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EFFICACY AND SAFETY STUDY OF INFLIXIMAB AND ETANERCEPT IN THE TREATMENT OF AXIAL SPONDYLOARTHRITIS

Gautam Mullick* Department of Rheumatology, INHS ASVINI, Mumbai, India. *Corresponding Author

Anuj Singhal Department of Medicine, Command Hospital, Pune, India.

Vivek Hande Department of Medicine, INHS ASVINI, Mumbai, India.

ABSTRACT Spondyloarthritis (SpA) is a spectrum of enthesitis related autoimmune disorders comprising of axial and peripheral manifestations. The management of SpA is a step-wise approach wherein NSAIDs and Disease Modifying Anti-Rheumatic Drugs remain the first line therapy. Refractory cases and those with high disease activity are subjected to treatment with TNF blockers. In the present study we assess the efficacy of two such biological agents which have been the corner stone of TNF blocker therapy of SpA since times immemorial, viz. Infliximab (INF) and Etanercept (ETN). Data was collected from patients with SpA attending the Rheumatology outpatient department at the INHS Asvini Hospital, Mumbai, over 2 years between July 2016 and June 2018. SpA patients who were judged to be having therapeutic failure after adequate therapy with NSAIDs for at least 6 months were put on treatment with either ETN or INF. To monitor the disease activity, BASDAI (Bath AS Disease Activity Index) and ASDAS (AS Disease Activity Score) – ESR scores were recorded at baseline, and after 6 months and 12 months of therapy initiation. All data was recorded electronically and analyzed using SPSS v22; $p<0.05$ was considered to be statistically significant for all tests applied. Overall, the reduction in disease activity, as evidenced by reduction in the mean BASDAI and ASDAS-ESR scores over 12 months of treatment was statistically significant for all patients when considered together, as well as when ETN and INF were considered separately ($p<0.0001$ in all cases).

KEYWORDS : Spondyloarthritis; TNF Blockers; Inflixmab; Etanercept.

INTRODUCTION

The concept of Spondyloarthritis (SpA) as a group of interrelated diseases has been recognized since the early 1970s. It is a chronic, progressive inflammatory disease characterized by inflammatory back pain, due to sacroiliitis, spondylitis, and enthesitis that affects young men and women, commonly starting in the second and third decades of life.[1] An association with the HLA-B27 antigen is usually demonstrable. Based on the predominant clinical manifestation, SpA is classified into Axial (ASpA) and Peripheral (PSpA) varieties.[2] ASpA comprises of conditions affecting predominantly the spine and/or the sacroiliac joints, such as Ankylosing Spondylitis (AS), non-radiographic axial Spa, psoriatic arthritis and reactive arthritis with axial involvement, and arthritis associated with inflammatory bowel disease.[3]

The 2015 American College of Rheumatology recommendations suggest the use of TNF-α (tumour necrosis factor-α) inhibitors for adult Axial SpA patients not responding to NSAIDs (Non-steroidal anti-inflammatory drugs).[4] The presently approved TNF-α inhibitors include Infliximab (INF), Adalimumab, Etanercept (ETN), Golimumab, and Certolizumab pegol.[3] Though the biological response modifiers (BRMs) have been proven to be effective in patients with Axial SpA not responding to NSAIDs, their exorbitant cost is the major hindrance for their regular usage, especially in India where most of the treatment is borne by the patient through out-of-pocket spending.[5] Despite the arrival of biosimilars, the cost of therapy with BRMs is still comparatively higher and consequently many Asian Indian patients with Axial SpA are deprived of the benefits of these agents. ETN is composed of two recombinant forms of the human TNF receptor P75 fused to an Fc portion of human immunoglobulin G1, and is administered subcutaneously 50 mg a week or 25 mg twice a week. It has a differences regarding way of action and pharmacokinetics, what implies differences with antibodies in effectiveness and safety. INF is a chimeric monoclonal antibody which inhibits the functioning of tumor necrosis factor alpha, given via intravenous route at a dose of 5 mg/kg at 0, 2, and 6 weeks and every 6 weeks there after.

Our site is a state-owned healthcare organization which provides biological response modifiers for patients with Axial SpA and other rheumatological conditions through government procurement. Our objective was to know the comparative clinical outcomes of the usage of different biologic response modifiers for patients with AS who have therapeutic failure with NSAIDs. With this background we report a study on the efficacy of INF and ETN in the treatment of Axial Spondyloarthritis.

