ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 05 | May - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECTIVENESS AND SAFETY PROFILE OF TNF ALPHA INHIBITORS IN REFRACTORY SPONDYLOARTHOPATHIES: AN OBSERVATIONAL STUDY.

Pharma

Dr. Pradipta Das MD, Assistant Professor (Pharmacology) (Jagannath Gupta Institute of Medical Sciences, West Bengal)

Dr. Suparna Chatterjee* MD, Professor, Department of Pharmacology, Institute of Postgraduate Medical Education & Research, 244B AJC Bose Road, Kolkata- 700020, West Bengal, India *Corresponding Author

Dr Nafisha Yasmin MD, Assistant Professor, Department of Pharmacology, Institute of Postgraduate Medical Education & Research, 244B AJC Bose Road, Kolkata- 700020, West Bengal, India

Dr. Alakendu Ghosh DNB, PhD, Professor, Department of Rheumatology, IPGMER, 244 AJC Bose Road Kolkata

ABSTRACT

Background About 40% patients of Ankylosing Spondylitis (AS) are refractory to first line therapy. This observational longitudinal study evaluated the effectiveness and safety of infliximab, a TNF alpha inhibitor in refractory AS in an Indian cohort. **Methods** Adult AS patients who were prescribed infliximab were enrolled. Clinical effectiveness was assessed by changes in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score from baseline to study end visit. Safety was assessed by observing the frequencies, type, severity and outcome of adverse drug reactions. **Results** 31 adult AS patients with mean age of 33.84 yr were enrolled. 67.74 % had >5 years disease duration. 29%, 42%, 26%, 3% received 1, 2, 3 and 4 doses of infliximab respectively. The BASDAI scores were significantly reduced from baseline values in all patients ($p<0.0001$) and 55 % of the patients achieved >50% reduction of the baseline BASDI score at 6 months. 35% of the cohort reported at least one ADR and none were serious in nature. **Conclusion** Infliximab is an effective, safe biologic and provides a statistically as well as clinically significant reduction in disease activity scores in refractory AS patients. A larger cohort size and longer follow up period shall provide further insights in this regard.

KEYWORDS

Ankylosing spondylitis, anti-TNFα agents, infliximab, effectiveness, safety, observational study, India

INTRODUCTION

Ankylosing spondylitis (AS) is a seronegative arthropathy with a global prevalence varying between 31.9, 23.8 and 16.7 per 10,000 population in North America, Europe and Asia respectively. [1] India too has a high disease burden reporting a mean AS prevalence per of 7 per 10,000 population (95% CI, 4-12).[1]The disease is associated with significant morbidity and affects the quality of life to a great extent.

The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) published recommendations for treatment of adults with AS in 2015.[2]Pharmacotherapy of AS entails not only the use of non-steroidal anti-inflammatory drugs (NSAID) directed towards symptomatic pain relief but also Disease modifying anti-rheumatic drugs (DMARD), which play an important role in controlling disease progression and prevention of deformities for those non responsive to conventional therapy or have high disease activity at presentation.[2] Biologic response modifiers, are a subset of DMARD and amongst them TNF alpha inhibitors are being increasingly used globally for AS.

The advent of these agents have revolutionized the management of refractory spondyloarthopathies.[3-7]Of the five anti-TNF agents- infliximab, adalimumab, golimumab, etanercept and cetrolizumab approved for various indications,[1]infliximab is most commonly used for refractory rheumatoid disorders.[4]Although effective they have their own share of adverse effects and need close monitoring which is indeed often challenging in countries like ours. Studies have shown that high costs, associated adverse effects and inadequate response to therapy are important determinants of therapy dis continuation[8]. Literature review on efficacy and safety profile of TNF alpha inhibitors in seronegative arthropathy patients is comparatively sparse especially from developing countries like India. To address this issue we conducted this observational study to evaluate the effectiveness and safety profile of infliximab, a TNF alpha inhibitor in refractory AS at a tertiary health care setting in India.

