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Research Article

Biosimilar

A Multi-centre Study to Evaluate the Long-Term Efficacy and Safety of Biosimilar Infliximab (Infimab™) in Ankylosing Spondylitis in Real-world Clinical Settings - A perspective from Eastern India

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Introduction: Owing to dearth of data on infliximab biosimilars in Indian patients, a pan-India case database-based study with infliximab biosimilar BOW015 (Infimab™) was carried out to capture its efficacy and safety in real-world clinical settings in India. Here, we assessed its efficacy and safety in ankylosing spondylitis (AS) among patients in East India cohort. **Materials and methods:** Patients who were given BOW015 for other indications, prior innovator infliximab or other biologics were excluded from study. The primary variable was Ankylosing Spondylitis Disease Activity Scale (ASDAS) response defined as change of > 2 in ASDAS score from baseline by 4-6 months of follow-up. **Results:** The cohort consisted of 149 patients, predominantly male (69.8%), with a mean (±SD) age of 36.75 (±11.11) years and mean (±SD) body weight of 58.26 (±15.4) kgs. Of treated patients, 91 (61.1%) patients were administered four doses, 10 (6.7%) patients were administered three doses, 37 (24.8%) patients were administered two doses and 11 (7.4%) patients were administered only a single dose of BOW015. In final analysis set, 81 patients had data at baseline and 4th visit. Among 81 patients, 74 (91%) patients achieved major improvement, 5 (6%) patients achieved clinically important improvement and 2 (3%) were non-responders at 4th visit. **Conclusion:** Infimab™ (BOW015) showed significant improvement in ASDAS and BASDAI in patients with AS at end of 4-6 months of follow-up with its clinical benefits being apparent as early as first dose of BOW015.

Keywords: Biosimilar, Infliximab, Ankylosis Spondylitis, ASDAS, BASDAI, Real-World

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Introduction

Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory disease that typically develops in males mainly affecting the axial skeleton and the sacroiliac joints. [1-2]. AS is considered an inherited disease, as > 95% of the risk for its development relies on genes.(2) However, the HLA-B27 allele accounts for only ~20% of the genetic effect.[1]. The discovery of several inflammatory pathways led to the era of biological therapies. Tumour necrosis factor inhibitors (TNFs) were the first ones to be approved, but in the last few years, the interleukin-17 (IL-17)/IL-23 axis has gained relevance, culminating in the license of new biological disease-modifying antirheumatic drugs (bDMARDs) blocking IL-17.[3].

Biologics made a major transformation in the therapeutics of many chronic immune-mediated diseases.[4-5]. Although biosimilars usually have identical amino acid sequences to the reference product, there is a possibility of altered glycosylation due to their production in different cell lines. These structural changes can affect their pharmacology, pharmacodynamic (PD) effect, and immunogenicity.[6]. So, manufacturers need to provide evidence of similar efficacy and safety outcomes with a comprehensive immunogenicity assessment for European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approvals.[7]. Infliximab (IFX) is a chimeric monoclonal IgG1κ anti-TNF monoclonal antibody, effective in treating patients with chronic auto-immune inflammatory diseases such as rheumatoid arthritis (RA) and AS.[3-8]. BOW015 (Infimab™) has been developed as a biosimilar to reference IFX (rIFX, Remicade®). Studies comparing BOW015 to rIFX in the TG 197 human TNF transgenic mouse arthritis model demonstrated comparable pharmacokinetic (PK) profiles.[9]. Treatment of transgenic mice with either BOW015 or rIFX (3, 10, and 30 mg/kg) intraperitoneally twice weekly from week 3 to week 10 significantly inhibited the signs and symptoms of arthritis in a dose-dependent manner, with; corresponding weight gain. The first-in-human study of BOW015 compared the PK, safety, and immunogenicity of single IV doses of BOW015 and rIFX in healthy volunteers to establish bioequivalence and biosimilarity according to the guidelines established by FDA and EMA.[10-13]. Results from phase I and phase III Clinical trials have shown the 'bioequivalence' and clinical comparability' of BOW015 to IFX innovator, as measured by the American College of Rheumatology 20 (ACR 20) response in severe RA patients.[14]. Recently the bioequivalence of BOW015 to reference IFX innovator in healthy volunteers was established, based on single-dose pharmacokinetics, safety, and immunogenicity.[15]. Mumbai-based research demonstrated that biosimilar IFX was well-tolerated, and the majority of the RA patients achieved remission on a short-term and long-term basis.[16]. This study was performed to evaluate the long-term efficacy and safety of AS patients treated with biosimilar IFX in real-world clinical settings in India.