STUDY DESIGN & METHODOLOGY

We collected data from patients with SpA attending the Rheumatology outpatient department at the INHS Asvini Hospital, Mumbai, over 2 years between July 2016 and June 2018. SpA patients who were judged to be having therapeutic failure after adequate therapy with NSAIDs for at least 6 months were put on treatment with either ETN (given as 50 mg per sitting, subcutaneously; dosing was once a week up to 4 months, once every 2 weeks for 4 months, and once a month for 4 months) or INF (given as 5mg/kg intravenous infusion every 2nd month for 8 doses). Mean dose for ETN was 24 injections; the dose of ETN was tapered following a fixed protocol (weekly dosing for 3 months – 12 doses; fortnightly dosing for 3 months– 6 doses; and monthly dosing for 6 months - 6 doses; thus a total of 24 doses). The allocation of treatment was determined by patient convenience and physician discretion. NSAID therapy was stopped in these patients. Further, since this was not a clinical trial but a compilation of experience with different agents, informed consent waiver was obtained from the institutional ethics committee.

At the initiation of therapy demographic details, time to diagnosis of AS, the duration of disease, presence of low backache, early morning stiffness, peripheral joint involvement, ocular, dermatological, gastrointestinal and genitourinary involvement were recorded, total joint count and peripheral joint count were noted, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein) values and HLA-B27 score were obtained. Baseline values of scores of BASMI-3 (Bath AS Metrology Index) and MASES (Maastricht AS Enthesitis Score) were calculated. To monitor the disease activity, BASDAI (Bath AS Disease Activity Index) and ASDAS (AS Disease Activity Score) – ESR scores were recorded at baseline, and after 6 months and 12 months of therapy initiation. All data was recorded electronically and analyzed using SPSS v22; $p<0.05$ was considered to be statistically significant for all tests applied.

RESULTS

In this study a total of 30 patients with Axial SpA treated with biologic response modifiers were included. Out of these 30 patients, 15 patients received INF and 15 received ETN. 2 were female (1 ETN, 1 INF) and 28 were male (14 ETN, 14 INF). The demographic and baseline parameters of the patients are summarized in [Table-1]. Overall, both groups were comparable in all parameters except in the baseline BASMI-3 score which was significantly higher in patients who received ETN.

[Table-1]: Baseline and demographic parameters of patients with AS treated with ETN and INF. (†independent samples T test)

Parameter (meanvalues)	Overall (n=30)	ETN group (n=15)	INF group (n=15)	p-value†
Age(years)	32.74±7.88	33.53±9.55	31.45±6.48	0.474

Time to diagnosis (months)	22.54±26.90	25.40±29.97	20.40±24.93	0.604
Duration of disease (months)	79.60±47.18	87.60±48.82	73.60±46.25	0.397
Baseline BASMI-3score	1.77±2.10	2.73±2.66	1.05±1.19	0.034
Baseline MASES score	0.37±0.91	0.20±0.56	0.50±1.10	0.302
Total Joint Count	0.54±0.92	0.60±0.91	0.50±0.95	0.754
Swollen Joint Count	0.40±0.81	0.33±0.72	0.45±0.89	0.671
ESR (mmat1 hour)	36.49±16.45	41.47±19.96	30.75±12.50	0.151
Baseline BASDAI score	4.22±1.34	3.91±1.42	4.45±1.26	0.252
Baseline ASDAS -ESR score	3.33±0.84	3.05±0.79	3.53±0.83	0.092

From these 30 patients, 29 patients (14 ETN, 15 INF) had history of early morning stiffness. Further, 13 patients (7 ETN, 6 INF; all males) gave history of peripheral joint involvement in the knee (5), ankle (3), neck (2), shoulder (2) and elbow (1); three patients had both knee and ankle joint affliction. All patients had low backache, two patients had a skin rash, and no patient gave history of gastrointestinal, ocular or genitourinary involvement. A total of 25 patients (11 ETN, 14 INF) were positive for HLAB27 status, and 25 patients (5 ETN, 20 INF) had positive values for CRP.

