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Treatment of Rheumatoid Arthritis with Biological Agents

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1. Introduction

Cytokines and Rheumatoid Arthritis

The term “cytokine” is coined from the combination of “cyto”, a prefix which means cell, and “kine”, which denotes movement.

Cytokines all have the following features:

1. They are low-molecular-weight glycoproteins that are not hormones.
2. They have an effect at very small concentrations.
3. Different cytokines can have the same function (redundancy).

For example, both tumor necrosis factor (TNF) and interleukin-6 (IL-6) have synovial proliferation activity and destroy articular cartilage and bone.

4. One cytokine can act on various organs at the same time (pleiotropy).

For example, TNF causes synovial proliferation, destroys articular cartilage, and promotes fever.

5. Each cytokine has a specific receptor and acts by binding to that receptor.

Inflammatory cytokines play a central role in rheumatoid arthritis. In the treatment of rheumatoid arthritis with biological agents, the effects of cytokines are suppressed by blocking the cytokine from binding to its specific receptor (Figure 1).

With respect to these cytokines, antibodies and antibody fusion proteins that inhibit the action of IL-1, IL-6, and TNF have already been commercialized, and development of an IL-17 inhibitor is underway (Figure 2, Table 1).

Antibodies for the treatment of rheumatoid arthritis can be divided into three groups: chimeric antibodies, humanized antibodies, and human antibodies. Experimental monoclonal antibodies are usually produced by immunizing a mouse with an antigen, and therefore, the antibody is 100% mouse antibody. When such an antibody is used as a therapeutic agent in humans, it causes a strong anaphylactic reaction. In an effort to reduce as far as possible the content of heterologous proteins, various chimeric antibodies, humanized antibodies, and human antibodies have been developed for the treatment of rheumatoid arthritis.