Materials and Methods

Duration and type of study: This was a prospective, multi-centre study conducted at 10 centres across East India among 149 patients with AS from April 2017- December 2018 (20 months).

Inclusion criteria: Male and female patients of all age groups, with an established diagnosis of AS, having 4-6 months of follow-up data during the last year, were included in the study. As per study protocol, patients who tested positive for latent tuberculosis were enrolled after two months of treatment according to standard protocol.

Exclusion criteria: Patients who were given BOW015 for other indications, prior innovator infliximab or other biologics were excluded. The study excluded patients who were either: Incapacitated, largely or wholly bedridden or confined to a wheelchair and who had little or no ability for self-care; were allergic to any of the excipients of infliximab or had a history of any clinically significant adverse reaction to murine or chimeric proteins (including but not limited to allergic reactions); had participated in any clinical study of an investigational product within the previous 3 months and had a history of any medical or psychiatric disorder.

Data collection procedure: The demographic and clinical characteristics of the AS patients, such as age, gender, weight, and extra-articular manifestations, such as enthesitis, uveitis, dactylitis, inflammatory back pain, and family history of spondyloarthropathy (SpA), HLA-B27 positivity status, CRP levels (in mg/L) were

Recorded at baseline. To monitor the disease activity, BASDAI (Bath AS Disease Activity Index) and ASDAS (AS Disease Activity Score) – ESR scores were recorded at baseline and every visit after therapy initiation. (Table 3).

Disease activity measurements: The BASDAI is composed of six questions (either scored on a numerical rating scale or a 10 cm visual analogue scale) that assess fatigue (1), spinal pain (2), peripheral joints (3), entheses (4), the intensity of morning stiffness (5) and duration of morning stiffness (6). The total BASDAI score is calculated by summing the first four questions and the average of the last two questions and by dividing the result by 5. The score ranges from 0 (no disease activity) to 10 (very active disease). A cut-off of 4 is frequently used to define active disease, but this cut-off level does not have a firm justification.[17-19]. The ASDAS is a data-driven index that combines three BASDAI-PRO- derived questions about spinal pain, peripheral joints and duration of morning stiffness, as well as the 'patient global assessment of disease activity, with either the CRP (ASDAS-CRP) or the erythrocyte sedimentation rate (ESR) (ASDAS-ESR) according to a weighted formula. The ASDAS-CRP is recommended by ASAS, both for use in clinical practice and clinical trials. The ASDAS has formally validated cut-off levels for disease activity states: an ASDAS value below 1.3 is considered an inactive disease, 1.3 or higher and lower than 2.1 low disease activity, between 2.1 and 3.5 high disease activity, and above 3.5 very high disease activity.[19-21]. (Figure 1)

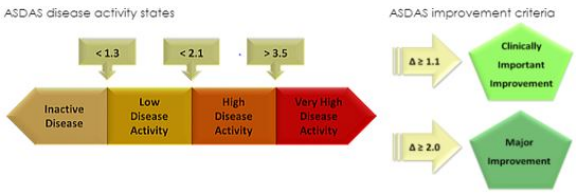


Figure 1: Categorization based on ASDAS

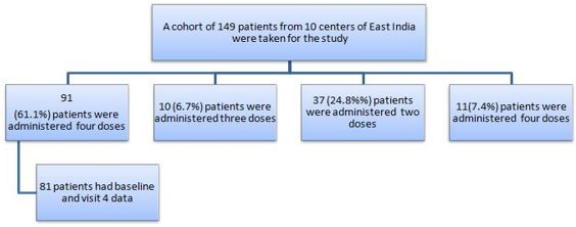


Figure 2: Flow chart of AS patients treated with biosimilar Infliximab (BOW015)

