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Effect of Adalimumab on Ankylosing Spondylitis: A three Month Clinical Response in Indian Scenario

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ABSTRACT
Introduction: *This study aimed to evaluate the clinical response and safety in patients of Ankylosing spondylitis (AS) from a Rheumatology clinic in Madhya Pradesh, city Indore, after three months of Adalimumab therapy. All the patients who fulfilled modified New York criteria for AS were enrolled in the study.*
Material and Methods: *A total of 82 patients completed the study. The study was done initiating Adalimumab therapy due to lack of efficacy for NSAIDs and/or DMARDs were recruited consecutively from 31st December 2016 till 31st July 2017 in a Rheumatology clinic. The patients were evaluated for disease activity using the BASDAI which assesses fatigue, spinal pain, joint pain, joint swelling, areas of localized tenderness, and morning stiffness, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Functional limitation was evaluated using Bath AS Functional Activity Index (BASFI), which assesses activities related to functional anatomy, and the patient's ability to cope with everyday life .Spinal movement was evaluated using Bath AS Metrology Index (BASMI), which measures cervical rotation, tragus to wall distance, lumbar side flexion, modified Schober's, and intermalleolar distance.*
Result: *The rate of improvement of Bath AS Disease Activity Index (BASDAI) ($p< 0.0001$), and Bath AS Metrology Index (BASMI) ($p=0.0009$) and BASFI (Bath Ankylosing spondylitis functional Index) were achieved (p value<0.001) after three months. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were significantly decreased ($p< 0.0001$, $p<0.0001$ respectively).No adverse effects were seen including tuberculosis in any of the patient. Significant improvement in Erythrocyte Sedimentaion Rate (ESR), C-Reactive Protein (CRP) was also seen after 3 months (P-value <0.001, P-value<0.001) Patients who showed inadequate response to conventional therapy for AS showed significant improvement with Adalimumab treatment in disease activity as well as inflammatory markers.*
Conclusion: *Patients who showed inadequate response to conventional therapy for AS showed significant improvement with Adalimumab treatment in disease activity as well as inflammatory markers.*
Keywords: *Ankylosing, Spondylitis, Adalimumab, Clinical Effectiveness; Safety.*

Introduction

Ankylosing spondylitis (AS) affects 1% of the population worldwide and is a chronic, progressive, inflammatory disorder of unknown etiology(1). Usually begins in sacroiliac (SI) joints with axial involvement gradually progressing with inflammation of the joints and entheses leading to new bone formation with ankylosis and syndesmophytes. Peripheral joint may also be involved. Nonsteroidal anti-inflammatory drugs (NSAIDs) had been proven

effective in AS[2], but a considerable number of patients suffer from gastrointestinal disturbances and cardiovascular toxicities. Disease-modifying Anti Rheumatic drugs (DMARDs) such as sulfasalazine may be effective in peripheral arthritis, but there is very less data to support the effect of DMARDs in Axial Spondylitis[3]. Tumor necrosis factor (TNF) plays an important role in AS as proven by many reports. Increased expression of TNF-α mRNA and TNF protein in the SI joints demonstrated that TNF-α have an important role in pathogenesis of AS and thus in treatment of AS, TNF Blockers might have a role[4]. Introduction of agents targeted against TNF, a proinflammatory cytokine, has provided an effective modality in treating AS. Adverse events due to TNF inhibitors include Tuberculosis, injection site reactions, development of antinuclear antibodies, worsening of Congestive heart failure and sometimes demy-linating diseases such as multiple sclerosis. Injection site reaction is relatively common, especially with etanercept, but it has been diminished due to repeated injections. These days, due to implementation of screening of Tb and guidelines for treatment of latent TB incidence of TB have been decreased in patients treated with TNF inhibitors. In this study, we report results of effectiveness in clinical parameters measured by improvement in function, disease activity, metrologic measurements, acute phase reactants after three months of Adalimumab therapy in patients with AS in our setup.