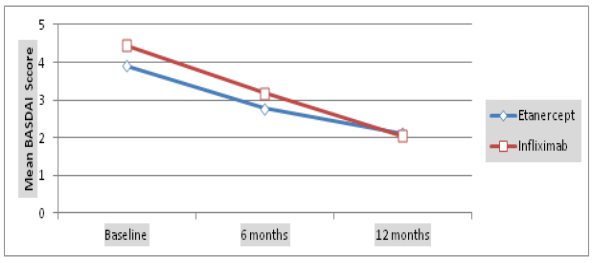
The average BASDAI scores at baseline, 6 months and 12 months is presented in [Table-2]. The distribution of mean BASDAI scores over 12 months is shown in [Figure-1].

[Table-2]: Mean BASDAI scores over 12 months in AS patients receiving ETN and INF. †Repeated measures ANOVA

Pointoftime	Overall (n=35)	ETNgroup (n=15)	INFgroup (n=15)
Baseline	4.22±1.34	3.91±1.42	4.45±1.26
6 months	3.00±0.78	2.77±0.82	3.18±0.71
12 months	2.07±0.41	2.12±0.62	2.04±0.13
P value†	<0.0001	<0.0001	<0.0001

Overall, the reduction in disease activity, as evidenced by reduction in the mean BASDAI scores over 12 months of treatment was statistically significant for all patients when considered together, as well as when ETN and INF were considered separately (p<0.0001 in all cases). However, there was no statistically significant difference in the magnitude of reduction in the mean BASDAI scores between patients who received ETN and those who received INF.

[Fig-1]: Mean BASDAI over 12 months in AS patients receiving ETN and INF



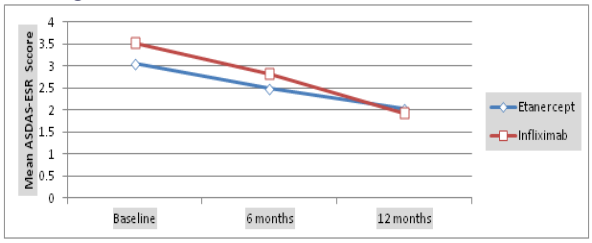
Average ASDAS-ESR scores at baseline, 6 months, and 12 months are presented in [Table -3]. The distribution of mean ASDAS-ESR scores over 12 months is shown in [Figure-2].

[Table-3] Average ASDAS-ESR scores at baseline, 6 months, and 12 months

Point of time	Overall (n=30)	ETN group (n=15)	INF group (n=15)
Baseline	3.33±0.84	3.05±0.79	3.53±0.83
6 months	2.68±0.61	2.49±0.43	2.83±0.72
12 months	1.98±0.39	2.03±0.24	1.94±0.46
P value	<0.0001	<0.0001	<0.0001

Overall, the reduction in disease activity, as evidenced by reduction in the mean ASDAS-ESR scores over 12 months of treatment was statistically significant for all patients when considered together, as well as when ETN and INF were considered separately (p<0.0001 in all cases). However, there was no statistically significant difference in the magnitude of reduction in the mean ASDAS-ESR scores between patients who received ETN and those who received INF.

[Fig-2]: Mean ASDAS-ESR over 12 months in AS patients receiving ETN and INF



Fifteen patients (7 in the INF group and 8 in the ETN group) had MRI performed at baseline and month 12. All patients had lesions on baseline MRI scans consistent with active disease, when reviewed by radiologists prior to entry into the study. Results from X-ray radiography demonstrated stages of disease between grade-II and grade -IV in ETN group. Similar kind of X-ray results were found in the INF group as well, but patients with grade-II disease were more in this group compare to ETN group. Post treatment MRI results were evident in stating the significant recovery. Post treatment X-rays were not available to evaluate. The improvement in the radiographic parameters was consistent with improvement in the functional and clinical parameters for the disease activity.

Both biologics were well-tolerated. Two patients who received INF reported mild, self-limited flu-like transfusion reaction, and two other patients had mild macular self-limiting rashes. Four patients on ETN had transient depression, epiphora and mild macular self-limiting rashes. There were no serious ADRs which required in treatment withdrawal or any other serious consequences to any patient.

