and 2.213 (1.003- 4.884, =0.049) respectively. Initial steroid dose and ESR values did not predict this subset. DEI.Tak scores of <9 was also not significantly associated with subset of responders, but it had a trend towards independent association, with an OR of 1.74 (0.948-3.2, p= 0.074) and therefore, it was included for construction of the prediction model below.

We constructed a model assigning the OR values of CRP, angiographic type 4 disease and DEI.Tak to those patients with values above respective cut-offs determined by ROC as mentioned above (**table-2**). At a composite score value of 1.98, the prediction model differentiated the subset with sustained inactive disease from other patients, with an AUC of 70.2 (63.3-77.2, p= 0.000) and sensitivity and specificity of 70% and 61.1%.

Table-2: Prediction model for sustained inactive disease in TA patients

Item	Value	Score assigned
CRP (mg/L)	<6.2	2.65
Type 4 disease	Present	2.21
DEI.Tak	<9	1.74
A total score of >1.98 predicted sustained inactive disease		

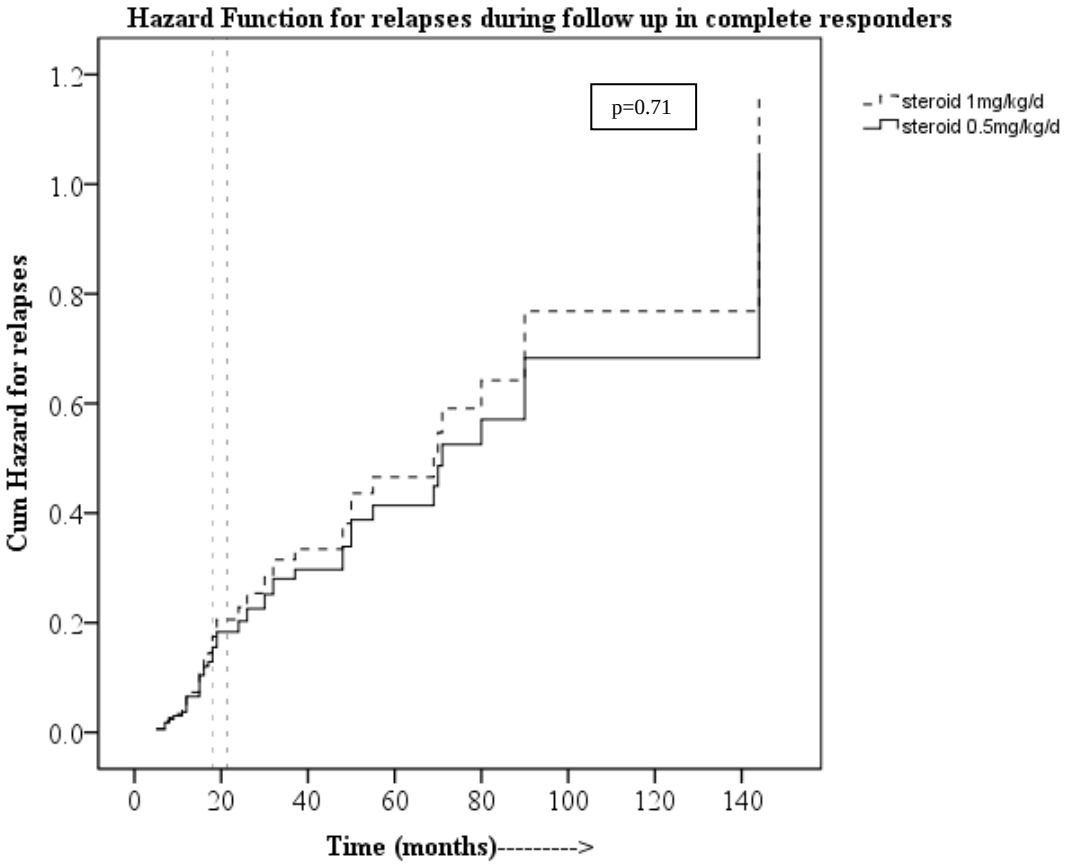
Analysis of predictors of refractory disease revealed that patients with refractory disease had higher age at onset [31 (25-36) vs 24 (16-30), p=0.019], lesser diagnostic delay [3 (4-11) months vs 9 (2-24) months, p=0.027], higher DEI.Tak score [11 (8-15) vs 9 (6-12)], p=0.074 and higher ITAS 2010 score [11 (8-15) vs 8 (1-12), p= 0.026]. Abdominal aorta involvement was less common in patients with refractory disease (2/15 vs 112/235, p=0.01). Multivariate analysis showed abdominal aortic involvement to be a significant negative predictor of refractory disease [OR 0.067 (0.006- 0.79), p= 0.01], thus, indirectly reaffirming the results of analysis reflecting predictors of sustained inactive disease.

