Assessment of Clinical and Biomarker Response to Anti Tumour Necrosis Factor Alpha Biological in Spondyloarthritis using ASDAS CRP Criteria

Vinod Raghava1, Krishnan Shanmuganandan2*, Pratap Shankar3, Rakesh Kumar Dixit3

1Department of Laboratory Medicine, Command Hospital, Lucknow-226002
2Senior Advisor, Rheumatology, Command Hospital, Lucknow-226002
3Department of Pharmacology & Therapeutics, King George’s Medical University, Lucknow, UP, India – 226003

ABSTRACT

Advanced laboratory techniques are playing an important role in the diagnosis of the disease which is a first and important step towards the treatment of the diseases. Spondyloarthritis (SpA) are a heterogeneous group of diseases characterized by the presence of inflammatory back pain, asymmetrical peripheral arthritis, enthesitis, dactylitis and uveitis. Infection with an unknown organism or exposure to an unknown antigen in a genetically susceptible patient (HLA-B27-positive) is hypothesized to result in the clinical expression of a spondyloarthritis. The association between HLA-B27 and ankylosing spondylitis remains the strongest known relationship between a major histocompatibility complex (MHC) antigen and a disease. The aim of the present study was to assess the response to Infliximab (anti TNF- alpha monoclonal antibody) in Patients with Spondyloarthritis using ASDAS-CRP criteria.

Key-Words: Spondyloarthritis, enthesitis, dactylitis, uveitis, inflammatory bowel disease.

INTRODUCTION

Spondyloarthritis (SpA) are a heterogeneous group of diseases characterized by the presence of inflammatory back pain, asymmetrical peripheral arthritis, enthesitis, dactylitis and uveitis. These include AS, reactive arthritis (ReA), psoriatic arthritis (PsA), SpA associated with inflammatory bowel disease (IBD), undifferentiated spondyloarthritis (USpA), enthesitis related arthritis, juvenile onset spondyloarthritis. Infection with an unknown organism or exposure to an unknown antigen in a genetically susceptible patient (HLA-B27-positive) is hypothesized to result in the clinical expression of a spondyloarthritis. Due to the advent of advanced laboratory techniques and imaging modalities, there has been an unprecedented rapid development in nearly all clinical and scientific aspects of the SpA.

The association between HLA-B27 and ankylosing spondylitis remains the strongest known relationship between a major histocompatibility complex (MHC) antigen and a disease. While the pathogenic role of HLA-B27 in the spondyloarthropathies is unknown, numerous theories have been proposed. These theories are reviewed in and many are applicable to the HLA associations with other autoimmune diseases. Some theories suggest that the pathogenic role of HLA-B27 is independent of its immune function; for example, suggesting that HLA-B27 acts as a receptor for a disease-causing microorganism or is even merely a genetic marker for the true gene responsible.

The arthritogenic peptide theory proposes that HLA acts to present antigens to T cells. Alternatively, it is possible that HLA-B27 itself acts as a source of antigen, providing peptides that can be presented by other HLA molecules. The classic role of MHC Class I molecules is to present peptides to CD8+ T cells, but HLA-B27 may also possess functions, which are unrelated to antigen presentation. Studies of transgenic rodents have indicated that HLA-B27 is directly involved in disease pathogenesis rather than merely being a marker for a linked disease associated gene. Several observations strongly implicate TNF-α in the pathogenesis of AS and suggest the therapeutic potential of anti TNF-α agents in this rheumatic disease.
disorder. Significantly higher TNF-α serum levels have been found in patients with AS. Several open label and randomized controlled studies have evaluated the efficacy of the anti-TNF agents in infliximab and etanercept on the axial manifestations and peripheral arthritis of AS.

Currently, the most accepted and widely used measure for assessing the disease activity of SPA is the BASDAI. However, BASDAI is a self-administered patient-directed questionnaire and does not include any objective measures of activity and cannot reflect the whole spectrum of disease activity. One discriminatory capacity of the measures in disease activity is the ASDAS- CRP criteria (100%) had inflammatory low backache as defined by ASAS criteria. Enthesitis was present in 46 (90.19%) patients (predominant site: chest wall), other clinical features included Uveitis (current or past) in 20 (39.21%) and peripheral arthritis in 15 (29.40%). It is pertinent to note that hip joint involvement which is a indicator of severe disease was present only in 5 (9%) patients The Baseline disease activity was very high in majority of the cases and the mean ASDAS-CRP was 4.3 with SD of 1.13. Out of the 231 patients who had Spondyloarthritis, 51 patients were eligible for Biological therapy and received 5mg/kg Infliximab. All patients were administered Infliximab (5mg/kg) at 0, 2, 6 and 8 weeks intervals as per protocol of the institute. During this study only NSAIDS were permitted in stable dose for patients who did not wish to have any concomitant drugs.

The clinical and biomarker response was assessed using ASDAS CRP criteria at baseline and after completion of 24 weeks of therapy. Improvement in disease activity was considered by noting the change in the mean ASDAS scores (Δ ASDAS). Patients were grouped as having marked improvement (Δ ≥ 2), clinically significant response (Δ ≥ 1.1, <2) and poor response (Δ <1.0) based on change in ASDAS-CRP values. The discriminatory capacity of the measures in improvement in disease activity status was analysed using ASAS 20 and ASAS 40 measure.

**STATISTICAL METHOD**

The data were presented as Mean ± SD. Proportion of the study parameters were estimated using percentages. The limit of significance was calculated using p-value. All the data were analyzed by Pearson’s correlation, two sided, independent sample T test. Pearson Chi-Square test was used to analyze treatment response. All statistics were performed by SPSS 16.0 software. A power of 80% and two sided significance of disease activity assessed by ASDAS.

