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EFFICACY OF TOCILIZUMAB IN PATIENTS WITH TAKAYASU ARTERITIS TERTIARY RHEUMATIC CARE CENTRE IN CHENNAI -- SINGLE CENTER PROSPECTIVE STUDY

Rheumatology

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ABSTRACT

BACKGROUND: Takayasu arteritis (TA) is a large vessel vasculitis that affects predominantly the aorta and its main branches.though it presents with limb claudication it can present with vasculitis involving internal organs with deleterious effects in heart .it is a CD4 T Helper cell mediated type IV hypersensitivity reaction leading to vascular inflammation . Interleukin-6 is one of the key cytokines. Steroids remain the cornerstone of therapeutic management.although mycophenolate mofetil,methotrexate and azathioprine are commonly used for maintenance drugs, Tocilizumab may be an effective, steroid-sparing agent for rapid control of disease activity in patients with life threatening indications. Recently reported multicenter studies, demonstrated the benefit of Tocilizumab in TA, for events free survival.
OBJECTIVES: To assess the clinical profile and the efficacy of Tocilizumab in patients with Takayasu arteritis.
METHODS: This is a prospective observational study was conducted over 6 months at Institute of Rheumatology, Madras medical college, Chennai. 30 patients with active disease (ITAS>1) presenting first time/follow up to the clinic are given 6 monthly infusions of Tocilizumab (8mg/kg i.v). Pregnant women, lactating women, those with active TB/HIV, renal failure were excluded. Baseline clinical characteristics, acute phase reactants, findings of CT angiogram were recorded. Steroid dose, ITAS 2010, ESRwere assessed on admission, 3rd and 6th month of Tocilizumab therapy.
RESULTS: Mean age, median disease duration and mean ITAS 2010 are 32±9.2 years, 9 months, and 13.3 ±4.3 respectively. Clinical presentation included Limb claudication (60%), Hypertension (47%), Constitutional (fever/weight loss) (20%), Stroke (13%), Cardiomyopathy (13%), Aortic regurgitation (13%), myocardial infarction (7%) and Carotidynia (3%). Type V (30%) is the predominant type seen in angiography. Mean Starting dose of steroids were 45.8±9.7mg and the dose is effectively reduced to 7.58±2.9mg at the end of 6 months of therapy. An ITAS score of 0 were seen in 90%, 100% of patients at the end of 3rd and 6th month of Tocilizumab infusion. All patients achieved a reduction in ESR at 3 months.
CONCLUSION: Tocilizumab may be an effective steroid-sparing option for rapid control of disease activity in TA. However, relapse free survival after the cessation of Tocilizumab needs to be studied.

KEYWORDS

Indian Takayasu Arteritis Score, India, Takayasu Arteritis, Tocilizumab.

INTRODUCTION:

Takayasu arteritis (TA) is a chronicprimary granulomatous large vessel vasculitis that affects predominantly the aorta and its main branches, coronary arteries and pulmonary arteries [1], leading to thrombosis, stenosis and/or aneurysms.TA occurs more frequently in females, usually from approximately 20 years of age. Presenting symptoms vary greatly depending on vascular involvement and the degree of disease progression. Even though steroids remain the cornerstone of therapeutic management, long term usage is limited by its toxicity. However, only 60% of patients achieve a sustained remission with less than prednisone 10 mg/day [2], patients frequently relapse during GC tapering [3].Huge list of immunosuppressants(such as methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide) are used as steroid sparing agent in the management of Takayasu arteritis.Recently reported the French multicenter experience showing the benefit of biological-targeted treatments in refractoryTA with substantial benefit in comparison to DMARDs for relapse free and vascular-events free survivals [4]. Elevated IL-6 levels are associated with increased disease activity[5,6].Interleukin-6 is a key cytokine for the vessel wall inflammation. Tocilizumab, a recombinant, humanised, anti- IL-6 receptor (IL-6R) monoclonal antibody, was first reported by Nishimoto *et al*for the successful treatment of a patient with TAK [7].Tocilizumab may be an effective, steroid-sparing agent for rapid control of disease activity in patients with life threatening indications.A recent randomized trial did not show the benefit of Tocilizumab for relapse-free survival after stopping the drug. [8].The aim of this observational study was to assess the clinical profile and the efficacy of Tocilizumabin30 patients with TA treated at the largest Rheumatic care center in southern India.