Efficacy and safety parameters: Efficacy of the BOW015 administered to AS patients depend on the proportion of patients achieving major clinical improvement: Change in ASDASCRP score > 2 from the baseline to 4th visit, change in BASDAI from the baseline to 4th visit, change in CRP/ESR values from the baseline to 4th visit. To evaluate the safety of biosimilar administered, a thorough clinical judgment and laboratory parameter will be ascertained at all visits as per the investigator's discretion.

Medical history, height and weight of the patients were recorded at baseline and end of study follow-up. A tuberculosis test was performed at the baseline and if the patient is positive for latent tuberculosis, he/she can be enrolled after two months of treatment according to standard protocol. Information on concomitant medications taken by the patients, ASDASCRP, BASDAI and ESR/CRP values, and adverse events were assessed at every infusion of the biosimilar IFX (BOW015).

Table 1: Schedule of assessment of various parameters recorded during the study duration

	Baseline	Post 1st dose Follow Up	Post 2nd dose Follow Up	Post 3rd dose Follow Up	Post 4th dose Follow Up	Post 5th dose Follow Up	Post 6th dose Follow Up	Week 54 Follow Up	End of study Follow Up
Verify Inclusion/Exclusion	X								
Medical History	X								X
Height	X								X
Weight	X								X
TB test	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
ASDASCRP	X	X	X	X	X	X	X	X	X
BASDAI	X	X	X	X	X	X	X	X	X
ESR and CRP	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X

Statistical Analysis: Analysis of primary and secondary outcome measures included patients who have a baseline and post-baseline data at the time point of interest (i.e., baseline and 54 weeks). Patients were classified into guideline-defined risk categories and the proportion of patients attaining treatment targets was assessed category-wise. Safety was analyzed in all patients receiving at least one dose of IFX. Data were analyzed using Statistical Package for the Social Science V22.

Results

The cohort consisted of 149 Ankylosing Spondylitis (AS) patients who had been prescribed IFX biosimilar BOW015 as per routine clinical practice.

The study population was predominantly male (69.8%), with a mean age of 36.75 (SD: 11.11) years and a mean body weight of 58.26 (SD:15.4) kgs.

Extra-articular manifestations seen in the AS patients at baseline were: Enthesitis (n=29, 19.5%), uveitis (n=3, 2%) and dactylitis (n=4, 2.7%).

In addition, inflammatory back pain (n=137, 91.9%) was common. Family history of SpA was found in 4% (n = 6) patients, HLA-B27 positivity in 89.9% (n=134) and elevated CRP at baseline in 84.6% patients (n=126).

At baseline, the mean ASDAS score was 7.9 (SD=1.43) and the mean BASDAI was 8.23 (SD= 1.80) (Table 2).

Table 2: Baseline characteristics of the cohort (n = 149)

Parameter	Values
Age (years), mean (SD)	36.75 (11.1)
Male, n/N (%)	104/149 (69.8)
Female, n/N (%)	45 (30.2)
Weight (kgs), mean (SD)	58.26 (15.4)
Extra-articular manifestations	
Enthesitis, n/N (%)	29/149 (19.5)
Uveitis, n/N (%)	3/149 (2)
Dactylitis, n/N (%)	4/149 (2.7)
Inflammatory back pain, n/N (%)	137/149 (91.9)
Family history of SpA present, n/N (%)	6/149 (4)
HLA-B27 positive, n/N (%)	134/149 (89.9)
Elevated CRP (mg/L), n/N (%)	126/149 (84.6)
ASDAS, mean (SD)	7.90 (1.43)
BASDAI, mean (SD)	8.23 (1.8)

SD-Standard deviation; ASDAS-Ankylosis Spondylosis Disease Activity Status; BASDAI-Bath Ankylosis Disease Activity Index; HLA-B27- Human Leukocyte Antigen-B27

Of the 149 AS patients treated with biosimilar IFX (BOW015), 91 (61.1%) patients were administered four doses, 10 (6.7%) patients were administered three doses, 37 (24.8%) Patients were administered two doses and 11 (7.4%) patients were administered a single dose.