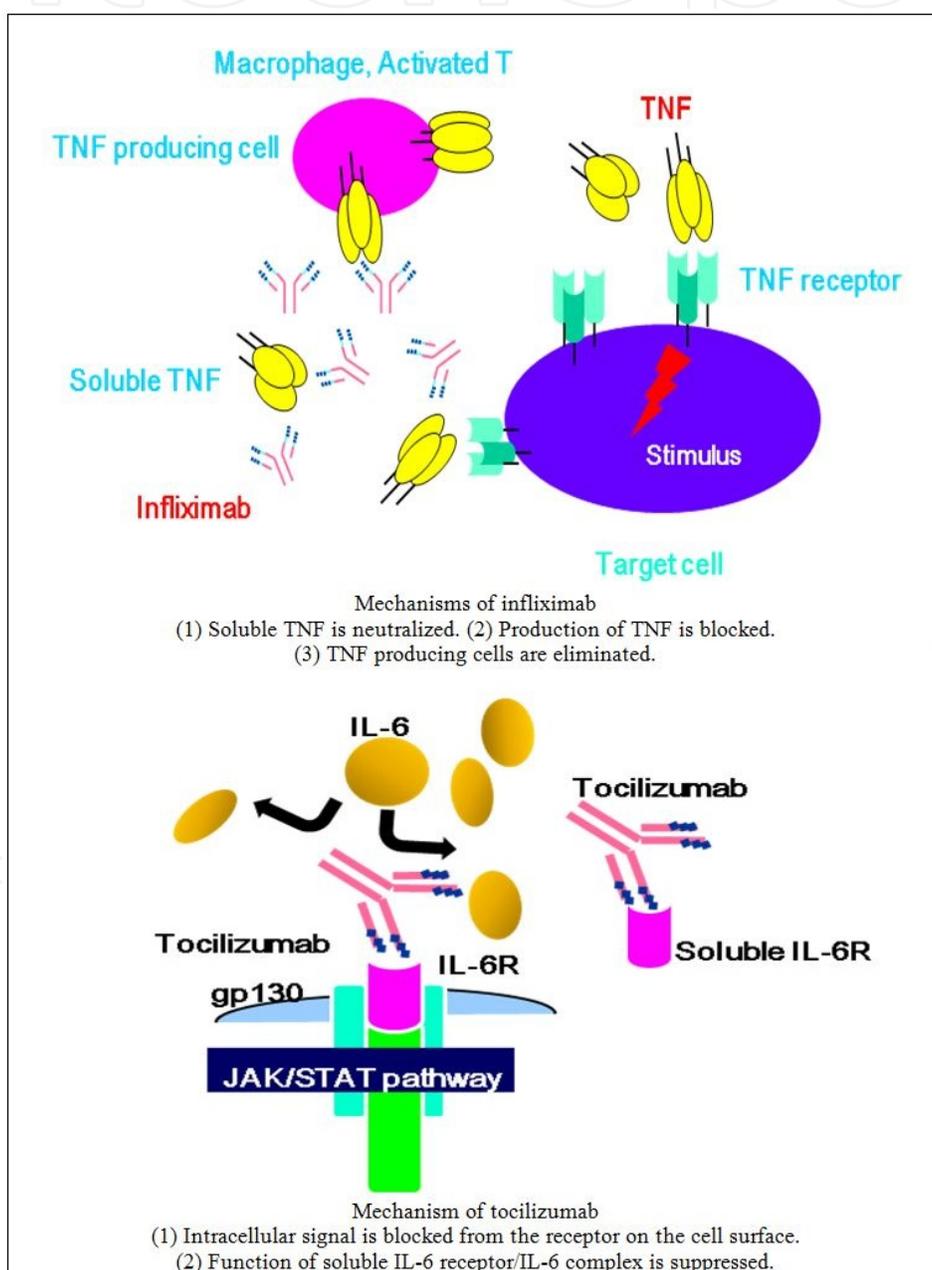


Figure 1. Mechanisms of infliximab and tocilizumab

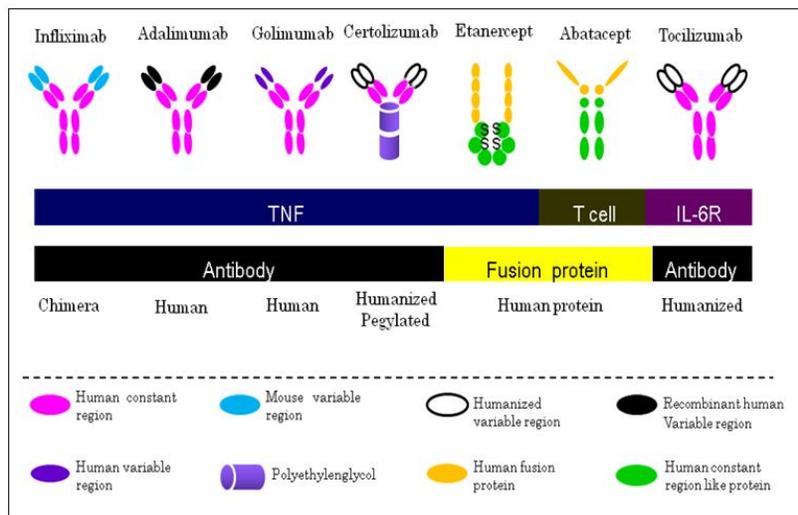


Figure 2. Types of biological agents developed for the treatment of rheumatoid arthritis.

A chimeric antibody is produced first as a mouse monoclonal antibody by immunizing a mouse with an antigen. Then the antigen binding site is preserved as it is, while the Fc site is artificially replaced with one of human origin such as IgG1 or IgG4. In chimeric antibodies, since about 25% mouse protein remains, anaphylactic reactions still occur about 10% of the time when they are administered. There are also reports of treatment with antibody preparations being impaired when antibodies to the chimeric antibody are produced.

A humanized antibody is produced first as a mouse monoclonal antibody, then only the variable parts of the antigen binding site on the heavy chain and light chain of the antibody are left as mouse protein, and the rest is replaced with human protein. Since protein which codes the CDR1, CDR2, and CDR3 regions accounts for about 10% of the total, there is still a small chance of anaphylactic reaction with multiple administrations, though less than that with chimeric antibodies.

Human antibodies are fully human antibodies produced by the phage display method. A typical example is adalimumab. This antibody is produced as follows: An antibody light chain and antibody heavy chain, each with a strong affinity for TNF- α , are selected, and then the two are bound together. Therefore, while it is a fully human protein, it is not an antibody that is physiologically produced in humans. Consequently, it is reported that antibodies against the antibody are detected in 40% of cases or more, reducing the function of the antibody preparation. Combined use of an immunosuppressant to prevent antibody production is recommended.