MATERIALS AND METHODS:

Type of study : Prospective observational study

Place of study : Madras Medical College, Chennai
Methods : Tocilizumab(8mg/kg i.v monthly once) for 6 infusions.

Inclusion Criteria : Patients with active Takayasu's arteritis (ITAS>1) either attending the clinic for the first time (DMARD naive) or follow up (on DMARD).

All patients satisfied 1990 ACR classification criteria and imaging (conventional angiography)was done for diagnosis of TA. Clinically active disease was defined as an Indian Takayasu Arteritis activity Score (ITAS-2010) of ≥ 1 with or without raised inflammatory markers. Raised acute phase reactants (APR) was defined as an erythrocyte sedimentation rate (ESR) > 20 mm in the first hour by Westergren method.

Exclusion Criteria :
(1) Pregnant women
(2) Lactating women
(3) Active TB/HIV
(4) Renal failure
(5) Patients who have interruption in the course of Tocilizumab infusions due to intercurrent infections /lost to follow up.

All the patients had been screened for active or latent tuberculosis by high-resolution CT (HRCT) scan and Interferon gamma-based assay (IGRA) prior to tocilizumabtherapy. None of them had latent or active TB.

Number of patients : 30
Duration of study : February 2018 to July 2018 (6 months)

Outcome assessed : Details of demography, angiographic type obtained on admission. Laboratory markers, clinical disease activity,

medications used, treatment outcome (ITAS 2010) and adverse events related to Tocilizumab were assessed on admission, 3rd and 6th month of Tocilizumab therapy.

Response to therapy was defined as attainment of ITAS of 0 during follow-up visits, with normalization of inflammatory markers and stable disease on conventional angiography or other imaging modalities, such as color Doppler or 18fluorodeoxyglucose-uptake study (positron emission tomography [PET]-computed tomography [CT] angiogram). In addition to attainment of ITAS of 0, reduction in dosage of steroids _ second line immunosuppresants to maintain stable disease was also considered as clinical response to tocilizumab therapy.

Statistical analysis : SPSS version 25

ITAS comprises of 44 items from six organ-based systems. Special importance is given to 33 items of cardiovascular systems. Any new appearance of items in the preceding 3 months is given a score of 1 or 2. The final score is the sum of all individual scores.Response to therapy was defined as attainment of ITAS of 0 during follow-up visits, with normalization of inflammatory markers. All the patients had consented to receive Tocilizumab after understanding about the efficacy and possible adverse events of the drug. This study was approved by our Institutional ethical committee.

RESULTS :

Mean age was 32±9.2years; Median disease duration was 9 months, Male (n=4),Female (n=26). 2 patients were Childhood Takayasu arteritis, one presented with hypertension and the other with cardiomyopathy.Clinical presentation **(Figure 1)**included most common being Limb claudication (60%), followed by Hypertension (47%), Constitutional (fever/weight loss) (20%), Stroke (13%), Cardiomyopathy (13%), Aortic regurgitation (13%), myocardial infarction (7%) and Carotidynia (3%). Type V (30%) was the predominant type seen in angiography.All patients achieved a reduction in ESR at 3 months and the difference was statistically significant($p<0.00001$)**(Figure 2)**.Mean ITAS at baseline was 13.3 ±4.3**(Figure 3)**. An ITAS score of 0 was seen in 90%, 100% of patients at the end of 3rd and 6th month of Tocilizumab infusion($p<0.001$). Mean Starting dose of steroids is 45.8±9.7mg and at the end of 6 months, the dose was effectively reduced to7.58±2.9mg ($p<0.001$)**(Figure 4)**.No major adverse events were noted with Tocilizumab during the study.

