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ORIGINAL ARTICLE

Effect of Infliximab Therapy in Functional Improvement in Patients with Ankylosing Spondylitis

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ABSTRACT

Introduction: Ankylosing spondylitis (AS), one of the spondyloarthropathies predominantly affecting younger people, is notorious for morbidity with pain, functional impairment, and disability. Infliximab, a chimeric tumor necrosis factor (TNF) alpha inhibitor, has been proven as a safe and effective biologic in respect to improvement in clinical and radiological parameters in AS. This study is a humble attempt to look for disability limitations by infliximab therapy in patients with AS.

Aims and objectives: To look for functional improvement in AS patients treated with Infliximab in comparison with control group who were treated conservatively.

Materials and methods: A randomized controlled trial was done in the Department of Physical Medicine and Rehabilitation, Institute of Postgraduate Medical Education & Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata, West Bengal, India, from December 2015 to May 2017, recruiting 20 AS patients who fulfilled the Assessment of Spondylo-Arthritis International Society (ASAS) criteria and had significant functional limitation. After Ethics Committee clearance, two groups were made randomly. Both groups I and II were included in the rehabilitation program. Group I, in addition, received injection infliximab on days 0, 14, and 42. Assessment by the Bath ankylosing spondylitis functional index (BASFI) and visual analog scale (VAS) for lower back pain was done before intervention and 2, 6, 12 weeks after initiation of treatment.

Results: Statistically significant positive outcome difference was seen in the first group in comparison with control group based on both outcome parameters.

Conclusion: Infliximab is a safe and highly efficacious biologic therapy in limiting disability in AS patients when treated early.

Keywords: Ankylosing spondylitis, Bath ankylosing spondylitis functional index, Disability, Visual analog scale.

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INTRODUCTION

Spondyloarthritis (SpA), a human leukocyte antigen B27-associated heterogeneous group of chronic interrelated inflammatory arthropathies, affects not only the spine, but also peripheral joints, entheses, and certain extra-articular sites, and is one of the most leading chronic diseases notoriously known for functional morbidity due to pain and deformity. Axial SpA (AxSpA) including AS is the most prevalent subtype of the spectrum having grave prognosis. The disease process, if not intervened early, leads to progressive spinal deformity. Eventually, ankylosis of sacroiliac joints and hip joints and calcification of spinal ligaments develop causing marked hindrances in activities of daily living. Early inclusion in rehabilitation programs has been proven of utmost importance for functional optimization. Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) have failed to show significant improvement in axial variant of spondyloarthropathy. Biologics have emerged as important drugs in clinical improvement in AxSpA. Due to limited options available for treatment, development and efficacy of TNF alpha inhibitor therapy are getting preference in the management of AxSpA, with definite improvement in disease process and radiological progression according to multiple literature. Five biologics of this group have been proven efficacious with chimeric murine human monoclonal immunoglobulin G1 antibody infliximab as per most of the studies. However, there is scarcity of data on the efficacy of infliximab therapy over conservative therapy in functional improvement in AS patients.

REVIEW OF LITERATURE

The AxSpA including AS is notoriously known for functional limitations due to pain, stiffness, and deformity. Functional limitations increase with disease duration.[1] Older age of onset, lower education level, and coping strategies contribute to higher disability in AS.[2] Most functional limitations in AS occur in the first 10 years of disease onset, associated with peripheral arthritis and radiological changes.[3] The proven treatment objectives in

AS are to relieve pain and stiffness by appropriate nonsteroidal anti-inflammatory drugs (NSAIDs), and to relieve fatigue, hinder deformity progression as well as enhance endurance by early enrolment in rehabilitation schedule.[4] A Cochrane review concluded that home exercises are better than no intervention and supervised exercises are better than home therapy with level A evidence.[1] Conventional synthetic DMARDs have failed to show any definite role in disease progression limitation.[5] Sulphasalazine, having proven efficacy in peripheral arthritis and uveitis, has no role in AxSpA.[6] Methotrexate has debatable role in AxSpA.[7,8] The new-age biologics therapy has emerged with a hope in management of AS with anti-TNF alpha being the most efficacious.[9,10] Infliximab, one of the five anti-TNF agents of proven benefit in AS according to pivotal phase III trial with level A evidence, has a definite role in clinical improvement in AS.[9] On the contrary, as per initial phase III open-label extension studies in AS and papers by Van der Heijde et al,[9,10] it is seen that anti-TNF alpha over 2 years has debatable preventive role in progression in radiological outcome in AS. Most of the articles on the efficacy of infliximab have evaluated the disease activity and radiological progression,[11] but not assessed the functional improvement.

