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Review on pain reduction when using Golimumab, Tofacilinib and Etanercept

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Abstract

Research Background: Biologic drugs are TNF alpha inhibitors, or similar drugs effective in treating AR that do not respond to NSAIDs and DMARDs. They are generally classified as potent drugs in the treatment of Rheumatoid Arthritis, Psoriatic Arthritis and other autoimmune forms of inflammatory arthritis. Biologic drugs are seen as the best way to treat chronic pain that has previously been incurable.

Purpose: To identify the effectiveness of the use of biological drugs in Rheumatoid Arthritis to reduce pain.

Methodology: The methodology that will be used in this study is an observational, cohort study, conducted at the Mother Teresa University Hospital Center in Albania. The sample taken in the study consists of 36 individuals who are currently undergoing biological drug therapy, and in previous treatments have been treated with Methotrexate or NSAIDs. The biological drugs used are Golimumab, Tofacilinib and Etanercept as a change therapy.

Results: The expected results suggest a reduction of pain after the use of biological drugs in the first 6 months of treatment.

Conclusions: Biologic drugs are 70-100% effective in reducing AR pain, mainly joint pain in the small joints of the hands and feet, knee and in advanced stages in the articular pain of the pelvis and spine. A therapeutic approach with biological drugs for patients suffering from chronic pain can improve pain reduction, the patient's daily life, and reduce disability states.

Keywords: Rheumatoid Arthritis; Biologic drugs; Pain reduction; TNF alpha; Chronic pain

1. Introduction

Tumor necrosis factor (TNF) alpha, is a soluble protein that acts as a potent cytokine. It is an autocrine and a paracrine inducer of other cytokines like: IL (interleukin)1, IL-6, IL-8, platelet growth factor B, eicosanoids, platelet-activating factors, and granulocyte-monocyte colony-stimulating factor (1). The recent advances in DNA hybrid technology have led to the development of biological drugs that target TNF-a (2). There are currently three anti-TNF-α drugs available: Etanercept, Infliximab and Adalimumab (3). The TNF plays an important role in both the pathological inflammation and joint destruction that are characteristic of RA. Anti-TNF therapy has revolutionized the approach to treating RA (4). Anti TNF-a drugs are FDA (Food and Drug Administration) approved for use in several conditions such as RA (Rheumatoid Arthritis, PsA (Psoriasis Arthritis), CD (Crohn's Disease), ulcerative colitis. Furthermore, approval is requested for sepsis and allergic diseases (5).

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The disadvantages of such drugs lie on cost and uncertainty about long-term effectiveness and safety (6). All three drugs block the biological effects of TNF-α, although there are some differences in their structure, pharmacokinetics, and mechanisms of action. Both infliximab and adalimumab are anti-TNF-α monoclonal antibodies that bind specifically to human TNF-α with high affinity and neutralize the biological activity of TNF-α by inhibiting its binding to its receptors. On the other hand, etanercept is a fusion protein that acts as a receptor for TNF-a and inhibits the binding of TNF to its cell receptor. Etanercept binds both to TNF-a and TNF-b, rendering them, biologically inactive by inhibiting their interaction with TNF receptors (7).

2. Indications

Table 1 Recommended use of biological drugs

Rheumatological indications	Severe and active RA, refractory to an appropriate trial of disease-modifying anti-inflammatory drugs (DMARDs). Active polyarticular juvenile idiopathic arthritis is refractory to one or more DMARDs. Ankylosing spondylitis. Psoriatic arthritis.
Gastrointestinal indications	Moderate to severe Crohn's disease (including fistulous Crohn's disease) with inadequate response to conventional therapies (TGA approved but not yet PBS listed).
Dermatological indications	Moderate to severe psoriasis.

2.1. Contraindications

Among absolute contraindications, active infections or recurrent chronic infections are the primary ones. Also, moderate to severe congestive heart failure, multiple sclerosis and optic neuritis are absolute contraindications for the use of TNF-a inhibitors. These drugs must not be used in combination treatment with anakinra (IL-1 receptor antagonist). Furthermore, a history of malignancies in the recent 10 years is a contraindication (8).

Among relative contraindication, we can mention pregnancy and breastfeeding. Also, infections such as HIV, hepatitis B and C should be taken into consideration (8).

Either way, therapeutic monitoring of TNF-alpha inhibitors may benefit people whose RA has a prolonged response to these drugs. Reducing the dose of the TNF-a inhibitor reduces unnecessary side effects like serious infections and the costs of treatment. Dose reduction is not a routine NHS practice and is based on the Patients history.