Another fully humanized antibody on the market is golimumab. This antibody is produced by a method different from that of adalimumab. First, a humanized transgenic mouse is produced, the mouse is immunized with TNF, and the antibodies produced are purified and commercialized. This method has made it possible to produce an antibody which is closer to human than adalimumab.

| | | | | | |
|--------------------------------------|---|---|---|--|--|
| Target | TNF- | | | | |
| Product name | Remicade | Enbrel | Humira | Simponi | Cimzia |
| Non-proprietary name | Infliximab | Etanercept | Adalimumab | Golimumab | Certolizumab pegol |
| Indications | rheumatoid arthritis, uveitis, Behcet's disease, plaque psoriasis, pustular psoriasis, arthropathic psoriasis, erythrodermic psoriasis, Crohn's disease, ulcerative colitis | rheumatoid arthritis, poly juvenile idiopathic arthritis. | rheumatoid arthritis, poly juvenile idiopathic arthritis, plaque psoriasis, arthropathic psoriasis, ankylosing spondylitis, Crohn's disease | rheumatoid arthritis | rheumatoid arthritis, Crohn's disease |
| Administration method | Drip infusion | Subcutaneous injection | Subcutaneous injection | Subcutaneous injection | Subcutaneous injection |
| Administration interval | At wk 0, wk 2, wk 6, then every 8 wks | Every 1–2 wks | Every 2 wks | Every 4 wks | Every 4 wks |
| Structure | Chimeric antibody | TNFR-IgG1 fusion protein | Human antibody | Human antibody | Pegylated humanized antibody |
| Representative clinical study | ATTRACT ^[1] ASPIRE ^[2] | ERA ^[3] TEMPO ^[4] | PREMIER ^[5] DE019 ^[6] | GO-FORWARD ^[7] AFTER ^[8] | GO-FAST4WARD ^[9] RAPID2 ^[10] |
| Target | IL-1 Receptor | IL-6 Receptor | CD80/86 | CD20 | |
| Product name | Kineret | Actemra (RoActemra) | Orencia | Rituxan (MabThera) | |
| Non-proprietary name | Anakinra | Tocilizumab | Abatacept | Rituximab | |
| Indications | rheumatoid arthritis | rheumatoid arthritis, poly juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, Castleman's disease | systemic rheumatoid arthritis | rheumatoid arthritis, lymphoma | non-Hodgkin's |
| Administration method | Subcutaneous injection | Drip infusion | Drip infusion | Drip infusion | |
| Administration interval | Every 1 or 2 days | Every 4 wks | Every 4 wks | Day 1 and 15, then every 24 wks | |
| Structure | IL-1 receptor antagonist | Humanized antibody | CTLA-4-IgG1 fusion protein | Chimeric antibody | |

| | | | | | |
|--------------------------------------|---------------------|---|---------------------|------------------------|---|
| | recombinant protein | | | | |
| Representative clinical study | [11, 12] | SAMURAI ^[13] OPTION ^[14] | AIM ^[15] | ATTAIN ^[16] | REFLEX ^[17] SERENE ^[18] |

Table 1. Characteristics of various biological agents

2. Types of Cytokine Inhibitors (Biological Agents) and their effects on Rheumatoid Arthritis

Cytokine inhibitors used in the treatment of rheumatoid arthritis are inhibitors of IL-1 (anakinra), TNF (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol), and IL-6 (tocilizumab). In addition, biological agents other than cytokine inhibitors used in the treatment of rheumatoid arthritis include abatacept, which inhibits the action of T-cell co-stimulatory molecules CD80 and CD86, and rituximab, which targets CD20.

These drugs each have a stronger effect than methotrexate(MTX), which is considered to be most effective taken orally, and each has strong action to suppress bone and joint destruction (Figure 3, Figure. 4) [19].

Treatment with any biological agent is more effective than MTX monotherapy, and each suppresses bone and joint destruction.