There is paucity of literature comparing infliximab therapy over conservative care addressing functional outcome using the well-tested functional indices like BASFI.[12]

OBJECTIVES OF THE STUDY

- To look for functional improvement in AS patients treated with infliximab.
- To compare the outcome with control group treated with conservative approach.

MATERIALS AND METHODS

Study Design

This study is a randomized controlled study where the two treatment groups are controls for each other. Single blinding was not possible because a noninvasive method was compared with an invasive method. A computer-generated randomization of the patients was done until the two treatment groups got equal number of patients. However, it was monitored throughout the study and the respective desired treatment of every patient was ensured.

Study Area

Department of Physical Medicine and Rehabilitation, Institute of Postgraduate Medical Education & Research and Seth Sukhlal Karnani Memorial Hospital (IPGMER, SSKM Hospital), Kolkata was chosen as the study area.

Study Population

Patients with clinical symptoms and radiologically confirmed AS, who also fulfilled the inclusion criteria of the study and attended the outpatient department and inpatient department of the Department of Physical Medicine and Rehabilitation at IPGMER and SSKM Hospital, Kolkata, India.

Study Period

18 months (December 2015 to May 2017).

Sample Size

Sample size for this study was calculated based on using BASFI as the primary outcome measure at 12 weeks. Totally 20 patients were included in this study, 10 in infliximab therapy group and 10 in control group. The calculation was done with the help of nMaster 2.0 software (Department of Biostatistics, Christian Medical College, Vellore, India).

Inclusion Criteria

- ASAS-criteria fulfilled AS patients
- Disease causing significant functional limitation
- Active disease for ≥ 4 weeks
- Bath ankylosing spondylitis disease activity index (BASDAI) ≥4
- Failed adequate NSAID trial
- Patients giving consent for the study
- Patient mentally sound enough to communicate and participate in the study and can understand the parameters well

Exclusion Criteria

- Active infection or septicemia
- Documented hypersensitivity
- Pregnancy
- Recent history of malignancy
- History of tuberculosis in the recent past
- Congestive cardiac failure (New York Heart Association class III–IV)
- Patients with postmyocardial infarction, poststroke, postmastectomy, and prolonged immobilization
- The presence of an unstable medical condition like uncontrolled systemic disease, including cancer, diabetes, endocrine disease, major depression, schizophrenia

Study Tools

- Visual analog scale
- BASFI questionnaire
- BASDAI questionnaire

Materials

- Consent form
- Influenza vaccine
- Normal saline
- Pneumococcal vaccine 23
- Infliximab (100 mg/vial)
- Inj soluble methyl prednisolone (125 mg)

METHODOLOGY

After taking Institutional Ethics Committee clearance, 20 patients were recruited based on inclusion and exclusion criteria. Individual informed consent was taken from the patients to participate in this study and patients were divided into two groups randomly. Before starting treatment, the following information like age, sex, duration of disease, initial VAS score for back pain, and BASFI were noted. Thereafter, all the patients were included in the rehabilitation program. The NSAIDs were given as and when required. Lifestyle modifications like 30-minute twice-daily prone lying, swimming, avoidance of body contact sports, daily 30-minute sun exposure, regular physiotherapy, and occupation therapy were advised. Energy conservation techniques and ergonomic modifications were also demonstrated.

For group I patients screening for infection, serology and routine blood tests was done and chest skiagram was obtained. Vaccination against Pneumococcus (23) and influenza was done. After pretreatment with injection soluble methyl prednisolone (125 mg), cetrizine, and paracetamol, injection infliximab (5 mg/kg body weight dissolved in 300 mL normal saline over 3 hours) was given intravenously on days 0, 14, and 42. The patients were examined and assessed at intervals of 2, 6, and 12 weeks using the parameters like VAS score for back pain and BASFI score. The data were analyzed by the standard statistical tools.