In the final analysis set, 81 patients had baseline and visit 4 data (Fig 2).

The disease activity status of 81 patients who had baseline and visit 4 data were categorized based on the change in the ASDAS score into three categories as shown in Table 3.

Of the 81 patients, 74 (91%) patients achieved major improvement, 5 (6%) patients achieved clinically important improvement (as shown in Table 3) and 2 (3%) were non-responders at visit 4.

Table 3: Distribution of study participants patients based upon the disease activity status from baseline to visit 4 (n = 81)

Disease activity status at visit 4 based on ASDAS criteria	Frequency (%)
Major improvement	74 (91)
Clinically important improvement	5 (6)
Non-responders	2 (3)

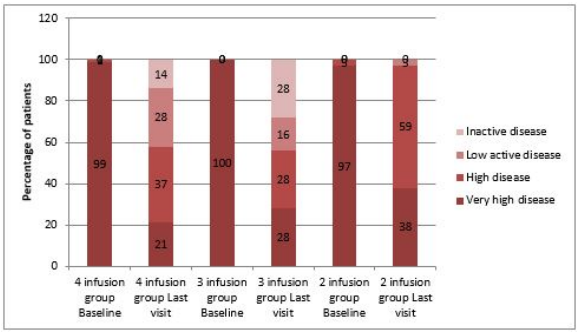
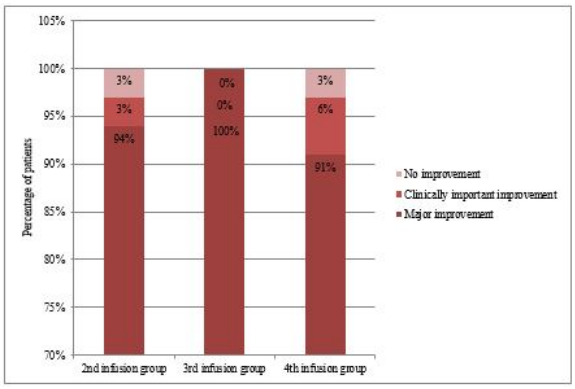


Figure 3: Cohort classification (n=149) according to AS disease activity

Based on the value of the end-line ASDAS score, the AS patients treated with BOW015 were classified as having very high disease activity, high disease activity, low disease activity and inactive disease (Fig 1).

The percentage of the patients having very high disease status had drastically decreased during the last visit in the 4-infusion group followed by the 3-infusion group and the 2- infusion group in that order, suggesting a dose-response relationship between the number of doses and the beneficial effect of the biosimilar.



ASDAS improvement criteria: Δ ASDAS≥2.0- Major improvement; Δ ASDAS≥1.1- Clinically important improvement

Figure 4: Percentage of patients achieving ASDAS response

Figure 4 shows the disease activity status based on ASDAS improvement criteria in patients at 2nd infusion, 3rd infusion and 4th infusion of BOW015.

The major improvement was seen in 94% patients of in the 2nd infusion group, 100% patients of in the 3rd infusion group and 91% patients of in the 4th infusion group.

A clinically important improvement was seen in 3% patients of in the 2nd infusion group and 6 % patients of in the 4th infusion group.

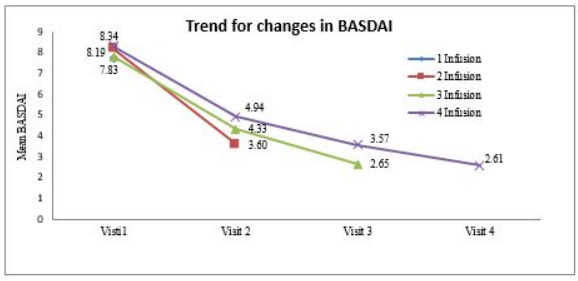


Figure 5: Cohort classification (n=81) based on mean BASDAI from baseline to visit 4

Figure 5 shows a decreasing trend of the mean BASDAI value from visits 1 to 4 which again demonstrates an improvement in the disease activity of the patients treated with BOW015. Again, a greater effect size is observed with an increasing number of infusions.