2.2. Examples of TNF alpha inhibitors

Infliximab is a recombinant chimeric monoclonal antibody that contains a mouse variable region and a human IgG1 constant region. It is specific for TNF-a in humans and blocks the binding of TNF-a to its soluble receptors. The use of infliximab promotes the lysis of TNF-α-expressing cell lines by complement and reduces the antibody-dependent cytotoxicity. It causes apoptosis and blocs the use of IFN-gamma in the colon and has anti-inflammatory effects (8,9).

Etanercept is a fusion protein that comprises two identical extracellular TNFR2 regions bound to the human IgG1 Fc fragment. This drug binds to TNF-a molecules and inactivates them by blocking the interaction with the receptors. It causes apoptosis of DCs in the plaque, which disrupts the positive feedback on TNF-a through apoptotic cell death (9,10).

Adalimumab is a fully human IgG1 monoclonal antibody that is able to specifically block the binding of human TNF-α to receptors because its function and structure are identical to those of natural human IgG1. It decreases the levels of TNF-a and IL-6 as well as reagents of the acute phase of inflammation. Furthermore, treatment of RA with adalimumab was found to inhibit IL-17 excessively secreted by Th17 cells by increasing the number of regulatory T cells (Tregs) compared to untreated patients (9,10).

Certolizumab Pegol (CDP87) is a humanized monoclonal antibody that has a polyethylene glycosylated (PEG) Fab fragment and lacks the Fc region. It is relatively novel and has been approved by the FDA for the treatment of CD, RA, PsA, As and PS plaque (9).

Novel TNF-a inhibitors are being developed in order to overcome deficiencies like the unresponsiveness of existing TNF-α inhibitors. Ozoralizumab is a monoclonal antibody used for the treatment of inflammatory diseases. Saddala and Huang created a new drug model, ZINC09609430, which could specifically inhibit TNF-α. The new anti-TNF-a drugs tend to have fewer side effects and more effectiveness (11).

3. Results

A total of 36 individuals receiving biological drugs at QSUNT were studied, of which 31 are female and 5 of them are male. The average age of patients is 55.8 years. For the history of rheumatoid arthritis diagnosis itself, there is a difference in time between the time of onset of symptoms and the time of medical diagnosis by the rheumatologist or physician. For this reason, the questionnaire asked patients initially if they remembered the time of onset of symptoms and the time of diagnosis.

The biological drug used was Golimumab in 20 patients, Etanercept in 14 patients and Tofacilinib in 2 patients.

For the period of onset of symptoms patients referred to their onset on average 16.1 years ago. For the time of their diagnosis patients were referred on average 11 years ago.

To study the level of pain during the use of biological drugs in this study the values of FR, ERS, CRP and DAS28 were taken as reference. Levels of these parameters have been studied for the calculation of DAS28 at the patient's entry into treatment and the current condition after treatment for at least 1 year.

The mean FR reference values per patient at the patient's entry into treatment was 82 UI / ml. The lowest value was 11UI / ml and the highest value was 384 UI / ml.

The mean ERS reference values per patient at the patient's entry into treatment was 42UI / ml. The lowest value was 20UI / ml and the highest value was 80UI / ml.

Reference values of CRP on average per patient at the time of patient entry into treatment were in the range of 12.64 mg / l. The lowest value resulted 0.1mg / l and the highest value resulted 123 mg / l.

The average DAS28 calculation by a rheumatologist per patient at the patient's entry into treatment was 6.08 on average. The lowest calculated value was 5.1 and the highest value was 7.3.

The calculation of pain reduction was studied after at least 1 year of treatment with biological drugs. Considering that the values of DAS28 at the beginning of treatment were higher than 5.1 and the expected decline of DAS28 is low after 6 months, decreasing even more after 1 year. The mean DAS28 after 6 months of treatment was at 4, and after 1 year of treatment, the value of DAS28 was reduced to 3.6.

At the end of the patients' follow-up, their subjective assessment of the pain value from 1-10 was taken into study. Improving pain perception was a reduction in pain in the range of 70-100% after the use of biological drugs, a reduction that is felt from the first 6 months of treatment.

4. Conclusion

In conclusion, the benefit of using biological drugs, more specifically anti-TNF alpha, is observed in patients resistant to other drugs or with a long history of the disease. According to the literature, during the use of TNF alpha inhibitors, a decrease in measurable levels of inflammatory proteins was specifically observed, which further results in relief of symptoms: especially pain symptoms. Improvement in pain and standard of living has been observed since the first year of anti-TNF alpha use. There was practically a decrease in the level of DAS28 in the first 6 months of treatment.

Recommendation

It is recommended that this study be extended to all patients currently receiving their biologic medication in Albania. It is recommended to create an accurate database for the data of patients treated with biological drugs and to be followed in dynamics every 6 months or 1 year.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors were not part of any conflict of interest while conducting this study.

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