RESULTS AND ANALYSIS

Data were entered in Microsoft Excel. Standard statistical tests were applied to compare between the two groups. A p-value < 0.05 was considered statistically significant. Statistical version 6 (Tulsa, Oklahoma: StatSoft Inc., 2001) software was used for analysis of data. Summary statistics mean, median, minimum, maximum, standard deviation, and standard error were calculated for BASFI score, VAS for back pain at baseline, 2, 6, and 12 weeks. Changes from baseline to 2, 6, and 12 weeks as well as in between follow-ups were done for both the scores. All numerical variables are normally distributed by Kolmogorov–Smirnoff goodness-of-fit and well comparable based on age, sex, and baseline study parameters.

In group I, there were 10 male patients and group II comprised 9 male and 1 female patient (Table 1). All of the patients had axial involvement, but only two in each group were suffering from peripheral joint involvement. The mean age of patients was 32.00 ± 5.25 years for group I and 32.30 ± 5.62 years for group II (Table 2).

As per Table 2, descriptive statistics of numerical variables in group I showed progressive improvement in VAS for back pain in all the three follow-ups like week 2, 6, and 12, with values being 7.40 ± 1.17 at baseline to 3.40 ± 1.71 at last follow-up. Similar marked improvement pattern was also noted in BASFI in all follow-ups, at baseline being 7.54 ± 1.18 to 4.44 ± 1.51 at the last follow-up (Table 2).

As per Table 3, descriptive statistics of numerical variables in group II treated with conservative care showed improvement pattern in back pain VAS and BASFI significantly in the first two follow-ups, i.e., 2 weeks (6.30 ± 1.64 and 7.20 ± 1.25 respectively) and at 6 weeks(5.20 ± 1.55 and 6.34 ± 1.28 respectively) from baseline (7.10 ± 1.19

Table 1: Comparison of categorical variables between groups I and II

	Male	*Female*	*Total*
1 Row%	10 100%	00 00%	10
2 Row%	09 90.00%	01 10.00%	10
Total	19	1	20

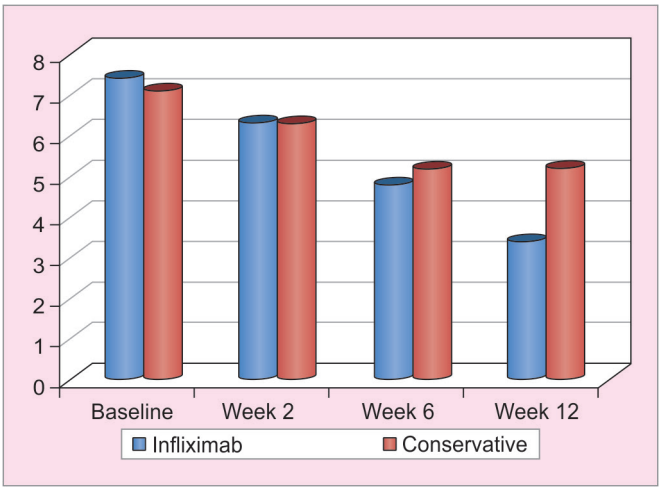
Fisher's exact test; 2-tailed p-value 1.000

Table 2: Descriptive statistics of numerical variables: Group I—infliximab (n = 10)

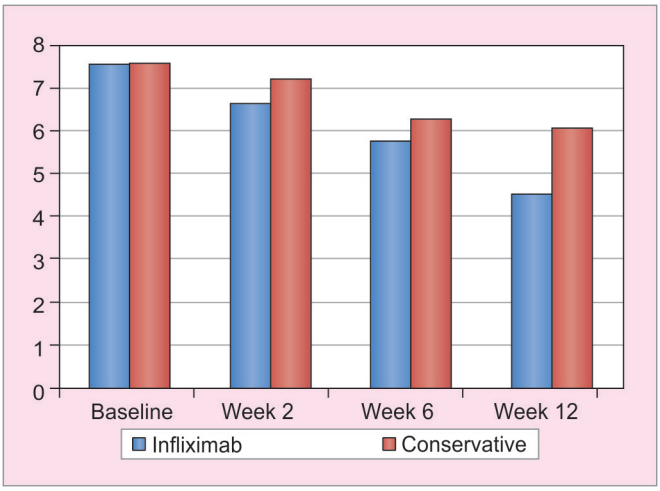
	Valid n	*Mean*	*Median*	*Minimum*	*Maximum*	*Standard deviation*
Age	10	32.00	31.50	24.00	41.00	5.249
VAS0	10	7.40	7.50	6.00	9.00	1.174
VAS1	10	6.30	6.50	4.00	8.00	1.418
VAS2	10	4.80	5.00	3.00	7.00	1.317
VAS3	10	3.40	3.50	1.00	6.00	1.713
BASFI0	10	7.54	7.75	5.60	9.10	1.179
BASFI1	10	6.66	6.70	4.80	8.60	1.272
BASFI2	10	5.76	5.60	4.00	8.20	1.323
BASFI3	10	4.44	4.05	2.80	7.10	1.509