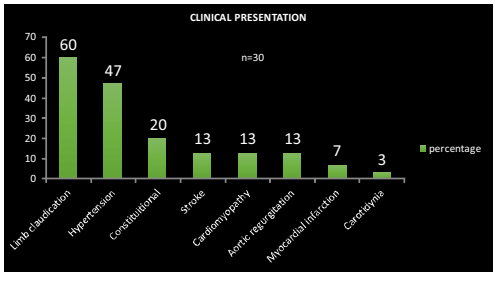
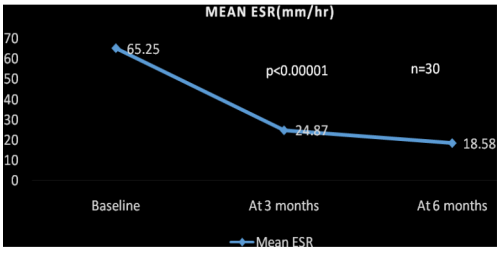


Figure 1



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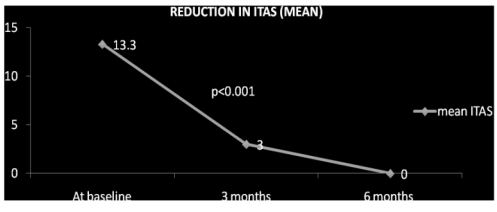

Figure 3

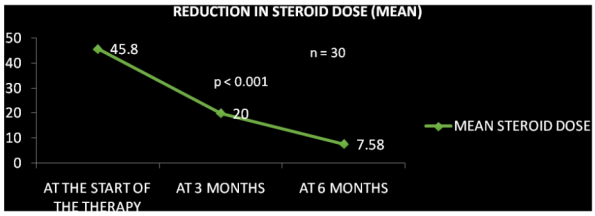

Figure 4

DISCUSSION:

As we know steroids are the first line drug in management of Takayasu arteritis, the main limitation factors are morbidity and mortality caused by steroids. Another important aspect is when we start tapering steroids, some of TA patients relapse. It necessitates a need for a DMARD to control disease activity. Till now there is no proper guidelines from ACR/EULAR as well as no RCT in TA. Based on the recent literatures Tocilizumab was found to be useful drug for control of disease activity. In our study, 30 patients were started on 6 monthly (8mg/kg I.V) infusions of Tocilizumab. Among 30 patients, 29 were new cases (DMARD naïve), 1 patient was on MMF (MMF was stopped three months before the study).None had evidence of infection, dyslipidemia or liver function abnormality after starting on tocilizumab therapy during study.

The observed finding was good control of APR/ reduction in ITAS and steroid dose reduction which were found to be statistically significant.

Parameters	Ruchika GOEL et al	TAKT study	Our study
Number of patients studied	10	36 (18 –Tocilizumab) (18 - Placebo)	30
Predominant angiographic type	Type V	Type V	Type V
Tocilizumab (TCZ) dose	8mg/kg I.V for 6 doses	162mg S.C weekly till time to relapse	8mg/kg I.V for 6 doses
Outcome measured	ITAS	Time to relapse	ITAS
Results	100% achieved reduction in ITAS & Steroid dose	No significant difference between TCZ and placebo, but supports the use of TCZ for refractory TAK	100% achieved reduction in ITAS & Steroid dose

Mekinian et al that Tocilizumab havesignificant steroid sparing effect and arelatively good safety profile. In steroid-resistant or -dependant TA patients, the adjunction of DMARDS (Methotrexate, Azathioprine, Mycophenolatemofetil) to the ongoing steroid therapy often allows a better disease control and tapering steroids [9,10]. Still clinical relapses and progression of vascular involvement remain one of the major therapeutic goals in TA. The uncontrolled TA vascular disease is one of major factor of vascular progression and risk of stenosis, thrombosis or aneurysm.

