

Overwhelming response to tumor necrosis factor- α inhibitor infliximab “innovator” versus adalimumab “bio-similar” in a previously therapy naive adult: A case report

Kanishk Yadav¹, Sachin Kuchya², Akshata Kalyani³

From ¹Resident, ²Head, ³Senior Resident, Department of Pharmacology, NSCB Medical College and Hospital, Jabalpur, Madhya Pradesh, India

ABSTRACT

Therapeutic options for the patient with spondyloarthritis (SpA) are limited. The pharmacotherapy for SpA comprises immunomodulator/suppressive drugs. In this case report, we describe the case of a 29-year-old postgraduate resident in medicine who was diagnosed with SpA and was managed by a combination of various disease-modifying drugs such as methotrexate and sulfasalazine, and immunomodulators such as systemic corticosteroids and tumor necrosis factor (TNF)- α inhibitors. After a series of therapeutic trials with them, the chimeric TNF blocker infliximab led to significant clinical improvement in symptoms and reduction in disease activity.

Key words: Spondyloarthritis, Tumor necrosis factor- α inhibitor, Infliximab, Adalimumab

Spondyloarthritis (SpA) describes a group of interrelated rheumatic conditions comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis/spondylitis with inflammatory bowel disease (IBD), and reactive arthritis. At present, anti-tumor necrosis factors (TNF) agents are the most promising therapy option when it comes to disease remission and outcome rates [1]. The concept of blocking a single pro-inflammatory cytokine such as TNF- α could restore homeostasis of a complex network and ameliorate signs and symptoms of chronic inflammatory diseases was a real breakthrough in medical practice. TNF- α inhibitors are monoclonal antibodies targeted toward both soluble (solTNF) and transmembrane forms of TNF (tmTNF) factors [2,3]. The TNF/TNF receptor (TNFR) superfamilies play central roles in adaptive or antigen-directed immunity and also coordinate the social context of cells that enables lymphocytes to maximally respond to pathogens. They also play an important role in acute inflammation and their secretion can be induced by toll-like receptors, lipopolysaccharide, bacterial DNA, and other pro-inflammatory factors. If left unchecked, they can lead to chronic inflammation, generalized wasting, and in high levels, septic shock. TNF- α inhibitors downregulate the production of a large range of inflammatory cytokines/chemokine, including interleukin (IL)-6, IL-1 β , IL-8, and monocyte chemoattractant protein-1 (MCP-1) [4,5]. Given the complexity of the cellular pathways involved, the molecular mechanism of the action of anti-TNF agents is still not fully elucidated.

CASE REPORT

A 29-year-old gentleman, a postgraduate resident, presented in the orthopedic OPD with complaints of the left-sided lower back and hip pain along with swelling of the left knee joint and morning stiffness in the involved joints for 2 weeks. There was a positive history of one episode of acute left eye uveitis in 2016. No other comorbidities were present. In family history, the patient's mother was positive for rheumatoid arthritis (RA) factor.

On general examination, the patient was well built, well-oriented, and conscious with adequate nutrition status and his vitals on presentation were normal. Local examination using the sacroiliac compression test and Gaenslen's test revealed pain and reduced range of motion (ROM) over the left sacroiliac joint and painless swelling of the left knee.

On radiological examination with contrast magnetic resonance imaging (MRI), lumbosacral spine, pelvis, and left-sided acute sacroiliitis were revealed. On clinical correlation, pathological findings revealed that the patient is HLA-B27 positive along with significantly raised values of both inflammatory markers, C-reactive protein, and erythrocyte sedimentation rate (ESR) (Table 1 and Fig. 1), giving an AS Disease Activity Score (ASDAS) of 5.5 on T-28 (Table 1 and Fig. 2). Based on these investigations, a final diagnosis of SpA was made taking the clinical, radiological, and pathological findings into account. Since the author himself is the case, written consent was not deemed necessary.

