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Original Research Article

Clinical and doppler monitoring of patients with Takayasu arteritis with ITAS 2010 and CDUS-K score respectively following medical intervention: a 12 months follow-up study

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ABSTRACT

Background: The objective of the present study was to monitor the disease activity of Takayasu arteritis clinically by the Indian Takayasu Activity Score 2010 (ITAS) and ultra sonographically by Colour Doppler Ultrasound-Kolkata (CDUS-K) Score after 12months of treatment with methotrexate and steroid, and to find the correlation between these two scores.
Methods: Around 25 Angiographically proven Takayasu arteritis patients were treated with Methotrexate (15mg weekly) and Steroids (1mg/kg/day for 6weeks and then tapered) for 12months. Wilcoxon matched pair signed rank test was done to assess the change in ITAS 2010 with treatment. A correlation study was done between ITAS 2010 and change in CDUS-K scores at the end of 12months.
Results: By Wilcoxon's matched pair signed rank test, a non-significant change of ITAS 2010 (p=0.066) was observed at the end of 12months, which means that the treatment helps to control the disease progression by preventing a significant increase in ITAS 2010. Strong correlation (correlation coefficient of 0.878, 95% CI = 0.602 to 1.000) was found between the ITAS 2010 and change in CDUS-K scores at 12months follow up.
Conclusions: The combination of Methotrexate and steroids helps to control the disease progression in Takayasu arteritis. Colour doppler ultrasonography may serve as a reliable and safe surrogate disease activity measure at follow up, as it avoids the radioactivity exposure and invasiveness of angiography.

Keywords: CDUS-K, Follow-up, ITAS 2010, Takayasu arteritis

INTRODUCTION

Takayasu arteritis (TA) is a chronic inflammatory arteritis affecting large vessels, predominantly the aorta and its main branches.[1] Vessel inflammation leads to arterial wall thickening, fibrosis, stenosis, and thrombus formation. Symptoms reflect end organ ischemia. More acute inflammation can destroy the arterial media and lead to aneurysm formation.[2] The Indian Rheumatology Association Vasculitis Group (IRAVAS) has developed an index of disease activity severity and extent known as the Indian Takayasu Activity Score (ITAS), which may be used for assessing the patients at baseline and at follow up.[3] It incorporates 6 domains, namely systemic symptoms, gastro-intestinal, genito urinary, CNS, renal (systolic and diastolic hypertension) and cardio vascular findings. Diastolic hypertension, stroke, bruit, pulse inequality, new loss of pulses, claudication and carotidodynia are ascribed 2 points each and the rest allotted 1 point each. Maximum score of ITAS is 51. A

further attempt was made to incorporate Acute Phase Reactants into the score by adding extra 1-3 points for elevated ESR or CRP. The ESR values (in mm 1st hr) were categorized as follows: <18 = 0; 18-29 = 1; 30-45 = 2; >45 =3. ITAS- A was calculated by adding ESR categories to ITAS values. ITAS of 2 or more and/or ITAS-A of 5 or more suggests active disease. Colour Doppler ultrasound (CDUS) is gaining importance as an objective disease monitoring instrument in TA. The Colour doppler ultrasound Kolkata score (CDUS-K), was devised by our group based on the presence of stenosis and altered flow patterns, distal to a stenotic site.[4] Stenosis, biphasic and monophasic flow patterns was given one point each. Stenosis had been identified by direct visualization in B-mode image along with changes in the peak systolic velocity, pulsatility index in duplex study and/or aliasing in colour flow imaging. Loss or diminution of the late antegrade diastolic component was taken as a biphasic waveform and monophasic flow was characterized by almost continuous flow pattern without any systolic or diastolic variations, both are seen distal to a vascular obstruction. A significant degree of correlation was found between ITAS 2010 and the CDUS-K score (r = 0.7144, 95% CI for r = 0.3852 to 0.8823). An inter-rater agreement analysis was done between CDUS-K scores and angiographic scores in selected arterial sites and a high degree of correlation was also found between the two. (Kappa value 0.725 on inter-rater agreement analysis).

The objective of the present study was to monitor the disease activity of TA, clinically by the Indian Takayasu Activity Score 2010 (ITAS 2010) and ultrasonographically by Colour Doppler Ultrasound-Kolkata (CDUS-K) Score, over 12 months of treatment with methotrexate and steroid. Also, to find the correlation between the two scores (ITAS 2010 and CDUS-K).