Materials and Methods

Inclusion criteria -A total of 82 patients with Ankylosing spondylitis were taken in our study who didn't respond to NSAIDs as well as conventional DMARDs for atleast 3 months as defined by BASDAI (Bath AS Disease Activity Index) of over or equal to four and bilateral grade two or unilateral grade three sacroilitis[5] were included and given Adalimumab for 3 months .All patients were screened for TB by detailed history, chest radiograph, TB Interferon gold test.

Exclusion criteria: Patients with history of recent close contact with a known TB patient, active TB or evidence of TB on radiograph were excluded. Patients with other rheumatologic diseases, chronic infection, congestive heart failure, or malignancy were also excluded. Patients who had received a biologic agent in the past were excluded. Informed consent was taken from each patient.

Methods

Adalimumab was administered 40mg subcutaneo-usly once in two weeks for three months. All other medications were continued or discontinued according to the investigators decision. The patients were evaluated for disease activity using the BASDAI which assesses fatigue, spinal pain, joint pain, joint swelling, areas of localized tenderness, and morning stiffness. Functional limitation was evaluated using Bath AS Functional Activity Index (BASFI), which assesses activities related to functional anatomy, and the patient's ability to cope with everyday life[6]. Spinal movement was evaluated using Bath AS Metrology Index (BASMI), which measures cervical rotation, tragus to wall distance, lumbarside flexion, modified Schober's, and intermalleolar distance[7]. Primary endpoint was the improvement in BASDAI, BASFI, BASMI after three months. Secondary end points were improvement in Acute phase reactants ESR, CRP after 3 months of treatment with Adalimumab. Patients were assessed for adverse events at three months by physical examination performed by the investigator, laboratory tests including complete blood cell count, liver function test, renal function test, and chest radiograph.

Statistical analysis A paired t-test was done to compare the mean differences between baseline and after three months of Adalimumab therapy, and a non-parametric test, Wilcoxon test, was used to compare CRP and ESR.

Result

A total of 82 patients completed the three month assessment and eight patients were lost to follow-up due to personal reasons. The mean age was 29.8 yr

with a male predominance of 81.7% (Ratio 134:30) and the mean disease duration was 13.0 yr and 90.2% of the patients were positive for HLA-B27. The percentage of patients with history of uveitis was 34.1% and 48.7% had peripheral joint involvement (Table 1). Eleven patients (13.4%) had a history of completely treated pulmonary TB with no active lesions on their chest radiography. All patients had significant AS diseases activity with BASDAI score of at least 4. Significant improvement in BASDAI score was achieved after three months ($p<0.001$) and BASFI and BASMI scores also showed a significant improvement ($p<0.001$ for both comparisons) (Table 2). Only 14 (9.9%) patients failed to show a BASDAI score of less than four after three months. Improvements were significant in all domains. CRP and ESR also improved significantly after 3 months ($p<0.001$ for both comparisons) (Table 2). At three months, patients taking NSAIDs decreased from 97.3% to 41.6%, methotrexate from 56.2 % to 33.3%, sulfasalazine 45.2% to 5.4%, and steroids 32.2% to 6.6%. (Table 3). Thirty four (34.1%) patients experienced an adverse event. The most common treatment-related adverse event was localized infusion site reaction including pruritis and rash. Upper respiratory infection was the second most common adverse event. None of the patients developed TB during the study. No serious adverse events occurred. There were no clinically significant changes in the values in serum chemistry, hematology or urine laboratory test, or vital signs.

Table 1. Characteristics of patients

Characteristics Age, mean±SD)	N(%) 29.8±7.3
Sex, M:F (male)	134:30 (81.7)
Disease duration mean±SD (yr)	13.0±5.9
HLA-B27 positive	75 (90.2)
History of uveitis	28 (34.1)
History of TB	11 (13.4)
Peripheral arthritis	40(48.7)
History of Dactylitis	22(26.8)

Table 2. Improvements in outcome measures from baseline

	Baseline	After 3 months	P value
CRP (mg/dL)	3.7±3.4	0.4±0.8	<0.0001
ESR (mm/hr)	47±35.3	9±12.0	<0.0001
BASDAI	6.9±1.8	3.3±1.9	<0.0001
BASFI	7.6±3.5	3.8±2.6	<0.0001
BASMI	5.0±1.8	4.3±1.9	<0.0001

