Original Article

Safety and Efficacy of Rituximab in Ankylosing Spondylitis — A One Year Prospective Clinical Study

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Purpose of the study : Ankylosis Spondylitis (AS) has got very few therapeutic options limited to Non-steroidal Inflammatory Drugs (NSAID's) and biologics such as inhibitors of the tumour necrosis factor (TNF)-alpha; and additionally immunomodulators like methotrexate and sulfasalazine are therapeutic options in AS with predominantly peripheral joints involvement. Presence of abundant CD20+ cells in the histopathology specimens of AS was the main reason why we had chosen rituximab as the immunosuppressant in our study.

Study design : The modified New York Criteria was used as the diagnostic criteria for AS in our study. Patients fulfilling the criteria of AS with the disease duration of more than 10 years and those with evidence of active tuberculosis were excluded. We administered 2 doses of injection rituximab at 14 days interval (methyl-prednisolone was used as pre-medication in all cases) and patients were periodically followed-up till 48 weeks. We also monitored all the possible clinical and laboratory parameters for the assessment of its efficacy and also the possibility of any adverse drug reaction during the time-frame.

Results : Total fifteen patients (13 male and 2 female; 12 with predominantly axial involvement and 3 with predominantly peripheral involvement) were included in our study and all the parameters including the inflammatory ones had a significant improvement such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) which showed an improvement of more than 50% in comparison to the pre-treatment values among all the groups. No significant major side-effects are observed in all these patients.

Conclusions : Inhibitors of TNF-alpha, although a very efficient immunomodulating agent, has several adverse effects such as infusion-related adverse-reactions and reactivation of latent tuberculosis. Existing literature regarding the usage of rituximab as an immune-suppressant instead of TNF-alpha inhibitors are sparse and we are most probably studying it for the first time in such manner with a year-long observation. Rituximab in this study was found to have a great promise in terms of safety and efficacy.

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Key words **: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), CD20+ cells, Latent Tuberculosis, Tumour Necrosis Factor (TNF) alpha inhibitors.**

Ankylosing spondylitis (AS) is the prototype spondyloarthropathy and it has some unique characteristics that includes only a few therapeutic options. Axial skeleton is primarily involved in AS sometimes along with variable involvement of peripheral joints. It is also associated with some extra-articular manifestations like unilateral uveitis[1]. There is a markedly high association of AS with the histocompatibility antigen HLA- B27 and the global incidences are directly proportional to the prevalence of this histocompatibility antigen. Non-steroidal anti-inflammatory drugs (NSAID) are being used as the primary therapeutic option for a pretty long duration and it has shown some disease-modifying activity also[2]. Inhibitors of Tumour necrosis factor alpha (TNF-alpha) have revolutionized management of symptomatic AS in terms of halting the natural progression[3]. Additionally sulfasalazine and methotrexate may be of some useful value especially when peripheral arthritis is significant. Cartilage and bone surface is the primary site of inflammation and resultant degradation in AS[4]. Presence of abundant CD20+ cells in the histopathology specimens of AS was the main reason why we had chosen rituximab as the immuno-

Editor's Comment :

- Spondyloarthropathies have only a few therapeutic options, and the medications with proven benefit are mostly associated with various adverse effects.
- TNF-alpha inhibitors have several adverse effects such as infusion-related adverse-reactions and reactivation of latent tuberculosis.
- Rituximab may be a good therapeutic option in patients with AS, in terms of the efficacy and safety

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suppressant in our study[5]. Different adverse effects of TNF-alpha inhibitor therapy mainly reactivation of latent infections such as tuberculosis may be a valid reason to introduce a different class of drug for AS[6]. Only a few literature has highlighted about the efficacy, safety and tolerability of rituximab in AS. A few case reports have shown some kind of efficiency and control of the inflammation in patients treated with rituximab[7,8]. In this study we have not only monitored various clinical parameters of AS, but also we have assessed the global health scenario and working ability of this patient after treatment.

Materials and Methods

Our study area was Rheumatology Clinic and General Medicine Ward of Midnapore Medical College & Hospital. We included the patients of ankylosing spondylitis (AS) who were on conventional therapy {NSAID's and disease modifying anti rheumatoid drugs (DMARDs)} but inadequately responding with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of more than 5. We excluded patients who underwent TNF-alpha inhibitor therapy for AS or patients suffering from serious co-morbid conditions like chronic liver disease, chronic renal disease, congestive cardiac failure etc. Immunocompromised patients due to any cause (leukemia, organ transplantation etc) were excluded from our study. Patients with active tuberculosis on anti-tubercular therapy or chronic hepatitis B or C were not included also. We didn't give rituximab in those AS patients with severe deformity or disease duration of more than 10 years. We got the ethical clearance for this study from the institutional ethics committee.