Correspondence to: Dr. Kanishk Yadav, HIG/C23, Maharana Pratap Ward, Sai Colony Road, Dhanvantri Nagar, Jabalpur - 482 007, Madhya Pradesh, India. E-mail: kanishk2619@gmail.com

© 2022 Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC-ND 4.0).


Access this article online	
Received - 08 February 2022 Initial Review - 18 February 2022 Accepted - 07 March 2022	Quick Response code 
DOI: 10.32677/ijcr.v8i3.3317	

Table 1: The values of inflammatory markers and global disease scores

Date	Days since symptom onset	Inflammatory markers		Global disease scores*	
		CRP mg/L	ESR mm/hr	BASDAI [9]	ASDAS [8]
October 11, 2020	T-0	5.2	N/A	4.6	3.76
November 7, 2020	T-28	77.2	18		
November 24, 2020	T-45	142	70		
November 30, 2020	T-51	15	62		
December 7, 2020	T-58	31.1	24	8.8	6.32
December 30, 2020	T-81	149.6	50		
February 12, 2021	T-122	143.1	120		
March 15, 2021	T-154	1.3	38	3.2	2.39
April 7, 2021	T-178	1.0	10		
May 30, 2021	T-231	2.4	N/A	1.4	1
August 1, 2021	T-294	1.1	15	0.9	0.87

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score

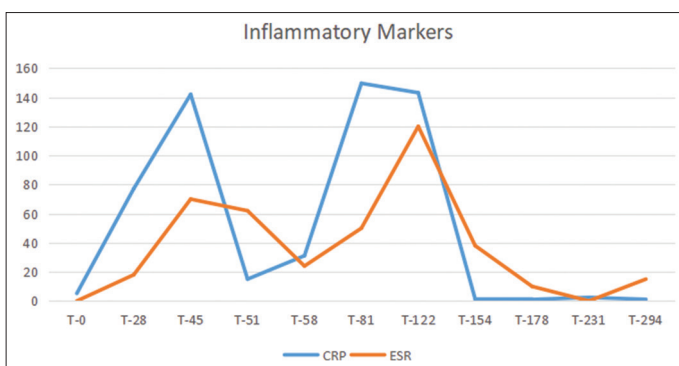


Fig. 1: Blood inflammatory marker values of the case during the observed time period

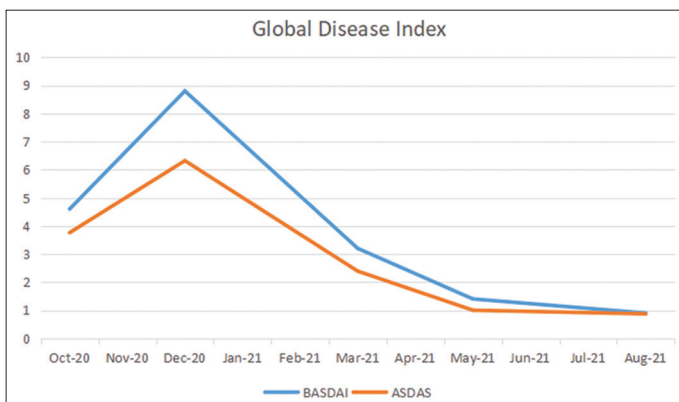


Fig. 2: The disease severity using BASDAI and ASDAS scores

The patient was advised first-line disease-modifying anti-rheumatoid drugs (DMARDs), NSAIDs (Tablet Intagesic-MR) (Chlorzoxazone – 250 mg+Diclofenac – 50 mg+Paracetamol – 325 mg), oral/I.V corticosteroids (Tablet Medrol [methylprednisolone – 16 mg] in a tapering manner for 21 days), IV dexamethasone – 4 mg for 5 days, and sulfasalazine (Tablet Saaz – 500 mg). However, in spite of 40 days of treatment, remission was not achieved rather progression of symptoms and additional involvement of other major joints such as the left shoulder joint and C7-T1 intervertebral joint was noted. Painful swelling of bilateral ankle joints, the right

knee joint, and increased severity of morning stiffness with a steep increase in inflammatory marker values (ASDAS 6) on T-43 were observed. The case was then referred to rheumatic disease OPD.