The IFX biosimilar was generally safe and well-tolerated. Still, 5 out of 149 patients (3.4%) reported infusion-related reactions.

Discussion

TNF-α-based biological response modifiers (IFX, Etanercept, Adalimumab, and Golimumab) are extremely reliable treatment options available at present for treating ASpA patients who do not respond to the first line of therapy which is the NSAIDs.[22]. Healthcare systems can make substantial savings if patients receiving reference biological products are switched to the more economical biosimilars and if biological-naive patients are started on biosimilars rather than reference products.[23].

AS is considered an inherited disease, as over 90% of the risk for its development relies on genes. However, the HLA-B*27 allele accounts for only 20% of the genetic effect.[1]. Other alleles, especially HLA-B, are thought to play an important role in the disease: HLA-B*13:02, HLA-B*40:01, HLA-B*47, and HLA-B*51 are some examples.[24]. The mechanism underlying the increased risk remains unclear; nevertheless, it is known that the presence of this gene is not related to the radiographic severity of the disease.[25]. In our study, of the 149 patients, 134/149 (89.9%) were HLA-B27 positive at baseline, establishing a strong clinico-molecular correlation in our patients. Active disease was defined by the presence of ESR ≥ 28 mm/h and CRP ≥ 20 mg/dl.[26]. In this study, 126/149 (84.6%) were recorded with elevated CRP levels at baseline.

In the analysis conducted by Lee et al, median BASDAI scores declined following treatment with an infliximab biosimilar (CT-P13) for patients overall and in naïve treatment groups, irrespective of the baseline dose group, while scores were maintained over time for switched patients.[27]. These findings are in concordance with previous reports of the effectiveness of infliximab treatment at doses lower than recommended doses for AS patients. In the one-year open-label extension, switching from reference infliximab to its biosimilar (CT-P13) was shown to be safe, with no adverse impact on efficacy. The approved maintenance regimen is 5 mg/kg infused once every six weeks or once every 6–8 weeks for AS patients.[28] To date, none of the studies has compared different biosimilars of Infliximab in AS conditions. The majority of the research has demonstrated that initiating infliximab treatment at low doses

(3 mg/kg) could be effective, but that treatment pattern amends would be required for a few patients. While dose escalation may be frequent for infliximab compared with other tumour necrosis factor inhibitors (TNFis) in AS patients, this could be demonstrated by the ease of adjusting intravenous doses of reference infliximab compared with the fixed doses inherent to the subcutaneous administration of other TNFis.[29-33]. A meta-analysis involving AS patients at week 12 (n=2,395) and week 24 (n=1,337), has demonstrated that there is no significant difference in the efficacy of infliximab-biosimilar and other biological drugs in terms of ASAS20 improvement; the results showed no significant differences in the safety of infliximab-biosimilar and biologicals either.[34]. Agrawal et al reported that BOW015 showed significant improvement in ASDASCRP and BASDAI in patients with AS during a six-month follow-up period and the clinical benefits were apparent as early as the first dose of BOW015.[35].

Limitations: The major limitation of our study is that we included a relatively small number of patients.

Conclusions

This study serves as first-hand, real-world evidence of the efficacy and safety of the IFX biosimilar (BOW015) in AS patients. Infimab™ (BOW015) showed significant improvement in ASDAS and BASDAI in patients with AS at the end of 4-6 months of follow up and the clinical benefits were apparent as early as the first dose of BOW015. Its results shall serve as a guide to strengthen the treatment choices for Indian physicians treating AS in their clinical practice settings.

Highlights: This study has helped bridge the data gap with respect to efficacy and safety of biosimilar of IFX, viz. BOW015 in AS patients from eastern India by demonstrating the efficacy and safety of the biosimilar IFX in improving disease activity in terms of ASDAS, BASDAI and ESR/CRP value from baseline to 54 weeks.