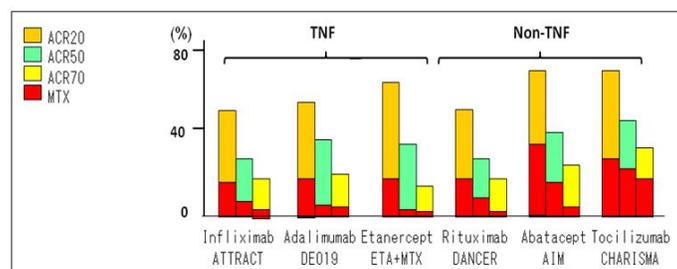


Figure 3. Improvement of clinical symptoms with biological agents

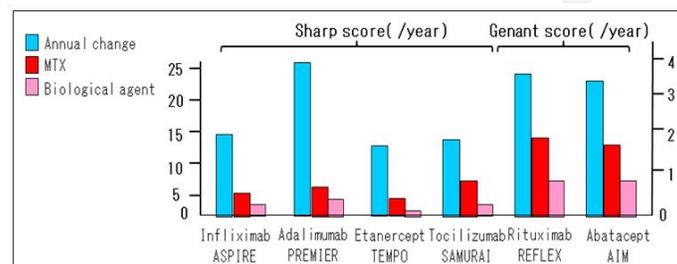


Figure 4. Suppression of joint destruction with biological agents

3. Recommendations for the Use of Biological Agents

Opinion is divided on which biological agent should be used to start with when active rheumatoid arthritis is diagnosed. Among typical rankings for the use of biological agents, there is the 2012 recommendation of the American College of Rheumatology (Figure 5) [20].

According to this recommendation, in the United States the first biological agent (1st Bio) recommended for treatment of early rheumatoid arthritis with disease duration of less than 6 months is a TNF inhibitor. For treatment of established RA with disease duration of 6 months or more, a TNF inhibitor and abatacept or rituximab are recommended as the 1st Bio.

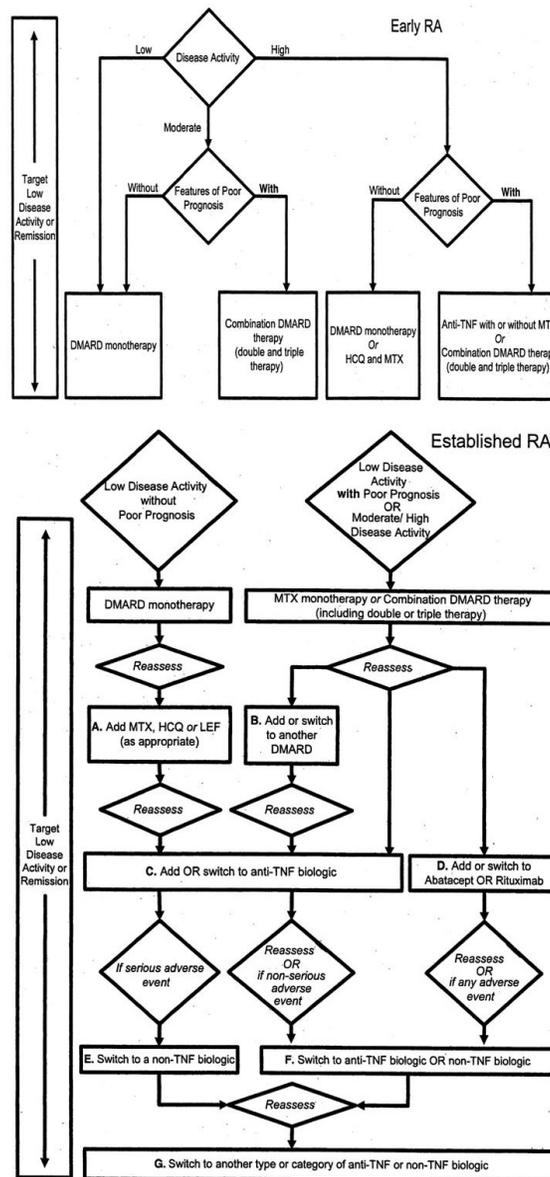


Figure 5. American College of Rheumatology 2012 Recommendation

On the other hand, the British National Institute for Health and Clinical Excellence (NICE) specifies the following guidance on usage (Figure 6) [21–27]:

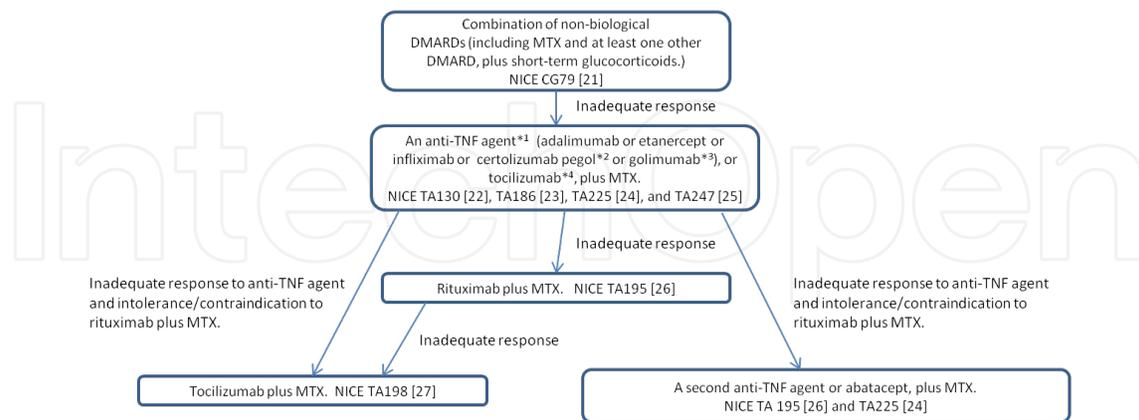


Figure 6. *¹The annual cost of the biological agent is also specified and does not exceed £9,295 a year.*²If certolizumab pegol is the 1st Bio, there should be a system wherein the manufacturer provides the first 12 weeks for free [23]. *³If golimumab is used as the 1st Bio, compensation from the manufacturer is necessary so that the drug price of 50 mg and 100 mg is the same [24].*⁴Tocilizumab can be used as the 1st Bio with a discount provided by the manufacturer. Therefore, whichever biological agent is used first, the annual cost of any is £9,295 or less [27]. NICE guidance on the treatment of patients with rheumatoid arthritis.

4. Selecting Biological Agents by Efficacy and Safety

Among TNF inhibitors, there are several biological agents to choose from, with no strict standards for which biological agent to use first in either the United States or the United Kingdom. Most physicians choose one based on their own experience. Recently however, data has begun to accumulate suggesting which usage is best.

Regarding efficacy, there is data indicating that etanercept is more effective than infliximab for active rheumatoid arthritis with high levels of anti-cyclic citrullinated peptide antibodies and rheumatoid factor [28]. In addition, among infliximab, adalimumab, and etanercept, it is reported that etanercept shows the highest efficacy in patients with high levels of anti-SS-A antibody [29].

With respect to adverse reactions, the occurrence of tuberculosis among patients treated with anti TNF agents has been shown to be low for the fusion protein preparation etanercept and high for the antibody preparations infliximab and adalimumab. It has been suggested that the reason for this could be that the antibody preparations, unlike the fusion protein preparation etanercept, simultaneously suppress the function of macrophages [30, 31].

Therefore, from the point of view of adverse reactions, etanercept may be the best choice for rheumatoid arthritis patients with a risk of tuberculosis.

The same could possibly be considered for tocilizumab, an IL-6 inhibitor which does not directly suppress macrophage function. A postmarketing survey of tocilizumab as used in a

real-world clinical setting has shown an incidence of tuberculosis of 0.22% [32], which is lower than that of TNF inhibitors.

In comparative studies of related biological agents, almost no difference in efficacy was seen between infliximab and abatacept [33] or between adalimumab and abatacept [34]. However, in a study comparing adalimumab and tocilizumab, tocilizumab was shown to be more effective than adalimumab [35] (Table 2).

| | ATTEST Study | AMPLE Study | ADACTA Study |
|-------------------------|--------------------------------|--|---------------------------------|
| Agents | Abatacept vs. Infliximab | Abatacept + MTX vs. Adalimumab + MTX | Tocilizumab vs. Abatacept |
| Primary endpoint | DAS28(ESR) | ACR20 | DAS28(ESR) |
| Study period | 1 year | 1 year | 24 weeks |
| Result | -2.88 vs.-2.25 (n.s) | 64.8% vs. 63.4% (n.s) | -3.3 vs. -1.8 (p < 0.0001) |

Table 2. Comparative study of related biological agents

Considered this way, the non-TNF cytokine inhibitor (IL-6 inhibitor) tocilizumab could be a biological agent with greater pharmacological effect than TNF inhibitors with fewer adverse reactions due to tuberculosis if used appropriately. Comparison of TNF and IL-6 shows mostly the same pharmacological effects due to cytokine redundancy. Examples of this include the induction of synovial proliferation, induction of inflammatory cytokines, and articular destruction.