Following rheumatology consultation, methotrexate (15 mg/week) for 4 weeks was added to the current line of management but did not lead to either symptomatic or clinical improvement. There was further worsening of symptoms along with daily evening moderate grade fever and abdominal cramps at T-70 (ASDAS 7.7). Considering the patients declining physical and mental state, S/c adalimumab biosimilar (Brand name Exemptia) (40 mg every 2 weeks) for 10 weeks was initiated as add-on to weekly methotrexate. Monitoring of liver and kidney function was done. Primary failure to adalimumab was determined with no significant clinical improvement or pathological response with persisting high inflammatory marker values (ASDAS score 6.3) after the seventh dose at T-142 and the patient was shifted to other TNF- α inhibitor, intravenous infliximab (Brand name Remicade) an “Innovator” molecule (5 mg/Kg). Fig. 3 illustrates the timeline of progressive therapeutic management.

An overwhelming response was evident within 24 h after the administration of the first dose of infliximab, clinically with symptomatic reduction of pain, swelling, and morning stiffness in all the involved joints. Patient showed rapid improvement with complete subsidence of fever and recovery from gastric symptoms followed by a steep reduction in inflammatory marker values to almost normal with subsequent reduction of disease activity score ASDAS to 0.9 at T-160. Pertaining to the overwhelming response to the first dose, the follow-up doses were planned consecutively every 2 months with the same dose of (5 mg/kg) in addition to 10 mg weekly S/c methotrexate, along with monthly monitoring of renal and liver function tests. The patient disease activity score gradually improved to ASDAS 1.2 at T-220 days. The follow-up is being pursued actively. Table 2 and Fig. 4 describe additional data about complete blood counts during the course of treatment.

Table 2: Illustrating complete blood picture during the course of active disease

Date	Time interval	Hb g/dl	S. creat mg/dl	ALT IU/L	AST IU/L	Lymphocytes %	PLT /c.mm	WBC /c.mm
November 7, 2020	T-28	13.2	0.8	14.7	10.2	10	133,000	9800
November 24, 2020	T-45	13.4	NA	NA	NA	27	311,000	8700
November 30, 2020	T-51	12.4	NA	NA	NA	13	494,000	20,500
December 7, 2020	T-58	12.8	NA	NA	NA	18	396,000	14,900
January 18, 2021	T-100	10.3	0.7	NA	NA	32	321,000	9300
February 12, 2021	T-122	9.9	0.8	19.3	14.88	15	376,000	12,000
March 15, 2021	T-154	10.8	0.9	48.2	23.2	38	254,000	6500
April 7, 2021	T-178	12.9	0.8	122	50	40.9	228,000	5800
May 30, 2021	T-231	13.9	0.7	34	23	47	180,000	5800
August 1, 2021	T-294	14	0.8	31	21	45.3	2,090,000	49,000