Author contribution: Pradip Kumar Sarma: Concept and design manuscript review; Sukumar Mukherjee: Literature search and data contribution; R N Sarkar: Experimental studies; Santosh Kumar Mandal: Data acquisition and analysis, Pradeepta Patra: Data acquisition and analysis;

Tanoy Bose: Manuscript preparation; Ajit Surin: Literature search; Santa Naorem: Literature search; Kaushik Basu: Manuscript editing; J. R. Parida: Statistical analysis;

CT Arunachalam: Data acquisition

Abbreviations

AS- Ankylosing Spondylitis

ASDAS- Ankylosing Spondylitis Disease Activity Score

BASDAI- Bath Ankylosing Spondylosis Disease Activity Index

RA- Rheumatoid arthritis

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Reference

01. Chen B, Li J, He C, Li D, Tong W, Zou Y, et al. Role of HLA-B27 in the pathogenesis of ankylosing spondylitis (Review). Mol Med Rep. 2017 Apr;15(4):1943-1951. *doi: 10.3892/mmr.2017.6248 [Crossref][PubMed] [Google Scholar]*

02. Reveille JD. The genetic basis of ankylosing spondylitis. Curr Opin Rheumatol. 2006 Jul;18(4):332-41. *doi: 10.1097/01.bor.0000231899.81677.04 [Crossref] [PubMed][Google Scholar]*

03. Garcia-Montoya L, Gul H, Emery P. Recent advances in ankylosing spondylitis: understanding the disease and management. F1000Res. 2018 Sep 21;7:F1000 Faculty Rev-1512. *doi: 10.12688/f1000research.14956.1 [Crossref] [PubMed][Google Scholar]*

04. Crommelin DJ, Storm G, Verrijk R, de Leede L, Jiskoot W, Hennink WE. Shifting paradigms: biopharmaceuticals versus low molecular weight drugs. Int J Pharm. 2003 Nov 6;266(1-2):3-16. *doi: 10.1016/s0378-5173(03)00376-4 [Crossref] [PubMed][Google Scholar]*

05. Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF. How cytokine networks fuel inflammation: Toward a cytokine-based disease taxonomy. Nat Med. 2013 Jul;19(7):822-4. *doi: 10.1038/nm.3260 [Crossref][PubMed][Google Scholar]*

06. Cortes A, Pulit SL, Leo PJ, Pointon JJ, Robinson PC, Weisman MH, et al. Major histocompatibility complex associations of ankylosing spondylitis are complex and involve further epistasis with ERAP1. Nat Commun. 2015 May 21;6:7146. *doi: 10.1038/ncomms8146 [Crossref][PubMed][Google Scholar]*

07. Jacobs I, Petersel D, Isakov L, Lula S, Lea Sewell K. Biosimilars for the Treatment of Chronic Inflammatory Diseases: A Systematic Review of Published Evidence. BioDrugs. 2016 Dec;30(6):525-570. *doi: 10.1007/s40259-016-0201-6 [Crossref] [PubMed][Google Scholar]*

08. Smolen JS, Emery P. Infliximab: 12 years of experience. Arthritis Res Ther. 2011 May 25;13 Suppl 1(Suppl 1):S2. *doi: 10.1186/1478-6354-13-S1-S2 [Crossref][PubMed][Google Scholar]*

09. Keffer J, Probert L, Cazlaris H, Georgopoulos S, Kaslaris E, Kioussis D, et al. Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis. EMBO J. 1991 Dec;10(13):4025-31. *doi: 10.1002/j.1460-2075.1991.tb04978.x [Crossref][PubMed][Google Scholar]*

10. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Statistical approaches to establishing bioequivalence: Guidance for industry. Rockville, MD, USA, 2001. http://www. *fda.gov/downloads/Drugs/Guidances/ucm070244.pdf (accessed September 2015) [Crossref][PubMed] [Google Scholar]*

11. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Scientific considerations in demonstrating biosimilarity to a reference product: Guidance for industry. Rockville, MD, USA, 2015. http://www. *fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf(accessed September 2015) [Crossref][PubMed][Google Scholar]*