**RESULTS**

Out of these fifty one patients, 40 were male and 11 were female. The mean age of patients was 31 years with range 16-52 years. There were 41 (80.39%) patients who were below 40 years of age. The mean duration of disease was 4.5 years with the range of 1-20 years. Five (9.80%) had positive family history of SPA. 44 patients (86.27%) were HLA B27 positive. All patients (100%) had inflammatory low backache as defined by ASAS criteria. Enthesitis was present in 46 (90.19%) patients (predominant site: chest wall), other clinical features included Uveitis (current or past) in 20 (39.21%) and peripheral arthritis in 15 (29.40%). It is pertinent to note that hip joint involvement which is an indicator of severe disease was present only in 5 (9%) patients. The Baseline disease activity was very high in majority of the cases and the mean ASDAS-CRP was 4.3 with SD of 1.13. Out of the 231 patients who had Spondyloarthritis, 51 patients were eligible for Biological therapy and received 5mg/kg Infliximab on Week 2, 6, 14 and weekly thereafter as per protocol. Out of 51 patients, 46 patients follow up data was available for 46 patients and was included for analysis. The Disease activity after treatment was assessed in these 46 patients by ASDAS- CRP. The Mean ASDAS CRP which was 4.56 at base line fell to 2.81 at 8 weeks, 2.29 at 16 weeks and 1.6 at 24 weeks indicating significant improvement as per ASDAS criteria. There were total 43 (9.48%) patients who showed clinically and statistically significant response to Infliximab. (p<0.05), 15 (32.61%) patients showed ASAS 40 and 28 (60.87%) patients showed ASAS 20 response. 03 (6.522%) patients who did not show any statistically significant improvement.

**DISCUSSION**

The present study has attempted to evaluate the clinical and biomarker (CRP) response to TNF-α.
inhibitors in Indian patients of SPA using ASDAS CRP criteria. Treatment outcome were also assessed as per ASAS 20 and ASAS 40 for comparison. To the best of knowledge, this is one of the few studies in Asia subcontinent that has used ASDAS criteria to objectively assess response to anti TNF blocker therapy in Spondyloarthritis. In our study, out of 321 patients with spondyloarthritis, fifty one patients (15.88%) fulfilling ASAS criteria with SPA were included for the consideration of biologicals. This reflects the heterogeneity of the disease process and limited use of expensive biological only to patients with high disease activity. Out of the 51 patients, 46(90.1%) patients completed the 24 week follow up indicating good follow up protocols of the Institution. The remaining 05 (29.41%) dropped out of the study due to various reasons. Two patients had enter current infections needing cessation of biologics as per standard guidelines. One patient had severe hip involvement and underwent Total Hip Replacement and hence biological was precluded. 2 patients were lost to follow up and treatment due to compelling domestic circumstances at various duration of the study and were unable to take infusions as per protocol.

The mean age of the patients in our study was 31 with maximum patients in the age group 28-36 years and 81 % of patients were below 40 years. This age profile confirms to the fact that this disease predominantly affects young males in the most productive years of their life. The mean time to diagnosis of SpA was relatively less, 03 years in our study, compared to published literature. This reflects a good referral system and increasing awareness about Spondyloarthritis among peripheral health care providers and also early use of MRI as a diagnostic instrument for SPA resulting in an early diagnosis. HLA B27 was detected in 86% of patients with SPA. This is in concordance with a prevalence of 50-70% reported in literature20,21,22. In our study, 100%, 80% and 43% had Inflammatory backache (IBA), Enthesitis and Uveitis respectively. This is in agreement with that of prevalence reported in literature21,22. No patient developed tuberculosis which is an important adverse effect of anti TNF therapy indicating good screening for latent tuberculosis prior to initiation of biological response modifier therapy.

The mean improvement by ASDAS CRP from baseline was maximally achieved in first 8 weeks and persisted till 24 weeks. The response to treatment was analyzed according to ASAS 20 and ASAS 40 improvement. There were total 43(93.48%) patients who showed clinically and statistically significant response to Infliximab. (p<0.05) 15(32.61%) patients showed ASAS 40 and 28(60.87%) patients showed ASAS 20 response. The study by Heidje17 et al also showed an ASAS 20 response to Infliximab in 61% patients at 24 weeks. Higher proportion of statistically significant response as compared to other studies could be due to subjective factors of patients regarding improvement indices and also due to use of different response criteria.

Disease response indices which incorporate acute phase reactants are more sensitive and accurate than those responses with pure subjective parameters. It is pertinent to mention that while patients rate disease activity on the basis of subjective symptoms, whereas physicians rate disease activity objectively on the basis of severity and inflammation. Thus correlation between the assessment of the two perspectives is poor (r = 0.30) and they do not necessarily reflect the same construct. Hence it is necessary to include both the perspectives in an index. Van der Heijde et al17 and Lukas et al18 have already showed that the ASDAS correlated well with both doctor and patient perceptions of disease activity. Furthermore, ASDAS also demonstrated construct validity and high responsiveness during treatment with TNF-α inhibitors in SpA patients19. In our study, we used the ΔASDAS CRP in SPA patients as the main response index to monitor the response to Infliximab. The study has few limitations: retrospective nature of study, short duration of follow up and modest number of subjects. The study was also hampered by lack of comparator arm like BASDAI. To conclude ASDAS CRP is a sensitive and accurate disease activity marker to assess response to costly anti TNF biologicals as it is a composite marker combining both clinical and biomarker response. Also, it is evident from the ASDAS response that there is a significant decrease in disease activity with use of Infliximab in patients with Spondyloarthropathy.
REFERENCES