3.5 Comparison of efficacy of various immunosuppressive agents:

Initial response (Induction regime): As far as steroid dose is concerned, there were 2 subsets namely those initiated on 1mg/kg/d (n=93) and those on 0.5mg/kg/d (n=113) of prednisolone or equivalent dose of deflazacort (in major proportion). The smaller group of patients on 0.75 mg/kg/day and those on <0.5mg/kg/day comprised a heterogeneous category and hence were not analysed in the comparison. A comparison between those initiated on 0.5mg/kg/d and 1mg/kg/d steroid showed that early complete response was not significantly different between the two groups (74.3% vs 62.4% respectively), p=0.065. Cumulative hazard for relapse in patients with initial complete response was not different either between the two steroid regimens [HR=0.889 (95%CI 0.481-1.641), p=0.71] after adjusting for baseline CRP, ESR, juvenile onset type, type 4 disease, compliance to treatment and use of tocilizumab (**Figure 4**).

Figure 4: Comparison of cumulative hazards for relapse between patients on 1mg/kg/day and 0.5mg/kg/day of steroids

Vertical lines denote median time to relapse in two groups (18 months in patients on initial steroid dose of 1mg/kg/d and 21.5 months in patients on initial steroid dose of 0.5mg/kg/day)



Seventy patients switched amongst the steroid sparing immunosuppressive agents during follow up. Response was achieved in 142/161 patients (CR in 116, 72%; PR in 26, 16.1%) on mycophenolate, 53/54 (CR in 48, 88.9%; PR in 5, 9.3%) patients on azathioprine and 17/20 (CR in 12, 60%; PR in 5, 25%) patients on methotrexate. Complete response was maintained throughout the follow up (with any dose of steroids) in 77 (47.8%), 25 (46.2%) and 8 (40%) patients on these drugs respectively. Though statistically not significant, sustained inactive disease was observed in numerically higher proportion of patients on MMF (59/161, 36.9%) followed by azathioprine (16/54, 29.6%) and methotrexate (5/20 (25%). MMF was not associated with any serious adverse events, whereas cytopenia requiring hospitalisation was noted in 12 patients on azathioprine (0 vs 12, p 0.01). Tocilizumab was used in 44 patients during the total study period. Details of clinical profile and outcome of patients on biologics are not discussed here.

Discussion:

This is the largest single centre study describing long term outcome of a large cohort of patients with TA. We studied 251 patients over a median follow up period of 42 (IQR: 24-81) months using objective instruments like ITAS-A(CRP), TADS, other common biomarkers and angiography. We used steroid sparing immunosuppressants (predominantly Mycophenolate) from the beginning along with tapering schedule of steroid (predominantlly Deflazacort, an oxazoline derivative of prednisolone). In some cases with aggressive disease, we used TCZ for rapid control of disease activity and could achieve significant steroid sparing action. With this strategy, the majority (92.8%) of our patients had at least one period of stable disease (complete or partial response), and only 7.2% of our cohort had disease truly refractory to treatment till the last follow up (**figure 2**).

At the very first follow up evaluation after initiation of our immunosuppression protocol, 215 patients (86.7%) responded to treatment by our response criteria defined in the methodology, with complete response in176 (70.1%) and partial response in 42 patients (16.7%). Only 36 patients (14.3%) were non-responders at that point of follow up.