Table 3. Decreased in Oral drug intake after 3 months of Adalimumab therapy

	Before3 months	After 3 months
NSAID	97.3%	41.6%
Methotrexate	56.2 %	33.3%
Steroids	32.2%	6.6%
Sulfasalazine	45.2%	54.%

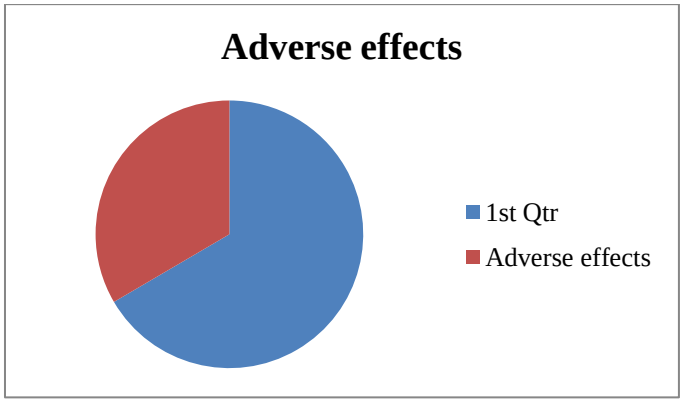

Figure 1

Discussion

This study was from a prospective cohort of patients who were started on Adalimumab for treatment of AS at our setup. There were many studies done for effect of Adalimumab on AS, Heijde D et al[8] concluded that Adalimumab was well-tolerated during the 24-week study period and was associated with a significant and sustained reduction in the signs and symptoms of active AS. In another open-label pilot study by Haibel et al of Adalimumab treatment of AS showed a clear improvement in clinical as well as MRI outcome measurements, similar to that observed with the other TNF-blocking agents, indicating a group effect for TNF-blockers in the therapy of active AS.[9] In our study, all the patients were from central India, state Madhya Pradesh. The study was relatively short in duration of follow-up, but it provides the information on safety and efficacy in real life until

further long-term study is available. This study showed that Adalimumab for treatment of AS was effective in decreasing pain and disease activity. BASMI score as a whole improved significantly, indices couldn't be compared individually. This was to be expected since BASMI primarily measures structural damage and correlates poorly with functional outcome[10]. Introduction of TNF Blockers, has provided an effective modality in treating AS. Other than Adalimumab, both etanercept, a dimeric fusion protein of the TNF receptor and the Fc portion of IgG1, and infliximab, a monoclonal antibody that targets TNF, were significantly effective in improving pain and function in AS in randomized clinical trials[11-13]. Current guidelines recommend adalimumab for the treatment of severe, active AS. Some evidence from studies of adalimumab suggests that patients in the early stages of disease or preradiographic AS have a greater response rate to TNF inhibitors than patients with established AS. Therefore, earlier diagnosis of AS may become critical if treatment with biologic therapy proves to have significant effects on future disease progression. Furthermore, adalimumab has shown efficacy in patients with complete ankylosis of the spine. These patients were previously thought to obtain little benefit from further treatment. Currently, international criteria do not recommend treatment with biologics for patients with TSA, but modification of future standards are expected to recognize this subset of patients. Additionally, patients with elevated CRP or ESR or greater amounts of inflammation on MRI may also exhibit a more profound response to adalimumab, especially earlier in the disease course. The extent to which suppression of inflammation on MRI correlates with attenuation of structural damage as measured by plain radiography remains to be elucidated.[14] Adalimumab was taken in our study to know the short term effects as in our country due to financial constraints, most of the people are not able to afford Biologics and therefore we tried to study whether a short three months course of Biologic is able to prove that at least even a small duration of biologic therapy is sufficient to provide a healthy life style and a good clinical response. Whether Adalimumab can reverse structural damage or not is still under investigation and even if it does have such an effect it would not be evident only after three months of therapy. TNF blockers are effective in improving symptoms, physical function, mental well-being, quality of life, and may possibly prevent deforming complications, but once ankylosis develops it is considered irreversible. So, TNF blockers should be used without delay in AS patients with inadequate response to NSAIDs. Adverse events also occurs and although there was no serious adverse events after three months therapy, over 30% of patients experienced minor adverse events. Our great concern was reactivation of latent TB[15] especially in relative TB endemic areas. Prophylactic treatment of latent TB has been shown to be effective in preventing active TB in patients receiving biologic agents[16]. It has been only ten years since the introduction of these biologics, but anti-TNF agents have revolutionized the treatment of AS. Preliminary studies have even demonstrated short term radiographic improvements on magnetic resonance images with these agents. However, long-term follow-up will be needed to answer long-term effects and adverse events.