12. Committee for Medicinal Products for Human Use. "European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) guideline on the evaluation of anticancer Medicinal products in man. " London, UK: European Medicines Agency (2006). . *[Crossref][PubMed] [Google Scholar]*

13. EMA. European Medicines Agency–Committee for Medicinal Products for Human Use (CHMP). Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product. EMA/CHMP/806058/2009/Rev. *02, February 2013." (2013) [Crossref][PubMed][Google Scholar]*

14. GaBI Online - Generics and Biosimilars Initiative. Positive phase III data for Epirus infliximab biosimilar [www. gabionline. net]. *Mol, Belgium: Pro Pharma Communications International; [cited 2014 Oct 3]. Available from: www.gabionline.net/Biosimilars/Research/Positive-phase-III-data-for-Epirusinfliximab - biosimilar. Accessed on July 01, 2019 [Crossref][PubMed] [Google Scholar]*

15. . . gabionline. net]. *Mol, Belgium: Pro Pharma Communications International; [cited 2014 Oct 3]. Available from: www.gabionline.net/Biosimilars/Research/Positive-phase-III-data-for-Epirusinfliximab - biosimilar. Accessed on July 01, 2019 [Crossref][PubMed] [Google Scholar] [Crossref][PubMed][Google Scholar]*

16. Lambert J, Wyand M, Lassen C, Shneyer L, Thomson E, Knight A, et al. Bioavailability, safety and immunogenicity of biosimilar infliximab (BOW015) compared to reference infliximab. Int J Clin Pharmacol Ther. 2016 Apr;54(4):315-22. *doi: 10.5414/CP202530 [Crossref][PubMed][Google Scholar]*

17. Amin SN, Kapadia A, Shamil M. Short-term and long-term outcomes of biosimilar infliximab (BOW015) treatment in rheumatoid arthritis- A single-centre retrospective study. ABS312. Int J Rheumat Dis. *2017;20(1):17-131 [Crossref] [PubMed][Google Scholar]*

18. 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 Dec;21(12):2286-91. *[Crossref] [PubMed][Google Scholar]*

19. Pham T, Landewé R, van der Linden S, Dougados M, Sieper J, Braun J,

Et al. An international study on starting tumour necrosis factor-blocking agents in ankylosing spondylitis. Ann Rheum Dis. 2006 Dec;65(12):1620-5. *doi: 10.1136/ard.2005.042630 [Crossref][PubMed][Google Scholar]*

20. Landewé R, van Tubergen A. Clinical Tools to Assess and Monitor Spondyloarthritis. Curr Rheumatol Rep. 2015 Jul;17(7):47. *doi: 10.1007/s11926-015-0522-3 [Crossref][PubMed] [Google Scholar]*

21. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Assessment of SpondyloArthritis international Society. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. *2011 Jan;70(1):47-53. doi: 10.1136/ard.2010.138594 [Crossref][PubMed] [Google Scholar]*

22. Machado PM, Landewé R, Heijde DV; Assessment of SpondyloArthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis. 2018 Oct;77(10):1539-1540. *doi: 10.1136/annrheumdis-2018-213184 [Crossref] [PubMed][Google Scholar]*

23. Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Ther Adv Musculoskelet Dis. 2013 Feb;5(1):45-54. doi: 10. *1177/1759720X12468658 [Crossref][PubMed] [Google Scholar]*

24. Gulácsi L, Brodszky V, Baji P, Kim H, Kim SY, Cho YY, et al. Biosimilars for the management of rheumatoid arthritis: economic considerations. Expert Rev Clin Immunol. 2015;11 Suppl 1:S43-52. *doi: 10.1586/1744666X.2015.1090313 [Crossref] [PubMed][Google Scholar]*

25. Rubin LA, Amos CI, Wade JA, Martin JR, Bale SJ, Little AH, et al. Investigating the genetic basis for ankylosing spondylitis. Linkage studies with the major histocompatibility complex region. Arthritis Rheum. *1994 Aug;37(8):1212-20. doi: 10.1002/art.1780370816 [Crossref][PubMed] [Google Scholar]*