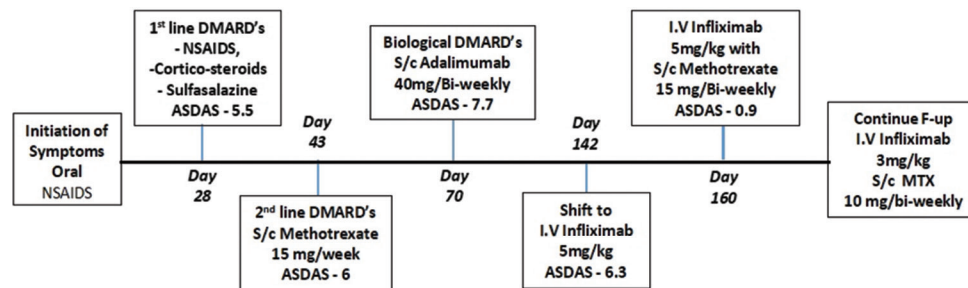


Fig. 3: Timeline of therapeutic management plan

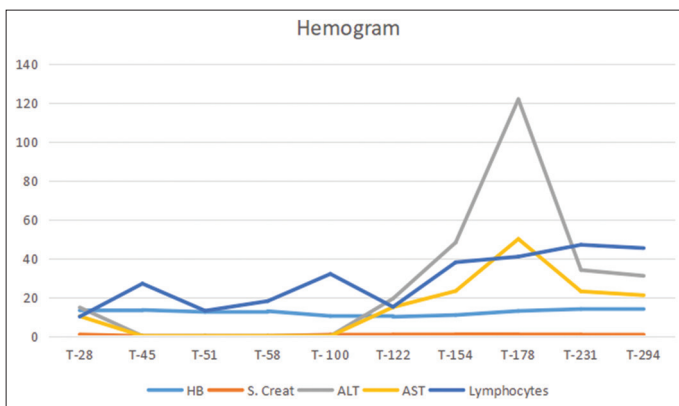


Fig. 4: The gradual changes in the blood count picture of the case during observed time period

DISCUSSION

At present, there are five TNF inhibitors approved for the treatment of various autoimmune diseases: Etanercept, infliximab, adalimumab, certolizumab, and golimumab and their biosimilars. All the inhibitors competitively inhibit the binding of TNF to its receptors. However, they differ in both the pharmacokinetic and pharmacodynamic properties, leading to significant differences in their clinical efficacy and indications [6]. A biosimilar is a biologic product that is highly similar to and has no clinically meaningful differences from an approved innovator. They are synthesized through chemical processes rather than generated in living systems, are considered bioequivalent to and, therefore, in most cases, automatically substitutable for their innovator/originator molecule. There are also notable differences between the approval, uses, and interchangeability of biosimilars and their originator molecules

between the US and other countries [7]. The observed heterogeneity in the treatment responsiveness may also be associated with genetic factors. Namely, different polymorphic variants of the TNF gene have recently been linked to autoimmune diseases [5,6].

Adalimumab is a humanized bivalent mouse IgG1 monoclonal antibody. It was approved by the FDA in 2002 for the treatment of RA, followed by the approval for the treatment of PsA, AS, juvenile idiopathic arthritis (JIA), and Crohn's disease (CD), as well as, uveitis. It binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with both TNFR1 and TNFR2 receptors. Its approved biosimilars in India are Adfrar and Exemptia; infliximab is a chimeric bivalent IgG1 human murine protein containing about 25% mouse-derived amino acids. It binds with high affinity to both soluble and tmTNF, but not to lymphotoxin- α (TNF- β). It also has an approved biosimilar in India named Infimab; infliximab was initially FDA approved for the therapy of CD in 1998 and later also for RA. It was further approved for the treatment of AS, PsA, CD, and PS. Other approved biologic molecules, namely, Etanercept a fusion protein, was permitted by FDA in 1998 for the treatment of JIA and PsA, RA, PS, and AS a while more potent and efficacious molecules such as certolizumab and golimumab are also humanized monoclonal antibodies to TNF- α . Both are widely used for the therapy against infarct-related artery occlusion, AS, IBD, and PsA. Table 3 shows the comparative differences between the two monoclonal antibodies infliximab and adalimumab [8-11].

Unfortunately, the therapeutic response against SpA shows large interindividual variability independently of their target or molecular nature. This heterogeneity is observed with all the anti-rheumatic drugs including the commonly used TNF- α inhibitors.