Conclusion

Patients who showed inadequate response to conventional therapy for AS showed significant improvement with Adalimumab treatment in disease activity as well as inflammatory markers. The limitations in our study was we couldn't record ASAS20 and ASAS 40, ASAS 5/6, and ASAS partial remission in our patients and also other domains such as SF-36, and EQ-5D. We focused ourselves more on disease activity and other metrological indices and important inflammatory markers such as ESR and CRP and found that there was significant change in these parameters and thus it was proven in our study that Adalimumab in a short period of time is also effective and its disease modifying effects are significant in terms of various clinical and biochemical parameters.

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References

1. Ahearn JM, Hochberg MC. Epidemiology and genetics of ankylosing spondylitis. J Rheumatol Suppl. 1988;16:22–28. [PubMed]
2. Sturrock RD, Hart FD. Double-blind cross-over comparison of indomethacin, flurbiprofen, and placebo in ankylosing spondylitis. Ann Rheum Dis. 1974;33:129–131. [PMC free article] [PubMed]
3. Chen J, Liu C. Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. J Rheumatol. 2006;33:722–731. [PubMed]
4. Chen J, Liu C. Is sulfasalazine effective in ankylosing spondylitis? A systematic review of randomized controlled trials. J Rheumatol. 2006;33:722–731. [PubMed]
5. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21:2286–2291. [PubMed]
6. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, Jenkinson T. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21:2281–2285. [PubMed]
7. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol. 1994;21:1694–1698.[PubMed]
8. van der Heijde D1, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J, Dougados M, Reveille JD, Wong RL, Kupper H, Davis JC Jr; ATLAS Study Group.Efficay and safety of adalimumab in patients with Ankylosing Spondylitis:results of multicenter,randomized,double blind placebo controlled trial. Arthritis Rheum. 2006 Jul;54(7):2136-46.
9. Haibel, H., Rudwaleit, M., Brandt, H. C., Grozdanovic, Z., Listing, J., Kupper, H., Braun, J. and Sieper, J. (2006), Adalimumab reduces spinal symptoms in active ankylosing spondylitis: Clinical and magnetic resonance imaging results of a fifty-two–week open-label trial. Arthritis & Rheumatism, 54: 678–681. doi:10.1002/art.21563.
10. Jauregui E, Conner-Spady B, Russell AS, Maksymowych WP. Clinimetric evaluation of the bath ankylosing spondylitis metrology index in a controlled trial of pamidronate therapy. J Rheumatol. 2004;31:2422–2428. [PubMed]
11. Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med. 2002;346:1349–1356. [PubMed]
12. Calin A, Dijkmans BA, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, Mola EM, Salvarani C, Sanmarti R, Sany J, Sibilia J, Sieper J, van der Linden S, Veys E, Appel AM, Fatenejad S. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004;63:1594–1600. [PMC free article] [PubMed]
13. Van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, Braun J. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT) Arthritis Rheum. 2005;52:582–591. [PubMed]
14. Hennigan S, Ackermann C, Kavanaugh A. Adalimumab in ankylosing spondylitis: an evidence-based review of its place in therapy. Core Evidence. 2007;2(4):295-305.

15. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthr-itis Rheum. 2003;48:2122–2127. [PubMed]
16. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, Carreno L, Figueroa M. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005;52:1766–1772.[PubMed]