26. Díaz-Peña R, Vidal-Castiñeira JR, López-Vázquez A, López-Larrea C. HLA-B*40:01 Is Associated with Ankylosing Spondylitis in HLA-B27-positive Populations. J Rheumatol. 2016 Jun;43(6):1255-6. *Doi: 10.3899/jrheum.151096 [Crossref][PubMed] [Google Scholar]*

27. Ezard C, Kumari R, Willott R, Butt S, Gadsby K, Deighton C. What is meant by active disease in the NICE recommendation on use of combination therapy in early RA? Rheumatology (Oxford). 2012 May;51(5):947-8. doi: 10. *1093/rheumatology/ker513 [Crossref][PubMed] [Google Scholar]*

28. Lee SS, Kim TH, Park W, Song YW, Suh CH, Kim SK, et al. Impact of Infliximab Biosimilar CT-P13 Dose and Infusion Interval on Real-World Drug Survival and Effectiveness in Patients with Ankylosing Spondylitis. J Clin Med. 2021 Oct 1;10(19):4568. *doi: 10.3390/jcm10194568 [Crossref][PubMed][Google Scholar]*

29. Park W, Yoo DH, Miranda P, Brzosko M, Wiland P, Gutierrez-Ureña S, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017 Feb;76(2):346-354. *doi: 10.1136/annrheumdis-2015-208783 [Crossref][PubMed][Google Scholar]*

30. Maksymowych WP, Jhangri GS, Lambert RG, Mallon C, Buenviaje H, Pedrycz E, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. J Rheumatol. 2002 May;29(5):959-65. *[Crossref] [PubMed][Google Scholar]*

31. Maksymowych WP, Salonen D, Inman RD, Rahman P, Lambert RG; CANDLE Study Group. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. J Rheumatol. 2010 Aug 1;37(8):1728-34. *doi: 10.3899/jrheum.091043 [Crossref][PubMed] [Google Scholar]*

32. Cherouvim EP, Zintzaras E, Boki KA, Moutsopoulos HM, Manoussakis MN. Infliximab Therapy for Patients With Active and Refractory Spondyloarthropathies at the Dose of 3 mg/kg: A 20-Month Open Treatment. J Clin Rheumatol. 2004 Aug;10(4):162-8. *doi: 10.1097/01.rhu.0000135551.47780 [Crossref] [PubMed][Google Scholar]*

33. Tenga G, Goëb V, Lequerré

T, Bacquet-Deschryver H, Daragon A, Pouplin S, et al. A 3 mg/kg starting dose of infliximab in active spondyloarthritis resistant to conventional treatments is efficient, safe and lowers costs. Joint Bone Spine. 2011 Jan;78(1):50-5. *doi: 10.1016/j.jbspin.2010.04.017 [Crossref][PubMed] [Google Scholar]*

34. Kim TH, Lee SS, Park W, Song YW, Suh CH, Kim S, et al. A 5-year Retrospective Analysis of Drug Survival, Safety, and Effectiveness of the Infliximab Biosimilar CT-P13 in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. Clin Drug Investig. 2020 Jun;40(6):541-553. *doi: 10.1007/s40261-020-00907-5 [Crossref][PubMed] [Google Scholar]*

35. Baji P, Péntek M, Szántó S, Géher P, Gulácsi L, Balogh O, et al. Comparative efficacy and safety of biosimilar infliximab and other biological treatments in ankylosing spondylitis: systematic literature review and meta-analysis. Eur J Health Econ. 2014 May;15 Suppl 1(Suppl 1):S45-52. *doi: 10.1007/s10198-014-0593-5 [Crossref][PubMed] [Google Scholar]*

36. Agrawal, I. , et al. AB0690 Clinical experience with infliximab biosimilar (BOW015) in ankylosing spondylitis-efficacy and safety analysis from an indian perspective. " (2017): 1295-1295. *[Crossref] [PubMed][Google Scholar]*