The initial complete response mentioned above was sustained throughout the entire follow up period in 65.9% of these responders in-spite of de-escalation of treatment as per our protocol (46.2% of the entire cohort). This was much higher than the figure of 17% reported in an earlier series from the Cleveland clinic foundation (CCF). In the CCF cohort, steroid sparing immunosuppressant was added only after patients relapsed on tapering of steroids [17] (**figure-5**). These 2 contrasting results emphasise the role of upfront use of steroid sparing immunosuppressant along with steroid from the very initial phase of treatment.

Figure-5: Comparison of outcome data of TA from literature

Parameter	Kerr etal, NIH (1994)	Ishikawa etal (1994)	CCF, USA (2007)	Mayo Clinic, USA (2013)	Japanese Ohigashi etal (2012)	China (Yang L etal, 2014)	Present study CMC Vellore (2017)
Year	1970-90	1957-90	1992-2004	1984-2009	2000-2010	2002-2013	1998 - 2016
Design	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective / prospective
Follow up described (patients screened)	45 (60)	120 (120)	30 (75)	79 (126)	35 (106)	326 (556)	251 (503)
Follow up duration (years)	5.5	15	3	5.5 (IQR:2.9-10)	0.5- 5.0	5.0 ± 0.2	3.5 (IQR: 2-6.8)
Steroids used (%)	80	80	93	92	79.2	85.9	95.2
II line agent used (%) (MTX/AZA/ MMF/CSA in %)	41.7 Not specified	-	73 (43/7/7/0)	66 (58/ 19 /18/0)	18.9 (50/0/0/ 35)	4.1 -	93 (9/19/62/0)
Initial response to treatment (%)	60	-	93	96	35	66.3	85.6
Cumulative relapse rate at median follow up (%)	80		96	46	70	-	27
Long term sustained complete response (%)	-	-	17	-	-	-	46.2
Death n, (%)	2 (3)	13 (16)	3 (4)	6 (4.8)	NR	32 (9.6)	2 (0.7)

Only 22.3% of our patients with initial complete response had relapsed on de-escalation of therapy as per our protocol, which is less than half of that reported by Schmidt et al (46%) [9]. The cumulative relapse free survival (sustained remission) at 1, 3, 5 and 10 years in our study were 93%, 73%, 66% and 52% respectively. Escalation of treatment led to response

even in the relapsed patients. Nearly 80% of patients had CR or PR (2/3rd had CR) at all the time intervals of follow up (**figure 3B**).

In 34.6% of our patients, sustained inactive disease was observed throughout the follow up period with steroid dose of ≤ 5mg/day at the last follow up visit.

Use of steroid sparing immunosuppressants in TA for maintenance of response has gained increased acceptance in recent times as compared to the past. Earlier reports from Mexico, Japan and India reported use of these agents only in minority of cases, in contrast to their use in >60% of TA patients in recently published series from France and USA [7, 9, 18- 21]. Our policy of concurrent initiation of immunosuppressants at the outset along with steroids in majority of our patients (97.3%) may be the reason for better long term response in our cohort. This was in contrast to the modest results of CCF cohort, who were subjected to sequential approach with initial steroid alone therapy followed by the introduction of steroid sparing second line immunosuppressants only in those patients with relapsing disease [17].

In addition, we followed a slow taper schedule of steroid therapy in our patients, as faster rate of reduction in steroid dose has been noted to be associated with relapsing disease [6]. Timely revascularisation procedures in our centre could have also contributed to good outcome by preventing ischaemic complications, as noted by Ishikawa et al [21]. Use of mycophenolate was much higher in our cohort as compared to other centres including CCF where methotrextae was the preferred 2nd line agent. We practise upfront institution of MMF, due to its higher safety data as well as its efficacy comparable to cytotoxics like cyclophosphamide in other autoimmune situations; our earlier study as well as the recent meta-analysis also reported efficacy of MMF in TA [22,23]. Therefore, it is likely that MMF along with steroids may have added to better outcome in our patients. We did not come across any serious adverse event with the use of MMF, whereas cytopenia requiring hospitalisation was significant amongst our patients receiving azathioprine (n=12 out of 54, p 0.01).