Methodology

This prospective observational study was initiated and spanned over a period of 18 months from February 2017. Participants attending the Rheumatology OPD of the hospital were screened for the study selection criteria. Diagnosed AS patients of age 18-60 years of either gender, who were advised TNF alpha inhibitor (infliximab) by their treating clinician (i.e therapeutic failure after adequate therapy with NSAID for at least 6 months) and willing to consent were enrolled provided they had not received any biologics previously. As per the institutional protocol, routinely all AS patients are screened for common contraindications of the drug before initiation of infliximab therap. As per standard treatment protocol, infliximab was prescribed at a dose of 5mg/kg by intravenous infusion and repeated at 2 months interval.

The drugs are provided free of cost by the institution and are administered under supervision at an inpatient setting. After overnight observation they were discharged and asked to come for follow up visits at 2 months intervals or earlier if needed. The number of doses of infliximab required for each enrolled subject was decided by the attending rheumatologist based on treatment guidelines.

Study data were collected at baseline and at 2, 4, and 6 months post anti-TNF alpha therapy follow up visits. Data for any unscheduled visit was also collected. Clinical effectiveness was assessed by the BASDAI score at baseline and at each of the study visits. The number of participants achieving at least 50% reduction of BASDI score or a ≥2 point reduction from baseline to 6 months was considered as the target effectiveness endpoint.

For safety assessment, solicited and unsolicited adverse drug reactions following therapy till the end of the study were recorded. Laboratory investigations as advised by the attending clinician were recorded.

Statistical analysis plan: formal sample size calculation was not undertaken as the study was not designed to test a hypothesis. Data with normal distribution were summarized as mean and standard dispersion (SD); non-parametric ones by median and interquartile range (IQR) and categorical variables as frequencies. Changes in BASDAI scores and CRP levels were computed using appropriate statistical test.

For statistical significance p value of <0.05 was considered statistically significant. For safety data analysis all subjects who had experienced at least one ADR were summarized using frequencies and percentage. Analysis was done using SPSS (Statistical Package for Social Sciences, version 16.0.1 of IBM, USA) and GraphPad Prism version 5.0 of GraphPad software, USA.

RESULTS

During the study period 31 subjects were enrolled as per the study selection criteria. Majority were male (92%) and were HLA B27 positive (96.77%). Their baseline demographic and disease characteristics are presented in Table 1. Of the 31 study participants, 9 (29%) received single dose of infliximab, 13 (42%) two doses, 8 (26%) three doses while only one received four doses of infliximab during the study period.

Table 1: Baseline and disease characteristics of the study population

Characteristic	Value n=31
Age (years) Mean ± SD Range	33.84 ± 10.2 18 - 55
Gender male n (%)	28: 3 (90.32%)
HLA B27 positive n (%)	30 (96.77)
Disease duration(y) n (%)	
• 1 – 5 years	8 (25.8)
• >5-10 years	13 (41.94)
• >10 years	10 (32.26)
H/O NSAID intake n (%)	
• < 1 year	1 (3.23)
• 2 – 5 years	16 (51.61)
• > 5 years	14 (45.16)
Comorbidities at baseline n (%)	
• Hypertension	3 (9.68)
• Diabetes mellitus	2 (6.45)
• Hypothyroidism	2 (6.45)
• Iron deficiency anemia	4 (12.9)
• Seizure disorder	2 (6.45)
• Beta thalassemia carrier	3 (9.68)

Table 2 depicts pooled analysis of BASDAI score in the study population receiving infliximab therapy. It is observed that there was a reduction of the median BASDI score from baseline to the subsequent visits. These changes were statistically significant (p= <0.00001) and was observed from the first follow up visit onwards and the trend continued till the study end visit.

Table 2: Changes in BASDI score in study population

	Baseline	2 month	4 month	6 month
Sample size	31	31	28	24
Mean(± SD)	6.05 ± 1.24	4.11 ± 1.31	3.42 ± 1.49	3.64 ± 1.84
Median(IQR)	5.6 (5-7)	4.6 (3.1- 5)*	3.1(2.2 -4.5) *#	3.1(2.1 -5.3) *

* Significant compared to baseline. (p<0.00001); # significant compared to 2 months [Analysis done by Friedmans ANOVA, post hoc test: Conover]

The changes in BASDAI score in AS patients over time following infliximab therapy are shown in figure 1.

