Case Report

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

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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-1β, 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.

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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 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.

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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 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.
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 and blocks it interaction with P55 and P75. Induces lysis of TNF-α expressing cells in the presence of complement. Potential biomarkers of response to ADA include only “C3” in the complement pathway. Mean steady-state through concentrations of approximately 5 mcg/ml were observed.

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

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