METHODS

The study comprised of 25 angiographically proven TA patients who visited the Rheumatology Outpatient clinic of Institute of Post-Graduate Medical Education and Research (IPGME&R) Kolkata from February 2013 to October 2014.

Inclusion criteria

Angiographically proven patients fulfilling ≥3 of the 1990 American College of Rheumatology classification criteria of TA.[5]

Exclusion criteria

- Coarctation of Aorta,
- Isolated bilateral renal artery stenosis,
- Atherosclerotic vascular disease,
- History of any previous endo vascular procedure/ surgery,
- Patients who refuse to undergo angiography,
- Patients who undergone stenting for TA,
- Patients with significant evidence of acute or chronic liver Disease,
- Normocytic, normochromic anemia, Hemoglobin less than 8gm/dl, TLC <4000/cu.mm. or Platelets <1lac/cu.mm,
- Patients with Serum Creatinine >2mg/dl,
- Patients pregnant or desirous of pregnancy or unwilling to use adequate contraception during the trial.

Necessary approval from IPGME&R Research Oversight Committee (Institutional Ethics Committee) and informed patient's consent were taken. The study was conducted in accordance with the Declaration of Helsinki (1964). Angiogram was done at baseline and ITAS, ITAS-A and CDUS-K scoring were done at 0, 6 and 12 months. The ITAS and the ITAS-A score sheets were filled up by a single physician throughout the study. CDUS studies were done by a radiologist throughout the study. The study was a double blinded study, as the radiologist who did the CDUS studies and the physician who scored the ITAS and ITAS-A was both unaware of each other's recordings. Patients were then treated with oral Methotrexate (15mg weekly) and Steroids (1mg/kg/day for 6 weeks, then tapered and maintained at 10mg per day) for a total duration of 12months. In each follow up visit, ITAS was scored only if there was new onset worsening of symptoms or signs, which were not present in the last visit.

For the purpose of statistical analysis, we compared the baseline ITAS with the ITAS at 12 months. Authors kept the entire baseline ITAS as 0 for statistical comparison, because ITAS at any follow up visit is actually recorded as development of any new sign/symptom after the last visit. The same results were also reproduced by comparing the ITAS values at baseline with ITAS at baseline + ITAS at 12months. The ITAS values were found not to be normally distributed, and comparison was done between 2 time points by Wilcoxon's matched pairs signed rank test. Analysis was 2-tailed and p value <0.05 was considered statistically significant. SPSS version 21 (International Business Machines Corporation, United States of America) has been used for our statistical purpose.

RESULTS

The mean age of the TA patients at presentation is 23.24 years, the maximum age being 43 years, and the minimum 12 years. In studied population, 20 (80%) were females and 5 (20%) were males. The mean duration for which the patient had symptoms at presentation is 11.8 months, the maximum being 36 months, and minimum, 2 months. In studied population, 13 (32%) patients presented with systemic manifestations, 19 (46%) patients with cardiovascular manifestations, 7(17%) with

central nervous system manifestations, and 1 (3%) each with gastrointestinal and skin manifestations. There was considerable overlap in between the groups. Of the 25 patients, 12 (48%) patients presented with aortic arch disease, 3 (12%) with thoracic and/or abdominal aorta lesions, and 10 (40%) with both. The most common angiographic type, according to the angiographic classification of Takayasu arteritis was found to be type 1 (n = 14; 56%), followed by type 5 (n = 8; 32%).6 angiographic types 2b and 3 were found in 1 patient each (4% each). No patient was found to have type 2a.

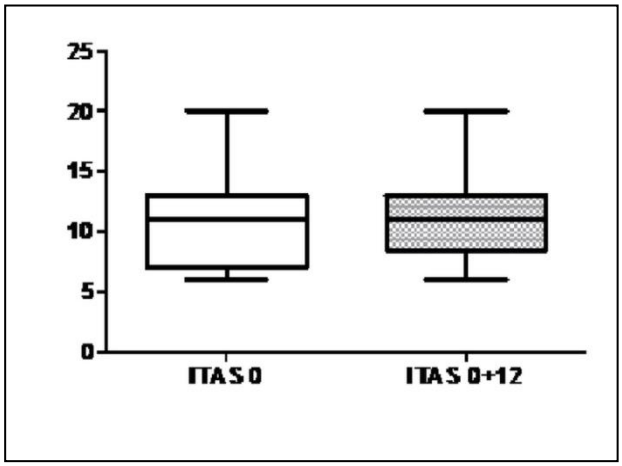

Figure 1: Box and whisker plot showing comparison between ITAS at baseline and ITAS at baseline and 12months.