Table 3: Comparison of pharmacological properties of adalimumab and infliximab [9-12]

Adalimumab (ADA)	Infliximab (IFX)
Fully humanized bivalent monoclonal antibody	Chimeric bivalent monoclonal antibody
High affinity and specificity for soluble TNF- α and blocks its interaction with P55 and P75.	Affinity to both soluble and transmembrane TNF- α and disrupts the pro-inflammatory cascade signaling
Induces lysis of TNF- α expressing cells in the presence of complement	Attenuates the production of tissue degrading enzymes synthesized by synoviocytes and chondrocytes.
Potential biomarkers of response to ADA include only "C3" in the complement pathway	Potential biomarkers of response to IFX were enriched in apolipoprotein members of the complement pathway and acute-phase reactants.
Mean steady-state through concentrations of approximately 5 mcg/ml were observed	Median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/ml

This means that about a third of the patients starting treatment with DMARD will not respond and will require a change to a different one [5]. Differences in the pharmacodynamic characteristics of ADA and IFX being that ADA has a demonstrated high affinity and specificity only for soluble TNF- α receptor blocking its interaction with membrane receptors p55 and p75 inducing lysis of TNF- α expressing cells in presence of complement, whereas, IFX, which binds to both soluble as well as tmTNF- α receptors, disrupts the pro-inflammatory cascade signaling and attenuates the production of tissue degrading enzymes synthesized by synoviocytes and chondrocytes [2]. Various exploratory studies and analyses have been able to identify potential serum protein biomarkers to predict the response and discriminate between non-responders (NR) and responders (R) to a given DMARD. However, this theory has been met with some resistance as, these biomarkers help identify patients that fail to respond to any DMARD, and therefore, they will not be useful for guiding therapeutic choices [3,5].

CONCLUSION

From our understanding, the key differences between the molecular structure, their routes of administration, and doses in

addition to their molecular targets could explain the specificity of biomarkers for the two biological antibodies. We conclude that the approach in our case, that is, the cycling of different DMARD's is well discussed although, not well understood due to the aforementioned disputable ideas which leave room for further exploration and reassessment for therapeutic approaches and management against SpA.

REFERENCES

1. Akgul O, Ozgoemen S. Classification criteria for spondyloarthropathies. *World J Orthop* 2011;2:107-15.
2. Van den Bosch F, Baeten D, Kruithof E, De Keyser F, Mielants H, Veys EM. Treatment of active spondyloarthritis with infliximab, the chimeric monoclonal antibody to tumour necrosis factor alpha. *Ann Rheum Dis* 2001;60 Suppl 3:iii33-6.
3. Menegatti S, Elisabetta B, Lars R. Anti-TNF therapy in spondyloarthritis and related diseases, impact on the immune system and prediction of treatment responses. *Front Immunol* 2019;10:382.
4. Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: Integrating mammalian biology. *Cell* 2001;104:487-501.
5. Ortea I, Roschitzki B, Ovalles JG, Longo JL. Discovery of serum proteomic biomarkers for prediction of response to infliximab (a monoclonal anti-TNF antibody) treatment in rheumatoid arthritis: An exploratory analysis. *J Proteomics* 2012;77:372-82.
6. Lis K, Kuzawińska O, Bałkowiec-Iskra E. Tumor necrosis factor inhibitors state of knowledge. *Arch Med Sci* 2014;10:1175-85.
7. Afzali A, Furtner D, Melsheimer R. The automatic substitution of biosimilars: Definitions of interchangeability are not interchangeable. *Adv Ther* 2021;38:2077-93.
8. ASDAS Calculator. Available from: <https://www.asas-group.org/instruments/asdas-calculator> [Last accessed on 2022 Jan 21].
9. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Available from: <https://www.bas dai.com> [Last accessed on 2022 Jan 21].
10. Infliximab (Rx). Available from: <https://reference.medscape.com/drug/remicade-infliximab-343202> [Last accessed on 2022 Jan 21].
11. Adalimumab (Rx). Available from: <https://reference.medscape.com/drug/amjevita-humira-adalimumab-343187> [Last accessed on 2022 Jan 21].

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Yadav K, Kuchya S, Kalyani A. Overwhelming response to tumor necrosis factor- α inhibitor infliximab "innovator" versus adalimumab "bio-similar" in a previously therapy naive adult: A case report. *Indian J Case Reports*. 2022;March 17 [Epub ahead of print].