Table 3: Descriptive statistics of numerical variables: Group II—conservative (n = 10)

	Valid n	*Mean*	*Median*	*Minimum*	*Maximum*	*Standard deviation*
Age	10	32.30	33.00	23.00	41.00	5.618
VAS0	10	7.10	7.00	5.00	9.00	1.197
VAS1	10	6.30	6.00	4.00	9.00	1.636
VAS2	10	5.20	5.50	3.00	8.00	1.549
VAS3	10	5.20	5.50	3.00	8.00	1.874
BASFI0	10	7.59	8.00	5.40	9.10	0.373
BASFI1	10	7.20	7.35	4.80	8.80	1.246
BASFI2	10	6.34	6.55	4.40	8.20	1.276
BASFI3	10	6.08	6.10	4.00	7.90	1.568



Graph 1: Intergroup comparison of back pain VAS



Graph 2: Intergroup comparison of BASFI score

and 7.59 ± 0.37 respectively). However, the improvement reached a plateau thereafter with no significant changes in final follow-up at 12 weeks from 6 weeks (Table 3).

Most importantly, comparison of numerical variables between groups I and II (Graph 1) by Student's unpaired t test concluded similar improvement patterns in back pain VAS in first two follow-ups among the groups and significant final outcome difference in last follow-up in favor of infliximab therapy group with p-value 0.0378.

Similar type of improvement pattern was noted in BASFI score among the groups with value at final follow-up (12 weeks) significantly surpassing control group with p-value 0.0284 (Graph 2).

DISCUSSION

This randomized controlled study conducted in the Department of Physical Medicine and Rehabilitation, Institute of Postgraduate Medical Education & Research and Seth Sukhlal Karnani Memorial Hospital, India, has shown significant improvement in VAS for back pain and BASFI score in AS patients due to infliximab therapy. As per the statistical analysis of the study, there was significant progressive improvement in VAS for back pain (mean change being 7.40 ± 1.174 to 3.40 ± 1.713 in infliximab group) and BASFI (mean change 7.54 ± 1.179 to 4.44 ± 1.509). Similar type of evidence was noted by Brandt et al[13] and Stone et al.[14] One Cochrane review of physiotherapeutic interventions and SpA therapy for patients with AS[15] showed importance of rehabilitation schedule including exercise therapy. Our study also noted improvement in back pain (mean change 7.10 ± 1.197 to 5.20 ± 1.874) and functional score (mean change 7.59 ± 0.373 to 6.08 ± 1.568) in control group treated with rehabilitation program alone in first two follow-ups, but became almost static after 6 weeks.

Intergroup comparison was done by Student's unpaired t test and showed significant outcome difference between both the groups, the most being in the last visit (6–12 weeks) in favor of infliximab receivers similar to the placebo-controlled trial done by van der Heijde et al[16] with the same parameters of back pain VAS and BASFI. Intragroup comparison showed sustained significant improvement in the infliximab therapy groups, the most being in the last visit (12 weeks). For control group, there is progressive persistent improvement in BASFI in all the follow-ups, but for back pain, VAS score improved only in the first two follow-ups.

However, like other studies, this study also has some limitations: Both the study parameters are subjective; no long-term follow-up of the patients was possible in the study period; and sample size was small. Extra-articular manifestations of AS were not accounted for.

CONCLUSION

- Infliximab therapy has shown definitive improvement in pain score of AS patients.
- Functional score of AS patients (BASFI) was significantly improved by infliximab therapy.
- Though conservative rehabilitation approach alone helps in significant improvement in back pain and functional status in patients with AS as shown by this study, it reaches a plateau at 12 weeks.
- Infliximab therapy along with rehabilitation program has shown persistent significant outcome difference in both back pain and functional status (BASFI) with p-value 0.0378 for back pain and 0.0284 for BASFI in comparison with conservative approach alone.

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