We had clinically examined the patients for assessing the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) after obtaining written informed consent. We then did blood investigations-like complete hemogram, liver function tests, creatinine, HBsAg, Anti-HCV, HIV, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Roentgenogram of chest (postero-anterior view) was also obtained. Global assessment of the patient was made using the ASDAS-CRP scoring index (Ankylosing Spondylitis Disease Activity Score- C Reactive Protein) which takes account of clinical as well as biochemical values. This score correlates well with working capacity of an AS patient[9]. Magnetic Resonance Imaging (MRI) of the sacro-iliac (SI) joint was performed for assessing the presence of sacro-ilitis and also the extent of inflammation. We had put our patients on two subsequent infusions of rituximab (375 mg/m^2 each) at an interval of 14 days pre-medicated with 80 mg of methylprednisolone. Then we followed those patients up at week 4, 8, 16, 32, 48 and measured the ESR, CRP, BASFI, BASDAI, BASMI, and ASDAS-CRP score each time and put those scores in a tabular form. Flare may be defined as a worsening of 1.5 point of BASDAI score in comparison to the previous day score. More than 20% improvement in the disease activity as per the assessment of Spondyloarthritis international society criteria (ASAS20) was considered as having a significant response[10]. Fortunately, none of our study patients had any flare-up reactions, so we followed them up-to 48 weeks as per the standard protocol. We did the routine blood investigations in each follow-up to detect any systemic organ involvement, ruled out any systemic infections and assessed the vital parameters also. As we have successfully completed the follow-up of 15 patients (13 were male, 2 were female), we plan to extend our study to 50 total patients in upcoming times.

Results

The non-parametric Wilcoxon signed rank test was used to compare changes between baselines to after-treatment values. In these 15 patients, 12 patients suffered from axial-predominant AS, rest of them had peripheral-predominant AS. Study subjects in various age-groups were evenly distributed but we got peripheral-predominant AS in younger age group only. Subjects were mostly from rural areas and they lost their earnings after the disease onset. Apart from predominant sacro-iliac joint involvement, hip-joint was also involved frequently causing severe disability. Characteristic extra-articular features were associated with axial-predominant AS (Table 1).

The most significant finding from this observational study is the marked reduction of these indexes in the 13 male patients just after 4 weeks of two doses of rituximab (Table 2). All these scores have reduction of 66%, 56% and 66% respectively from pre-treatment values. Now for the females BASDAI, BASFI, BASMI scores reduced 81%, 59%, 56% respectively from pre-treatment values with an initial delay (Fig 1). Inflammatory markers decreased steadily and got undetectable from 16 weeks after treatment. The ASDAS-CRP score reduced to 62% and 74% respectively improving there working capacity and all of them got back to their jobs now. We have also compared the improvements in the clinical indexes between axial and peripheral predominant AS groups, where we didn't get any significant differences (Table 3).

Table 1 — *Demographical, socio-economical and basic clinical profile of all fifteen (15) subjects*

Features	Axial-predominant AS		Peripheral-predominant AS	
	(n=12)	(%)	(n=3)	(%)
Age (18-60) :				
18-25	5	41.6	3	100
25-40	5	41.6	0	0
40-60	2	16.7	0	0
Sex Distribution :				
Male	10	83.3	3	100
Female	2	16.7	0	0
Locality :				
Rural	11	91.7	3	100
Urban	1	8.3	0	0
Loss of paid jobs (2 Females were home-maker)	9 (out of 10)	90.0	3	100
Joint where the inflammatory activity is most prominent				
Sacro-iliac (SI)				
Hip-joint	10	83.3	NA*	
Knee-joint	2	16.7	NA*	
Ankle-joint	NA*		2	66.7
	NA*		1	33.3
Extra-articlular manifestations				
Unilateral uveitis				
Inflammatory Bowel				
Disease (both symptomatic	3	25.0	0	0
& asymptomatic)	1	8.3	0	0
Psoriatic skin changes				
Aortic insufficiency				
Renal Involvement	1	8.3	0	0
	1	8.3	0	0
	1	8.3	0	0

*NA- Not Applicable

Last but certainly not the least we have seen the reduction of sacro-ilitis on MRI SI joint of these patients after 16 weeks of rituximab treatment. MRI detected bone marrow edema in sub-chondral bone by showing us strong contrast enhancement, which is most specific sign of active sacro-ilitis in AS.

These fifteen patients didn't have any major side effects like infusion related toxicities or hypersensitivity reactions and there were no reactivation of any chronic infections. Broncho-constriction was aggravated in one patient with obstructive airway disease while rituximab infusion which was relieved on inhaled broncho-dilators and steroids. One patient had an episode

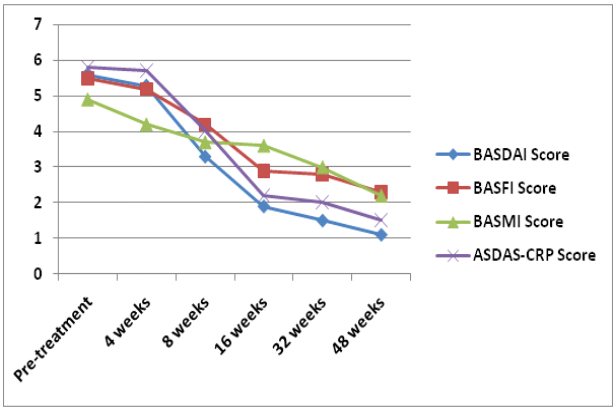

Fig 1 — Graphical representations of various AS indices values in 48 weeks of follow-up in 2 Female patients

of chills and rigor following rituximab infusion which was subsequently managed by anti-histaminics and it didn't repeat in subsequent dosing. After 48 weeks of follow-up they didn't complaint any specific problems except some epigastric discomfort which is probably attributed to prolonged use of NSAID's. Their blood investigations also didn't show any kind of abnormality in each follow-up visits.