	Baseline	2 month	4 month	6 month
Sample size	31	31	28	24
Mean(± SD)	6.05 ± 1.24	4.11 ± 1.31	3.42 ± 1.49	3.64 ± 1.84
Median(IQR)	5.6 (5-7)	4.6 (3.1- 5)*	3.1(2.2 - 4.5)*#	3.1(2.1- 5.3)*

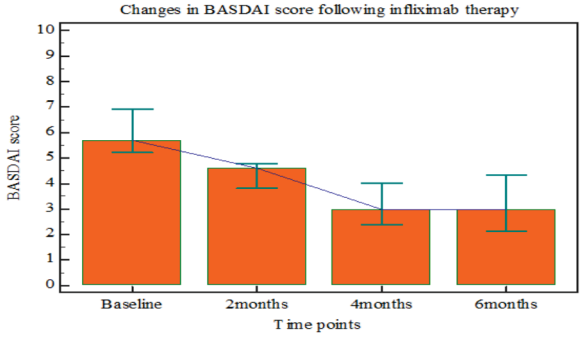

Figure 1: Changes in median BASDAI score following infliximab therapy in study population.

Error bars represent 95% CI of median.

A subgroup analysis of the BASDI changes based on the number of infliximab doses received is depicted in Table 3. A significant reduction was noted across all doses received by the study population from baseline to 6 months post treatment. Only one patient received four doses of infliximab having a baseline BASDAI score of 4.5 but the scores at 2 months, 4 months and at 6 months follow up were 4.75, 4.5 and 4.9 respectively indicating that his response was not optimal. For clinical effectiveness analysis, the proportion of participants achieving at least 50% reduction of BASDI scores or a ≥2 point reduction from baseline to 6 months was computed as the target effectiveness endpoint. 5 out of 9 participants who received single dose had attended the 6 month follow up visit and all participants (100%) had target achievement of clinical endpoint. Similarly 10 out of 13 participants, who received two doses, attended the 6 month follow up and 80% of them achieved target endpoints. All participants who received three doses came for the 6 month follow up and only 50% of them had target reduction of BASDI scores. For the single participant who received four doses of there was no reduction and further worsening of disease activity was noted as the BASDI score increased from 4.5 to 4.9 at 6 months.

The CRP levels showed inconsistent changes at different time points following infliximab therapy at different doses and not all patients could get the estimation done.

Table 3: Subgroup analysis of changes in BASDAI Score with number of infliximab doses received

Doses received (Infliximab)	BASDAI score at different time points	Range	Mean ± SD	Median (IQR)
Single dose	Baseline (n=9)	4.6 - 7	5.36 ± 0.71	5.2 4.95 – 5.60)
	2 month (n=9)	0.6 – 5.4	2.87 ± 1.31	3.0 (2.3 – 3.35)
	4 month (n=7)*	1.2 – 4.2	2.54 ± 1.02	2.6 (1.8 – 3.15)
	6 month (n=5)*	1.8 – 6.2	2.96 ± 1.88	2.0 (1.8 – 3.80)
	Friedman's Test (p= 0.00009)			
Two doses	Baseline (n=13)	4.6 – 9.2	6.43 ± 1.45	6.6 (5.0 – 7.45)
	2 month (n=13)	1.8 – 6.0	4.5 ± 1.12	4.8 (4.2 – 5.0)
	4 month(n=12)#	1.0 – 6.4	3.25 ± 1.59	2.7 (2.2 – 4.0)
	6 month (n=10)#	1.0 – 5.8	2.96 ± 1.29	2.8 (2.2 – 3.6)
	Friedman's Test (p=0.00003)			
Three doses	Baseline(n=8)	4.8 – 7.8	6.4 ± 1.03	6.4 (5.7 – 7.2)
	2 month(n=8)	3.8 – 5.8	4.8 ± 0.59	4.7 (4.6 – 5.1)
	4 month(n=8)	2.2 – 6.2	4.33 ± 1.33	4.6 (3.3 – 5.2)
	6 month(n=8)	1.6 – 7.4	4.76 ± 2.08	5.1 (3.15 – 6.3)
	Friedman's Test (p=0.022)			