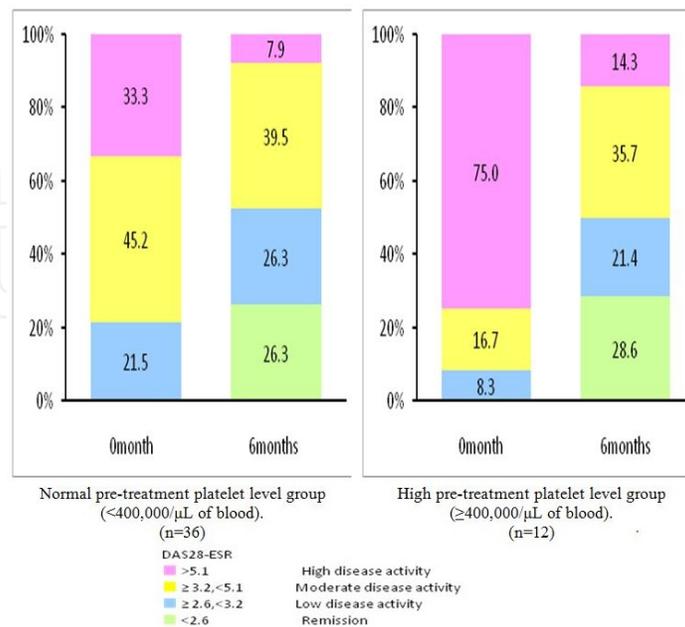


Figure 7. Degree of DAS28 remission with tocilizumab treatment (own data)

However, a characteristic effect of IL-6, which is stronger than that of TNF, is the induction of peripheral platelets in bone marrow megakaryocytes. The effect of IL-6 to induce C-reactive protein in hepatocytes is also thought to be stronger than the effect of TNF.

When the outcomes of cases in which tocilizumab was selected as the 1st Bio were compared in rheumatoid arthritis patients stratified by pre-treatment platelet levels, improvement in rheumatoid activity due to tocilizumab was found to be more marked in patients with high pre-treatment platelet levels ($\geq 400,000$ / μL of blood) than in those with normal platelet levels (Figure 7).

From these results, the effects of IL-6 are stronger than the effects of TNF in patients with rheumatoid arthritis of high activity and high platelet levels, which might be a good indication for the use of tocilizumab. In SCID-Hu-RA experimented mouse, which is implanted human RA synovium into back of the severe combined immune deficient (SCID) mouse, human RA synovium is markedly suppressed by tocilizumab treatment in compared with control mouse [36]. Tocilizumab not only improves clinical symptoms of rheumatoid arthritis, but is also effective in improving pathological findings in rheumatoid arthritis (Figure 8).

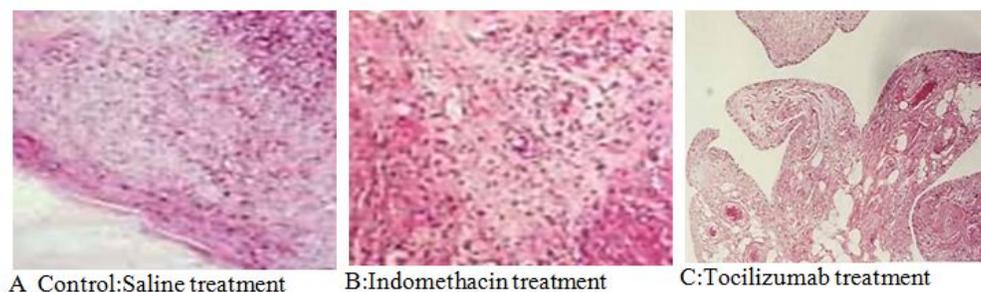


Figure 8. Typical changes in synovial membrane seen with tocilizumab treatment

Inflammatory cells in synovial membrane are suppressed by tocilizumab and replaced by fibrous tissue or adipose tissue.

5. Problems with Biological Agents

Biological agents are a very useful treatment for active rheumatoid arthritis, but there are still many problems which must be solved, including their high cost and the problem of adverse reactions such as infections. As described in the US recommendation and UK guidance, they should probably be used in patients who do not obtain symptomatic relief following treatment with DMARDs.

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