Discussion

Some other forms of therapy, apart from NSAID's and TNF-alpha inhibitors, have been postulated in AS considering the diverse pathogenesis such as- Oadanacatib (a cathepsin K antagonist), Bevacizumab (antibody against vascular endothelial growth factor), Denosumab (a monoclonal antibody targeting RANKL)[11]. Song *et al* investigated the efficacy of rituximab in 20 AS patients who had inadequate response to TNF-alpha inhibitors, where at the end of 24 weeks rituximab was not effective in those patients[12]. Rodriquez administered rituximab to a

Table 2 — *Parameters of 13 Male patients after 48 weeks of follow-up*

Various Indices	Pre-treatment (Mean)	4 week (Mean)	8 week (Mean)	16 week (Mean)	32 week (Mean)	48 week (Mean)
BASDAI	6.7	3.9	3.7	2.8	2.7	2.3
BASFI	6.5	4.8	4.2	3.8	3.7	2.9
BASMI	4.5	3.75	3.5	2.5	1.5	1.5
ESR/CRP	82/56	54/26	30/18	28/08	22/Neg	20/Neg
Global assessment score (ASDAS-CRP)	5.2	4.2	3.8	2.6	2.4	2.0

Abbreviations :
AS- Ankylosing Spondylitis
BASDAI- Bath Ankylosing Spondylitis Disease Activity Index
BASFI- Bath Ankylosing Spondylitis Functional Index
BASMI- Bath Ankylosing Spondylitis Metrology Index
ASDAS-CRP- Ankylosing Spondylitis Disease Activity Score- C Reactive Protein
ESR- Erythrocyte Sedimentation Rate (measured in millimeter/hour)
Neg- Negative (below 6 mg/L)

patient with chronic hepatitis B and that patient had a very good response without any flaring up of the secondary infection[15]. According to the data from the French Rheumatology Society, the effect of rituximab was assessed retrospectively in 26 patients of spondyloarthropathy. Out of 26, 11 of them had a very good response, 8 of them were TNF-alpha naïve, 3 of them were non-responders[14]. Some studies have also showed that rituximab is a very good choice for those patients who could not have TNF-alpha inhibitors due to contra-indications. Still there is a huge lacuna of knowledge regarding this effective option. No study with the primary use of rituximab and follow-up of 1 year has showed the efficacy profile in patients of AS. As we have already discussed the pivotal role of CD20+ B cells in the pathogenesis of AS, rituximab is expected to play an important role in the treatment of both types of AS (with axial and peripheral involvement). This study on these 15 patients (including both male/female and axial/peripheral) with a 48 weeks of follow-up revealed a significant reduction in BASDAI, BASFI, BASMI, ASDAS-CRP scores, inflammatory markers and most importantly global working capacity improvement. The principal adverse effects and hazards of TNF-alpha inhibitor therapy such as the reactivation of latent tuberculosis were not noted in these cases. Another important point of our study is that we had given rituximab in weight dependent dosing (375 mg/m^2) in contrast to the previously used fixed-dose regimens (1000 mg) published in different literatures. That's how we have reduced the unnecessary extra cost of this medicine which is very important in a developing nation like India. As our follow-up of fifteen patients' up-to 48 weeks have been completed, we hope to extend our study to fifty patients to get a comprehensive picture of this therapy. Principal limitation of this study remains the small sample size. Also the improvements in terms of immunological mechanism haven't been studied that much in our study. But as per our data of these 15 patients we can think of rituximab as a safe and effective immuno-suppressant in a patient of AS without introduction of TNF-alpha blocker therapy.

Table 3 — *Parameters of improvement in Axial/Peripheral type of AS*

Axial predominant AS			Indexes	Peripheral predominant AS		
48 week	16 week	Pre-treatment		Pre-treatment	16 week	48 week
1.9	2.5	7.1	BASDAI	5.2	1.8	1.3
2.5	3.6	6.8	BASFI	5.2	3.2	2.1
2.1	2.7	4.8	BASMI	3.2	2.3	1.9
14/Neg	26/10	96/68	ESR/CRP	65/36	18/Neg	15/Neg
2.2	2.5	5.6	Global assessment score (ASDAS-CRP)	4.8	2.3	1.7

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BASDAI- Bath Ankylosing Spondylitis Disease Activity Index
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BASMI- Bath Ankylosing Spondylitis Metrology Index
ASDAS-CRP- Ankylosing Spondylitis Disease Activity Score- C Reactive Protein
ESR- Erythrocyte Sedimentation Rate (measured in millimeter/hour)
Neg- Negative (below 6 mg/L).

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