* 2 patients were lost to follow up at 4th and 6thmonth respectively # 1 and 3 patients were lost to follow up at 4th and 6th month respectively [Data of the single patient who received 4 doses is not included in this analysis]

The nature, severity, outcome and causal relation of adverse events detected in the study population are depicted in Table 4. No adverse events were reported in majority of the cases (65%). Among the adverse drug reactions 7% were mild in nature, 72% were moderate and 21% adverse drug reactions were severe in nature. Majority of them resolved with symptomatic treatment except for one event of skin hypopigmentation which only showed partial resolution. None of the adverse events were serious in nature. All adverse drug reactions were also reported to the Pharmacovigilance program of India.

Table 4: Characteristics of adverse drug reactions in study population

	Number of ADR	Relatedness	Severity of ADR	Outcome
No reported ADR	20	Not applicable	Not applicable	
Nausea with or without vomiting	5	Yes	Moderate	relieved with symptomatic treatment
Anorexia	3	Yes	Severe	relieved with symptomatic treatment
Loose motion, Diarrhea	2	Yes	Moderate	relieved with symptomatic treatment

Constipation	1	Yes	Moderate	relieved with symptomatic treatment
Skin hypo-pigmentary changes	1	Yes	Moderate	Partially resolved
Transfusion reactions	1	Yes	Moderate	relieved with symptomatic treatment
Fever with Dysuria (UTI, not culture proven)	1	Yes	Mild	relieved with symptomatic treatment

ADR- Adverse Drug Reactions, UTI – Urinary Tract Infection

DISCUSSION

Ankylosing spondylitis (AS),a condition in the spondyloarthritis (SpA) family of diseases is characterized by sacroiliitis, enthesitis, and a marked propensity for sacroiliac joint and spinal fusion.[9]The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a traditional patient-reported outcome measure of disease activity in AS and is used routinely in clinical practice.[10-11]Treatment goals focus on reduction of symptoms, maintenance of spinal mobility and work ability while decreasing disease complications and functional limitations. For several decades, the mainstay of therapy included NSAIDs along with supportive physical therapy although a substantial proportion continues to have active disease. Traditional DMARDs including methotrexate and sulfasalazine have modest benefit in patients with relatively mild disease. Treatment of AS with biological agents, especially TNFα inhibitors has been a key therapeutic advance.[11]The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), Spondyloarthritis Research and Treatment Network (SPARTAN) 2015 reco mmendations, strongly advocates the use of TNF inhibitors in cases of active AS despite NSAID use.[2]Safety concerns of TNFα inhibitors is an important aspect to consider in therapy as serious adverse events include enhanced susceptibility for infectious diseases such as tuberculosis, invasive fungal infections, reactivation of hepatitis B virus apart from predictable and common adverse effects.[12]

In the present study, we evaluated the clinical effectiveness of infliximab in AS patients in terms of number of patients achieving 50% reduction or a ≥2 point reduction in BASDAI scores from baseline to 6 months. Over 80% patients receiving one and two doses and at least 50% patients receiving three doses of infliximab demonstrated significant clinical improvement at the end of 6 months. In our study comprising of thirty one patients, 55% (95% CI 37.7-70.9) demonstrated significant clinical improvement with infliximab at 6 months post treatment. (pooled data). Haibel *et al*[13]reported improvement in 66.3% of patients treated with multiple doses of infliximab at the end of 28 weeks. Glintborg *et al*[14] reported 63% patients of AS on TNFi therapy achieved clinical response at 6 months. Bosch *et al*[15] reported 40% patients achieved clinical improvement with golimumab or infliximab in a pragmatic cohort of AS patients at the end of 6 months. Our findings of clinical improvement in refractory AS patients on infliximab therapy corroborate with the results of studies from the Western countries. A study from western India by *Singhal* et al[16] reported significant reduction in mean BASDAI scores from baseline for all patients on infliximab or etanercept over 12 months of treatment. We observed statistically significant reductions in BASDAI scores from baseline to 6 months post initiation of therapy with single as well as multiple doses of infliximab.

