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Review

Different effects of biological drugs in rheumatoid arthritis

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ABSTRACT

Biological drugs have brought new hope to patients with rheumatoid arthritis (RA) in whom previously existing treatments could not control inflammation, joint destruction, or the progression of disability. The five currently available TNF blockers are approved for treating RA patients, but they have different structures, morphology, pharmacokinetic properties, and activity.
Randomised clinical trials (RCTs) have shown that they improve the signs and symptoms of both early and long-standing RA and other inflammatory arthritides, prevent radiographic progression, and improve the patients' health-related quality of life. However, they are more effective in combination with methotrexate (MTX) than alone. Combined treatment is generally well tolerated, and seems to be relatively safe in the short term, as confirmed by RCTs, long-term observational studies and in clinical practice. Patients who fail to respond or develop adverse **effects -** when treated with one anti-TNF agent can be successfully treated with a second TNF antagonist. However, in the case of primary failure, it is possible that biological agents with a different mechanism of action may be more successful. Tocilizumab alone or in combination with MTX is more effective than MTX monotherapy in reducing disease activity over 24 weeks. Abatacept is well tolerated and retains its efficacy over time, as does rituximab in non-responders to other anti-TNF drugs. Finally, although these drugs improve the quality of life of RA patients, they **considerably** increase direct medical costs.

Contents

1. Introduction

Rheumatoid arthritis (RA) is characterised by joint inflammation and destruction, and leads to functional limitations, working disability, and a poor quality of life [1]. It has an estimated adult prevalence of 0.8% worldwide, and is more common in females. Synovial

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inflammation can cause erosive changes that are generally irreversible and often occur early in the disease process [1].

Pro-inflammatory cytokines such as tumour necrosis factor alpha (TNFα) and interleukin(IL)-1β play a key role in the pathogenesis of RA [2]. The synovial membrane of RA patients is hyperplastic, highly vascularised, and infiltrated by inflammatory cells. When activated by an antigen, CD4 + T lymphocytes stimulate monocytes, macrophages, and synovial fibroblasts to produce IL-1, IL-6, and TNF; they also secrete matrix metalloproteinases (MMPs) as a result of cell-surface signalling by CD69 and CD118, and the release of soluble mediators such as interferon (IFN)-γ, IL-1, IL-6, IL-17, and TNF. Activated CD4 + T cells stimulate B cells by means of cell-to-cell contacts, and bind α sub 1 and β sub 2 integrin, CD 40 ligand, and CD28 to produce immunoglobulins (Ig), including rheumatoid factor (RF) [2,3]. They also express the receptor activator of NF-κB (RANK), which stimulates osteoclastogenesis via the RANK ligand (RANKL). Activated macrophages, lymphocytes, and fibroblasts can also stimulate angiogenesis, which is responsible for synovial hypervascularity [2–4]. Synovial endothelial cells are activated and express adhesion molecules that promote the recruitment of inflammatory cells. B cells produce the rheumatoid factor (RF) antibody that induces the formation of immune complexes at the sites of synovial inflammation, the activation of complement and leukocyte infiltration by the downstream products of complement activation (especially the soluble C5a anaphylatoxin), and the subsequent recruitment of the other components of the membrane attack complex [5]. B cells can act as highly efficient, antigen- presenting cells (APCs): they process and present antigenic peptides to T cells, which subsequently proliferate and switch on their pro-inflammatory action [2,5]. Furthermore, activated B cells can synthesise cytokines such as IL-4, IL10, etc., as well as membrane-associated molecules that provide non-specific help to adjacent T cells [2].

2. Rheumatoid arthritis therapy

Before the advent of biological drugs, RA was treated with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs), all of which were started after the patients had fulfilled the American College of Rheumatology (ACR) criteria: i.e., in patients with late-onset disease. However, since then, the European League Against Rheumatism (EULAR) has recommended that DMARD treatment be started as soon as possible after RA has been diagnosed, with the primary therapeutic aim of obtaining remission (especially in the case of early RA), although a low level of disease activity may be an appropriate alternative, especially in patients with long-standing RA [6–8]. Conventional DMARD treatment may be clinically and functionally effective, but does not always suffice to halt joint destruction [6,7]. The treatment target should preferably be reached within three months and definitely attained within a maximum of six months. Methotrexate (MTX) is considered the anchor drug in RA. An inadequate response to a first-line DMARD at an optimal or maximally tolerated dose may be followed by switching to an alternative DMARD, such as sulfasalazine or leflunomide, or a DMARD combination [8]. If the treatment target is not achieved using the first DMARD strategy, combined treatment with a tumour necrosis factor (TNF) inhibitor (adalimumab, certolizumab, etanercept, golimumab or infliximab) and MTX should be started [9,10] (Table 1).