The mean ITAS value was 10.560, the minimum being 6.00 and maximum 20.00. The mean ESR was 45.04mm in 1st hour, the minimum being 8 and the maximum 144 mm. A correlation analysis was done between the ITAS at baseline and the ESR values of the patients at presentation. No correlation (Spearman's rho correlation coefficient r=0.162; 95% CI=-0.558 to 0.282) was found between the two. The ITAS values at baseline were compared with the ITAS baseline + ITAS at 12months. The ITAS values were found not to be normally distributed, and comparison was done between 2 time points by Wilcoxon's matched pairs signed rank test. p value was found to be non-significant (p = 0.066), which means that the treatment helps to control the disease progression by preventing a significant increase in ITAS (Figure 1). A Wilcoxon matched pairs signed rank test was also done between the ESR values at baseline and at 12 months (Figure 2). p value was found to be non-significant (p value = 0.264). It suggests that the recommended treatment does not significantly reduce the ESR values after 12months of treatment. Comparison of ITAS-A at baseline and after 12months returned a significant p value (p=0.017), which means that the treatment given does not lead to a significant decrease in ITAS-A. Correlation between ITAS and CDUS-KS at baseline was good (Spearman's rho correlation co-efficient, r = 0.609, 95% CI =0.287 to 0.782). Correlation between ITAS and change in CDUS-KS at 12months was strong (r = 0.878, 95% CI = 0.602 to 1.000).

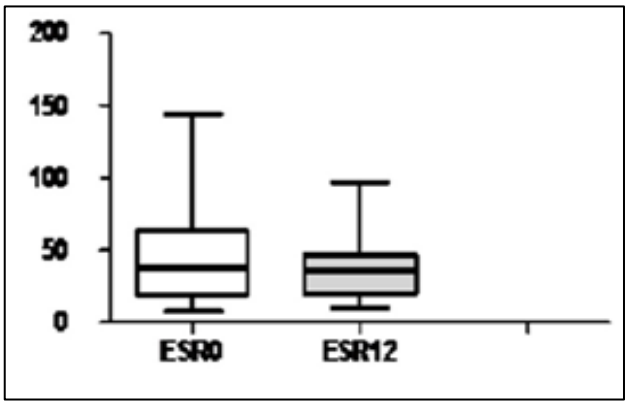

Figure 2: Box and whisker plot showing comparison between ESR at baseline and after 12months of treatment.

DISCUSSION

TA is not so uncommon large vessel vasculitis and is responsible for significant morbidity in younger age group especially females. The demographic and angiographic profiles of our study population were quite similar to some previous study.[6]

The real challenge in the management of TA is lack of definite objective tool for assessing disease activity and treatment response. ESR is the most often used tool to assess disease activity in Takayasu arteritis. However, some studies, have found that ESR and CRP are not able to differentiate clinically active TA from inactive TA.[7,8] Furthermore, histopathological studies have shown that over 40% of patients thought to be in clinical remission with normal acute phase reactants have active arteritis. The IRAVAS group found only weak correlation between CRP and ESR with the ITAS2010.[3] In present study, authors found no correlation between authors' clinical score, ITAS and ESR values. So possibly, when the patient presents, the activity of the disease is already over, and the residual stigmata of the disease is what the patient presents with. This is important, as if the active phase of the disease is already over, there will be hardly any response to treatment, and the prognosis will be guarded. In a recent study by Goel R et al, a significant drop in laboratory markers of inflammation with a reduction in mean Erythrocyte Sedimentation Rate (ESR) and mean C-reactive protein (CRP) was noted with treatment.[9] But, in present study authors could not document any significant reduction in ESR with medical therapy. The ITAS score sheet that has been used in present study, is a good way of documenting disease activity during follow up in Takayasu arteritis. Only the features of the disease that aggravates or appears newly are marked in the score sheet. Any increase in ITAS values means disease progression. There is no way of representing improvement of the disease. There are very