DISCUSSION

Axial SpA is a progressive inflammatory disease of uncertain etiology that primarily affects the spine column, which is characterized by excessive bone formation in the form of syndesmophytes and ankylosis. Evidences indicated that TNF-α seems to be a crucial effector cytokine involved in the key downstream effector pathways. Activation of Wnt/beta-catenin signaling up regulates the TNF-α expression, and thus TNF-α may, through the Wnt signaling pathway, regulate new bone formation. A previous study found that compared to AS patients without syndesmophytes, patients with syndesmophyte formation show lower serum levels of Dickkopf-1 (DKK1). In addition, the association between Del1 polymorphisms and AS susceptibility in Chinese Han population was reported. DKK1 and Del1 both were potent inhibitors of the Wnt signaling pathway. These evidences supported a potential involvement of this pathway in the etiology of AS.

Evidence indicates that the use of TNFα antagonists can significantly relieve pain, improve the quality of life, results in improvements in regression of disease activity for patients with AS. Anti-TNFα reagents (INF, adalimumab and ETN) have large treatment effects for spinal pain, mobility and function confirmed by dozens of RCTs[5,6,7]. TNF-α based BRMs represent the only reliable treatment option available at the present time for treating ASpA patients who do not respond to the first line of therapy which are the NSAIDs[3]. In PSpA patients with NSAID failure, there is an option of using slow-acting anti-rheumatic drugs and local corticosteroids[3] before initiating biologic therapy; however, such an option is not available for ASpA. The recommendations do not recommend any specific TNF-α inhibitors except in cases of ASpA with IBD where monoclonal antibodies are to be preferred over ETN[4].

In our study the baseline BASMI-3 score was higher in patients who received ETN; despite this difference, the impact of both the drugs on disease activity over a period of 12 months was comparable and not statistically significant, as evidenced by a similar reduction in the mean BASDAI and mean ASDAS-ESR scores over a period of 12 months. To the best of our knowledge, this is one of the initial attempts where the effect of different biologics on disease activity has been documented and reported in Indian patients with AS. Other previous

studies reported elsewhere concur with our observations that different biologic TNF-α inhibitors demonstrate similar efficacy as measured by % of patients achieving ASAS40 response in AS patients with NSAID failure[8,9,10,11]. A 2015 meta-analysis also reports that the TNF-α inhibitors, in comparison with placebo, significantly improve disease activity and functional capacity[12]. However, our study was a direct head-to-head comparison of efficacy and safety of two biologics in AS where we demonstrated similar efficacy and safety. In our study, overall reduction in disease activity, as evidenced by reduction in the mean BASDAI scores over 12 months of treatment was statistically significant for all patients when considered together, as well as when ETN and INF were considered separately ($p<0.0001$ in all cases). However, there was no statistically significant difference in the magnitude of reduction in the mean BASDAI scores between patients who received ETN and those who received INF.

In a previous study (ESTHER)[13] patients with active axSpA were randomized for treatment with either ETN 50 mg SC weekly or sulfasalazine for 1 year. At year 1, patients from both groups who were not in remission continued with ETN in a long-term open-label extension; patients who were in remission dropped their medication and were followed up for 1 year, and, in case of flare, ETN was (re)-introduced and continued in a long-term extension. The efficacy and safety data analyzed by both subgroups (AS and nr-axSpA) brought similar results, suggesting that clinical response to ETN is the same in nr-axSpA and AS (i.e. ASAS inactive disease was achieved by 40% of the patients treated with ETN in both axSpA subgroups), given the same level of inflammatory activity at baseline. Remarkably, this similar level of response remained also in the long-term extension up to year 4, indicating a similar course of the disease in non-radiographic and radiographic forms of axSpA. In our study, the allocation of treatment was determined by patient convenience and physician discretion. Out of 30 patients, exactly half of them were selected for ETN therapy and at the same point of time NSAID therapy was stopped in all these patients.

The efficacy of the four anti-TNF drugs available for SpA has not been directly compared in randomized clinical trials. Indirect comparisons are limited and do not show a significant difference in effectiveness between them. In our study, we aimed to compare such two anti-TNF drugs head to head (i.e. ETN and INF) in terms of efficacy profile. At 12 months, the difference in efficacy results between INF and ETN groups was non-significant. Survival rates extracted from national registries have been used as a surrogate marker of efficacy, but controversial results have been reported. Data from the Austrian national register show better 2-year survival rates with ETN than with adalimumab or INF, while the Danish national register shows no statistically significant differences between the three drugs. Similar results were found in our study where two drugs ETN and INF showed no statistically significant differences between them. Overall drug survival for patients with rheumatoid arthritis, psoriatic arthritis, or AS was better for ETN than for INF or adalimumab in the Norwegian registry, but this difference no longer exists when analyzing only first anti-TNF treatments. In the Czech registry, there were no differences in survival rates between the anti-TNF agents, although the difference between ETN and INF was near statistical significance ($P = 0.057$). In addition, they found a higher proportion of patients with BASDAI, 4 in the ETN group than in the INF group.[14]The drug survival rates were not measured in our study.