Intensive regimens using combinations of traditional DMARDs, or of one traditional DMARD and biological agents, not only induce a clinical response, but also prevent joint damage [8]. However, since about 30% of patients treated with an anti-TNF agent fail to achieve a 20% improvement in the ACR criteria, and even more of them experience the loss of efficacy or adverse events during treatment [11], switching to a second TNF inhibitor has become established practice although, in the case of primary failure, it is possible that other biological agents with different mechanisms of action (such as rituximab, abatacept and tocilizumab) may be more successful.

Table 1
Biological drugs approved for treating RA.

Biological DMARD	Target	Structure
Etanercept	TNF-a	Human TNF-a receptor p75Fc fusion protein
Infliximab	TNF-a	Chimeric human-murine anti-TNF-a monoclonal antibody
Adalimumab	TNF-a	Recombinant human anti-TNF-a monoclonal antibody
Certolizumab	TNF-a	Fab pegylated anti-TNFα
Golimumab	TNF-a	mAb anti-TNFα
Tocilizumab	IL-6	Humanised anti-IL-6R monoclonal antibody
Anakinra	IL-1	Recombinant human IL-1 receptor antagonist
Rituximab	B cell	Chimeric human-murine anti-CD20 monoclonal antibody
Abatacept	T cell co-stimulation	Human fusion protein (CTLA4-Ig)

3. Tumour necrosis factor alpha and anti-TNF drugs

TNF-α is a key cytokine in the pathogenesis of RA. It induces macrophages and other cells to secrete pro-inflammatory cytokines such as interleukin (IL) IL-1, IL-6 and IL-8, leads to T-cell activation, and causes endothelial cells to express adhesion molecules [3,4]. TNF-α is involved in the differentiation and maturation of osteoclasts (the main cells involved in arthritic bone destruction), and stimulates fibroblasts, osteoclasts and chondrocytes to release proteinases, which destroy articular cartilage and bone [2,3,12].

TNFα is synthesised as pro-TNF (26 kDa), which is bound to the membrane and released upon the cleavage of its pro-domain by the TNF-converting enzyme (TACE) [12,13]. TNFα acts via two distinct receptors (TNFR-1 and TNFR-2), although its affinity for TNFR-2 is five times higher than its affinity for TNFR-1. Understanding the role of TNFα in the pathogenesis of RA has been important for the development of drugs capable of controlling its clinical signs and symptoms, and halting its radiographic progression. Five TNF blockers have been approved in Europe for treating RA patients (the three monoclonal antibodies infliximab [IFN], adalimumab [ADA] and golimumab [GLM], the recombinant TNF receptor etanercept [ETN], and the pegylated certolizumab [CTZ] [14], but they have different structures, morphology, pharmacokinetic properties and activity.

3.1. Monoclonal antibodies

IFN, ADA and GLM are full-length, bivalent immunoglobulin G (IgG) monoclonal antibodies (mAbs) [14–17]. IFN is an intravenously administered, chimeric IgG 1 K monoclonal antibody, consisting of a constant human region and variable murine regions, that specifically binds human TNFα with an association constant of 1010 M1[15]. After initial parenteral administration, its serum half-life is approximately 8.9 days, and is maintained by dosing every eight weeks thereafter. Intravenous administration ensures that maximum serum concentrations are reached within one hour. The infusion of IFN induces a rapid and clinically highly efficacious TNF blockade, with a remission rate of 30-40% after a single dose [15].

ADA and GLM are fully human mAbs [16,17]. ADA only binds TNFa (not the other members of the TNF family) and has a dual mechanism of action: it neutralises TNFa and rapidly removes it from the circulation. The standard dose of ADA is 40 mg subcutaneously (s.c.) every other week, and it can be used alone or in combination with DMARDs. After administering a single 40 mg dose to a healthy adult, it reaches a maximum serum concentration of 4.7 k 1.6 g/ml within 131 ±5 hours [16].

Like ADA, GML is a fully human monoclonal antibody but has different light and heavy chain amino acid sequences that are similar to those of IFN [17]. It is administered s.c. every four weeks, and the median time to reach maximum serum concentrations ranges from two