scarce data regarding the treatment of TA. Till date, there are few published data regarding assessment of treatment response in TA patients using ITAS. In one study by Goel R et al, Mycophenolate mofetil was used for treatment of TA, and the other by Salvarani et al, who used tocilizumab.[9,10] Both the studies showed improvement of ITAS with treatment. There is no study of assessing treatment of Takayasu arteritis patients, with Methotrexate and steroids using ITAS 2010. Hall S et al, in a Mayo clinic study found that, of 16 patients with an absent pulse, eight had a confirmed return of the pulse.[11] Del LC et al, in a 7 year long follow up of a Takayasu patient, documented disappearance of symptoms, normalization of ESR, and improvement of the diameter of the abdominal aorta.[12] However, Mwipatayi et al found no improvement in stenotic lesions or return of absent pulses.[13] Present study also could not document any such instance of return of previously lost pulses, though treatment definitely helps to control the disease progression by preventing a significant increase in ITAS.

A good correlation has been found between the ITAS and CDUS-KS scores at baseline and after 12months of treatment, which suggests that both the modalities can be used effectively in the follow up of Takayasu patients. There are certain advantages of CDUS over the other imaging procedures. It may lead to an earlier diagnosis in patients presenting with TA, through detection of pre-stenotic lesions in the common carotid and subclavian arteries.[14-17] CDUS is particularly good for the assessment of common carotid arteries, where it is up to 10-fold more sensitive than MRI, displaying a resolution of 0.1-0.2mm.[18] It is non-invasive, has less radioactive exposure and is less costly than conventional angiography. It may thus offer a means by which disease activity and response to treatment can be monitored.[4]

There were certain limitations of ITAS over which CDUS-K score had an upper hand. Firstly, though there is adequate scope for expression of worsening of symptoms and signs in the ITAS score sheet, there is no scope for expression of improvement of symptoms. Whether signs and symptoms get better or remain the same, in either case, the ITAS remains 0, so there is no way of distinguishing. Secondly, Loss of bruits, though procuring lesser points in ITAS, may be worse than its presence, as it may signify increase in stenosis and reduction of flow. Thus, loss of bruits may be due to reduction or progression of stenosis, between which ITAS cannot differentiate but CDUS-KS can. Thirdly, abdominal aorta bruit has not been given any score in the ITAS score sheet, whereas CDUS-K score can detect any stenosis in it. Fourthly, assessment of pulse loss and/or inequality which forms the backbone of ITAS is at times subjective, whereas CDUS-K score is more objective in its perspective.

Bacon P et al, in their editorial, has raised some very pertinent questions regarding the use of CDUS in monitoring patients of Takayasu arteritis.[19] The justification behind evaluating 19 arteries including the distal arteries of upper and lower limbs was that in many large arteries like subclavian artery and thoracic aorta, CDUS may miss the stenotic site. In such cases, changes in the arteries distal to that site may give us an inkling of the proximal stenosis. Also, increased stenosis and aneurysm formation can be easily determined by CDUS. CDUS can give percentages of the stenosis of the common carotid arteries, that can be compared on follow up. Whether to give more points for higher degrees of stenosis is a matter of concern and needs to be extrapolated in a larger cohort of patient population. Angiography cannot give any better knowledge regarding the extent of stenosis. Degree of stenosis of the other arteries is difficult to be measured by any imaging modality. Aneurysm formation is also very well visualized in CDUS. Both CDUS and Angiography are unable to distinguish between stenosis resulting from current active inflammation and that due to the scars of previous disease. FDG-PET scan may be competent to do this, but it also has its own limitations like having radiation exposure, being expensive and being limited to relatively few centers. It may give false positive results in cases of atherosclerotic vascular stenosis as well.[20]

CONCLUSION

Authors have thus come up with this follow up study to gauge the changes of CDUS-K score in response to therapy. Authors conclude that CDUS-K score may serve as a safe surrogate disease activity measure at follow up of Takayasu arteritis patients, especially because it avoids the radioactive exposure, invasiveness and cost of angiography.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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