Recent RCT(TAKT study) compared 36 patients which received subcutaneous Tocilizumab or placebo [8]. Although time to relapse was not significantly different under Tocilizumab and placebo, longer time to relapsewas showed in the Tocilizumab group. In a recent literature review, 105 TA patients havebeen treated by Tocilizumab with an overall clinical and radiological response rate of 85.7%and 65.2%, respectively [11]. InTA the overall incidence of vascular complications reach more than 50% at 5 years with DMARDs [12] and was significantly reduced under Tocilizumab in the present study. In TA the event-free survival was significantly improved under Tocilizumab, in comparison to DMARDs [13]. The early use of Tocilizumab could be argued to better control the TA disease activity, and open-labeled trial is ongoing in France to show the benefit of first-line Tocilizumab for the control of TA activity andrelapse-free survival.Earlier reports from the literature showed presence ofsubclinical inflammation in TA as evidenced by angiographic progression in 60% and presence of histologically active disease in 44% of patients in spite of normalAPRs[14]. Radiological vascular improvementassessment is a major concern in TA patients, but there is currentlyno consensual recommendations for imaging methods to monitorthese patients. Mekinian et al, We showed a better event-free

survival under Tocilizumab therapy compared to DMARDs[3]. Tocilizumab might be used as first-line therapy and lead to good overall response in TA patients[3]. Even though Tocilizumab can be an alternative to steroids in TA, second line agents like (Mycophenolate Mofetil or Methotrexate or Azathioprine) may have to be initiated and continued along with Tocilizumab to sustain its steroid-sparing benefit even after withdrawal of Tocilizumab[15].

CONCLUSION :

Tocilizumab might be considered as first-line therapy in life threatening conditions in which rapid control of disease activity is required. Tocilizumab may be an effective, steroid-sparing measure in refractory and relapsing patients with TA for rapid control of disease activity. Tocilizumab leads to good overall response with good safety profile in TA patients.

Limitations in this study:

1. The efficacy and safety of Tocilizumab in combination with DMARDs in patients with TA were not investigated.
2. Effect of Tocilizumab on angiographic response was not studied.
3. Extended follow up after 6 months of study were not done.

Conflict of interest:

None

REFERENCES:

[1] Kerr et al Takayasu arteritis, Ann. Intern. Med. 120 (1994) 919e929.
[2] Schmidt et al, Diagnostic features, treatment, and outcomes of Takayasu arteritis in a US cohort of 126 patients, Mayo Clin. Proc. 88 (2013) 822e830.
[3] Mekinian et al, Efficacy of biological-targeted treatments in Takayasu arteritis: multicenter, retrospective study of 49 patients, Circulation 132 (2015) 1693e1700.
[5] Noris et al,Interleukin-6 and rantes in takayasu arteritis: a guide for therapeutic decisions? Circulation 1999;100:55–60.
[6] Park et al, Serum cytokine profiles and their correlations with disease activity in takayasu's arteritis. Rheumatology 2006;45:545–8.
[7] Nishimoto et al, Successful treatment of a patient with Takayasu arteritis using a humanized anti-interleukin-6 receptor antibody. Arthritis Rheum 2008;58:1197–200.
[8] Nakaoka et al, Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo- controlled, phase 3 trial in Japan (the TAKT study), Ann. Rheum. Dis. 77 (3) (2018) 348e354.
[9] Hoffman et al, Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate, Arthritis Rheum. 37 (1994) 578e582.
[10] Maksimowicz et al, Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients, Arthritis Rheum. 56 (2007) 1000e1009.
[11] Decker et al, Tocilizumab and refractory Takayasu disease: four case reports and systematic review, Autoimmun. Rev. 17 (4) (2018) 353e360.
[12] Comarmond et al, Long-term outcomes and prognosticfactors of complications in Takayasu arteritis: a multicenter study of 318 patients, Circulation 136 (2017) 1114e1122.
[13] Maksimowicz et al, Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients, Arthritis Rheum. 56 (2007) 1000e1009.
[14] Kerr et al, Takayasuarteritis. Ann Intern Med 120, 919–29.
[15] Ruchika GOEL et al Rapid control of disease activity by tocilizumab in 10'difficult-to-treat' cases of Takayasu arteritis, International Journal of Rheumatic Diseases 2013; 16: 754–761.