Our study comprehensively evaluated the frequency and nature of adverse effects following infliximab therapy. 11 patients (35%) in our study patients experienced 14 adverse reactions which were mostly mild to moderate in intensity and abated with symptomatic treatment, excepting for three cases of anorexia which were severe. None of the adverse events encountered were serious in nature and only one subject required dose adjustment due to transfusion reactions. In the BioTRAC study by Rahman *et al*[17], total of 1153 AEs were reported by 175 (54.7%) patients, 96%being non-serious while 43 serious adverse events (SAEs) were reported for 26 (8.1%) patients. Haibel *et al*[13] reported almost 11.8% (n= 101) patients stopped therapy owing to adverse effects. Infliximab was generally well tolerated by AS patients in our study and both frequency as well as nature of adverse events encountered was relatively milder to what has been reported in these studies. Singhal *et al*[16]reported four out of twenty patients treated with infliximab developed mild adverse events with no SAEs. Ma *et al*[18] reported incidence of adverse events (RR = 1.22, 95% CI: 1.12-1.33) and injection-site reaction (RR = 2.93, 95% CI: 2.02-4.23) with TNF-α inhibitors in AS patients was significantly higher than that with placebo. However, a recent meta-analysis by Hou *et al*[19] reported that the overall serious adverse events (OR, 1.34; 95% CI, 0.87-2.05), the risk of serious infection events (OR, 1.59; 95% CI, 0.63-4.01) and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95-2.54) in ankylosing spondylitis patients treated with TNF inhibitors were not significantly different from those treated with placebo.

Though the ACR/SAA/SPARTAN 2015 recommendations strongly recommend the use of TNFi in AS patients with active disease despite therapy with NSAIDs, they do not recommend any particular TNFi to be preferred excepting concomitant inflammatory bowel disease or recurrent iritis in such patients.[2]Until specific treatment guidelines are available for guiding therapy with biologics in AS patients, it is imperative that treatment protocols be framed locally by institutions and continuous prospective surveillance be done on drug usage and adverse reaction patterns. To the best of our knowledge, our study presents outcome data on effectiveness and safety following treatment of refractory spondyloarthopathies with TNF alpha inhibitors for the first time from an eastern Indian perspective as data regarding such in Indian population is largely limited. We explored outcomes of infliximab therapy in AS patients in a pragmatic approach in a resource limited setting. Our study demonstrated significant clinical improvements in NSAID refractory AS patients following infliximab administration and the persistence of benefit at six months post treatment even in patients receiving single or two doses of the drug. We could not explore factors predicting treatment outcomes due to a relatively small sample size, nevertheless our study results are important considering cost of treatment with biologics in resource limited settings are a challenge to achieving large sample sizes in a limited timeframe. Being an observational one, our study had some limitations inherent to its design. The baseline data collected were based on review of past medical records which in some cases was not exhaustive. Secondly, the sample size of our study was dependent on the number of patients receiving infliximab treatment in our hospital setting. As our study cohort comprised of a relatively younger age group, a longer duration of follow up would have helped in generation of long term safety concerns and the results may not be generalizable for older age group suffering from refractory spondyloarthopathies. Safety of infliximab treatment was assessed with the incidence of physician and patient-reported adverse events at every follow-up which may have led to underestimated rates due to patient recall bias. Finally, this being an observational study the advice for undertaking laboratory and other imaging investigations were dependent on the standard hospital practice guidelines and not driven for our research outcome assessment.