Despite the great benefit that anti-TNFα therapy has brought to many patients with SpA, the high cost of these drugs is causing a substantial impact on national health economies. Therefore, in the recent years, the treatment guidelines were trying to optimize the use of anti-TNF-α agents. The ASAS/EULAR recommendations of 2016 suggest the possibility of tapering the TNF-α inhibitors once the patient has achieved sustained remission.[15] The cost-effectiveness of anti-TNF-α medications in SpA is still controversial. The existing studies have focused on the disease progression in functional limitations and symptoms without considering the possible impact on ability to work that this treatment may have, such as reducing the risk of permanent work disability or sick days, decreasing the overall socioeconomic costs.[16] Other factors that might influence the cost effectiveness of TNFα inhibitors are the administration costs, the rebound assumption on patients after stopping the therapy and the long-term effect anti-TNFα therapy has on structural damage progression and therefore, on the physical function.[17] Considering all these parameters would help the institutional policy decisions and in designing better schemes and more cost-effective guidelines for the treatment of SpA.

The data available on safety of TNFα-inhibitors in patients with nr-axSpA are limited, however the results of the studies performed for those patients are similar to results observed in AS patients, without detecting new safety signals. All anti-TNFα agents are shown to be well tolerated and consistently safe in axSpA in short and long-term treatment. In our study, both biologics were well-tolerated. Two patients who received INF reported mild, self-limited flu-like transfusion reaction, and two other patients had mild macular self-limiting rashes. Four patients on ETN had transient depression, epiphora and mild macular self-limiting rashes. There were no serious ADRs which required in treatment withdrawal or any other serious consequences to any patient.

LIMITATIONS

Inadequate sample size, allocation of drug based on factors such as severity of disease/patient convenience and lack of costs benefit analysis were major limitations of this study.

CONCLUSION

In recent years, there have been no head-to-head trials comparing TNFα-inhibitors in nr-axSpA (or in AS). An indirect comparison based on the results of phase III trials is difficult, due to different inclusion/exclusion criteria, the presence of objective signs of inflammation, and in particular, study duration. The current indication for TNFα-inhibitors in nr-axSpA requires not only clinically active disease not responding to the first-line therapy, but also the presence of objective signs of inflammation. Nonetheless, even in patients representing the target population, the efficacy data still appear heterogeneous, most likely due to factors beyond symptom duration and inflammatory activity. Importantly, patients with comparable levels of inflammatory activity demonstrate similar response to TNFα inhibitors irrespective of the presence or absence of radiographic sacroiliitis. Long-term studies (up to 10 years) are underway now, as well as registries.

Despite major advances, several challenges in the treatment of nr-axSpA do remain. There are only limited data about the possibility of discontinuation of TNF-α inhibitors upon achievement of remission in nr-axSpA. Previous studies suggest that discontinuing treatment leads to relapse/loss of remission in 60–80% of patients after stopping the therapy for up to 1 year.[13] Currently, a number of trials investigate strategies for treatment discontinuation *versus* dose tapering *versus* continuous treatment with TNF-α inhibitors after achieving remission in nr-axSpA [ClinicalTrials.gov identifiers: NCT01808118, NCT02505542 and NTC02509026]. Finally, the potential prevention of structural damage development in the sacroiliac joints and spine by treating patients at the non-radiographic stage is of high interest and relevance for the long-term outcome. It needs to be proven in clinical trials if early and effective anti-inflammatory treatment might indeed prevent structural damage development in the axial skeleton, as suggested in observational studies.[19,20]

In summary, availability of TNF-α inhibitors for the treatment of patients with nr-axSpA certainly contributes to the improving of the short- and long-term outcomes in this disease by broadening the spectrum of possibilities for those who do not respond to first line treatments. In the near future, we will certainly see a further increase in the number of therapeutic options in axSpA, including nr-axSpA that would require development of optimized and ideally individualized treatment strategies to reach and maintain the remission status.

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