Unlike other autoimmune diseases like lupus, inflammation in TA is thought to be more smoldering, though such presumptions could be due to lack of well-designed controlled trials and outcome studies. Based on real life observations in our large clinic and a recent study by Yang et al using a relatively lower initial steroid dose in their Chinese cohort with TA [5], we have been switching over to initial steroid dose of 0.5 mg/kg/day (prednisolone or equivalent dose of deflazacort) in recent times from our earlier practice of using 1 mg/kg/day. This gave

us an opportunity to compare the effects of the two doses and we found that patients on the 0.5 mg/kg/day of initial steroid did just as good as the ones on 1mg/kg/day, in spite of the similar tapering schedule. This endorses the use of 0.5mg/kg/day as the initial dose of steroids in TA.

Breakthrough biologicals (predominantly TCZ) in select cases with aggressive disease, in addition to upfront institution of tapering steroid plus steroid sparing immunosuppressive agents, may have also contributed further towards good outcome especially in our 'difficult to control' patients.

Escalation of treatment as per our treatment protocol targeting an ITAS-A score of 0 during the follow up ultimately led to an overall response in 213 (84.9%) patients, with complete response in 176 (70.2%) and partial response in 37 (14.7%) at the last follow up visit. Although 35 (14.1%) of the entire cohort had active disease at last follow up, 20 of these 35 patients did respond to immunosupression earlier in the course, thus exhibiting a 'relapsing and remitting course' on de-escalation of immunosuppression as per our protocol. This kind of fluctuation of disease course while tapering immunosuppression is a common feature in most autoimmune rheumatic diseases. Figure 2 shows a total of 56 such patients at last visit. It is also reassuring that most of these patients with such grumbling course had also responded to aggressive breakthrough treatment as per our protocol.

Medical treatment, predominantly comprising of deflazacort and mycophenolate in the vast majority of our patients with TA could also arrest or minimise damage progression in 68% of patients as assessed by TADS score. The increment in damage was directly associated with persistent disease activity, thereby emphasizing the importance of strict and sustained control of disease activity in TA. There were only 2 fatalities (1.3%) in our total cohort, figures much lower than that published in literature.

Heterogeneity in definition of outcome measures renders comparison between various large series of TA difficult. Sustained inactive disease and sustained CR were objectivised as primary outcomes in our study, somewhat similar to the long term outcome measures addressed in the series by Cleveland clinic foundation. Such stringent outcome measure is desirable in a disease like TA, as clinically stable disease may have subclinical histological inflammation with disease progression in 20% to 40% of such patients [17].

Use of more recent objective tools to define disease extent, activity and damage progression are the strengths of this study. We have used ITAS-2010, a tool validated amongst Indian patients, along with laboratory and angiographic details to assess disease activity in contrast to studies from USA, France and China who used NIH criteria [3,5,7,9,16,17-21]. The major limitation of our study is the retrospective component of our study.

Overall, it was pleasing to note that only 15 of 251 patients were truly refractory to treatment till the last follow up; the vast majority had favourable long term outcome and were responsive to our medical treatment protocol with immunosuppression with or without biologics therapy.

Further, we could define the predictors of sustained inactive disease which may act as a useful model for future studies. Our attempt to develop such a prediction model identified low baseline ESR, CRP, low DEI.Tak scores and type 4 TA as predictors of sustained inactive disease with a sensitivity of 70% and a specificity of 61.1%. On the other hand, isolated abdominal aorta involvement and lower age of onset were found to be negative predictors of persistently refractory disease.

Randomised controlled trial or observational prospective cohort study with the aim to determine long term outcome using uniform treatment protocol is a need of the hour.

Conclusions: Combination of tapering steroids and steroid sparing immunosuppressants like MMF from the beginning was our primary medical regimen in TA. Biologics like TCZ was used only in select situations as a breakthrough option for rapid control of disease activity. Our strategy could stabilise disease activity in 92.8% of our patients at various time points of follow up; only 7.2% of our cohort were truly refractory to treatment. We could achieve 93%, 73%, 66% and 52% relapse free survivals at 1 year, 3 year, 5 year and 10 year respectively. Damage progression was also arrested in 68% of our patients and only 2 fatalities were observed in this cohort. Initial steroid dose of 0.5mg/kg/day with slow taper had similar response and relapse rate as 1mg/kg/day dose. MMF was the cornerstone steroid sparing immunosuppressant and the major maintenance agent to prevent relapses with better safety profile.

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