CONCLUSION:

In the context of sparse data on outcomes of biologics therapy in spondyloarthropathies in Indian population, our study exhibits treatment with infliximab in refractory AS patients is fairly safe and reasonably effective in improvement of clinical outcomes and control of disease activity. Medical management of refractory spondy loarthropathy patients with TNF inhibitors having satisfactory efficacy and acceptable tolerability when initiated early is beneficial in terms of both clinical response and patient-reported outcomes. Long term follow up studies shall provide further insights about the impact of drugs in such patients. Future studies with larger sample size and data from well-maintained biologic treatment registries on a local or national level can generate robust data about clinical efficacy and safety and possible predictors of response to TNF inhibitors especially in Indian spondyloartropathy patients and help in the formulation of specific treatment guidelines for the same.

Conflicts of Interest:

None of the authors have any potential conflicts of interest to declare.

Acknowledgements:

We wish to acknowledge the faculty members and postdoctoral trainees of the Department of Rheumatology, IPGMER for their whole hearted support and assistance in conducting the study.

REFERENCES:

1. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology.2014;53(4):650.7.
2. Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and

Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheumatol. 2016;68(2):282-98.
3. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis and Ankylosing spondylitis:a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11-34.
4. Corbett M, Soares M, Jhuti G, Rice S, Spackman E, Sideris E et al. Tumor necrosis factor alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. Health Technol Assess. 2016; 20(9):11-34.
5. Van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P et al. Efficacy and safety of Infliximab in patients with ankylosing spondylitis: results of a randomized, placebo controlled trial (ASSERT). Arthritis Rheum.2005;52(2):582-91.
6. Antoni CE, Kvanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U et al. Sustained Benefits of Infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis:results from the Infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005;52(4):1227-36.
7. Van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BA, Braun J et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double blind, placebo-controlled trial. Arthritis Rheum. 2006;54(7):2136-46.
8. Kavanaugh A, Tutuncu Z, Catalan-Sanchez T. Update on anti-tumor necrosis factor therapy in the spondyloarthopathies including psoriatic arthritis. CurrOpinRheumatol. 2006;18(4):347-53.
9. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369(9570):1379- 90.
10. 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(12):2286-91.
11. Grainger R, Harrison AA. Infliximab in the treatment of ankylosing spondylitis. Biologics. 2007;1(2):163-71.
12. Elalouf O, Elkayam O. Long-term safety and efficacy of infliximab for the treatment of ankylosing spondylitis. Ther Clin Risk Manag. 2015;11:1719-26
13. Haibel H, Song IH, Rudwaleit M, Listing J, Hildemann S, Sieper J. Multicenter open-label study with infliximab in active ankylosing spondylitis over 28 weeks in daily practice. ClinExpRheumatol. 2008;26(2):247-52.
14. Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis. 2010;69(11):2002- 8.
15. Van den Bosch F, Flipo RM, Braun J, Vastesaeger N, Kachroo S, Govoni M. Clinical and quality of life improvements with golimumab or infliximab in a real-life ankylosing spondylitis population: the QUO-VADIS study. ClinExpRheumatol. 2019;37(2):199-207.
16. Singhal A, Bhakuni D, Marwaha V, Hande V, Bagga G. Biologics Use in Asian Indian Patients with Ankylosing Spondylitis: A Physician's Perspective.J Clin Diagn Res. 2016;10(7):OC 29-32.
17. Rahaman P, Choquette D, Bensen WG, Khraishi M, Chow A, Zummer M et al. Biologic Treatment Registry Across Canada(BioTRAC): a multicenter, prospective observational study of patients treated with infliximab for ankylosing spondylitis. BMJ Open.2016;6(4):e009661.
18. Ma Z, Liu X, Xu X, Jiang J, Zhou J, Wang J et al. Safety of tumor necrosis factor-alpha inhibitors for treatment of ankylosing spondylitis: A meta-analysis. Medicine (Baltimore). 2017 Jun;96(25):e7145.
19. Hou LQ, Jiang GX, Chen YF, Yang XM, Meng L, Xue M et al. The Comparative Safety of TNF Inhibitors in Ankylosing Spondylitis-a Meta-Analysis Update of 14 Randomized Controlled Trials. Clin Rev Allergy Immunol. 2018 Apr;54(2):234-243.