# Biological therapy in rheumatoid arthritis – Notes for the pharmacist

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## Abstract

Progress in understanding the molecular biology of rheumatoid arthritis has led to the development of targeted therapies designed to ameliorate this disabling disease and improve patient outcomes. Biologic-based therapies are being developed to target specific cytokines in the inflammatory pathway, such as tumour necrosis factor (TNF), T-lymphocytes, B-lymphocytes and interleukin-6 (IL-6). An overview of biological therapies for rheumatoid arthritis forms the basis of this article.



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## Introduction

Rheumatoid arthritis (RA) is a chronic, progressive auto-immune disease affecting between 0.3% and 1% of the global population.[1,2] Despite limited epidemiological data, the estimated prevalence of RA in South Africa appears to be in line with the global incidence of 1%.[3] Rheumatic and musculoskeletal diseases are listed as leading causes of disability worldwide, with RA being a degenerative disease associated with severe disability, co-morbidities and a decline in quality of life.[3,4,5]

### *Rheumatoid arthritis: an inside job*

Although the aetiology of RA is unknown, the pathogenesis of this auto-immune disease is complex, involving immune, neuroendocrine and psychosocial variables.[3] The body's acquired immune system which evolves with age, is able to identify foreign invading entities (antigens) for destruction. The immune system responds with the aid of T- and B-lymphocytes to produce antigen-specific antibodies. In addition, a group of chemicals called cytokines also assist in this "fight" in protecting the body against an invading antigen. Successful immune defense requires activation, regulation, and resolution of the immune response.[2,3]

An auto-immune disease causes the immune system to attack the body's own tissues, and in the case of RA, there is a constant attack (immune-mediated) on the joint tissue. The result is inflammation of the joint, which becomes chronic if no intervention is made.[2] Characterised by an immune-mediated synovitis, untreated or inadequately managed RA leads to joint cartilage and bone destruction.[6]

## Treatment evolution

The treatment of RA has evolved over the last decade, with its ultimate goal still being remission. When remission is not possible, treatment should minimise disease activity, control symptoms and reduce damage to the affected joints. Traditional disease-modifying anti-rheumatic drugs (DMARDs) remain the standard of care.[7]

Over the last decade, drug development has focused on targeted therapy with biologics.[7] Biological therapies for RA are made from proteins and work by blocking the main chemicals or cells involved in inflammation which leads to joint swelling and other symptoms.[2] Numerous chemicals, called cytokines are released during the inflammatory process, including tumour necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6). TNF was identified as a crucial variable in inflammation and joint destruction.[6] As such, TNF became one of the first targets of biologic-based therapy.[2] By blocking TNF, great strides were made in reducing joint inflammation, and slowing the progression of joint damage.[6] Other targets for biological therapies have been identified giving rise to targeted approaches to other cytokines such as IL-6, as well as the B- and T-lymphocytes which are involved in inflammation.

## Targeted therapy

The use of biological agents that target specific mechanisms of inflammation has been shown to impact the clinical course of RA by slowing or stopping disease progression. However, in order to leverage off these novel treatment options, early detection and treatment is necessary.[7]

According to the most recent treatment algorithm from the European League Against Rheumatism (EULAR), a biological agent may be considered when prognostically unfavourable factors (high levels of RA markers, high disease activity, early joint damage, failure of two or more conventional DMARDs) are present and the patient has not had satisfactory outcomes on conventional DMARD therapy within six months.[8] Table I outlines the biologic-based treatment options available in South Africa.[9]

**Table I.** Anti-TNF agents available in South Africa for rheumatoid arthritis

**TNF Targeted therapy**

TNF is central to the inflammatory process during the pathogenesis of RA by prompting the production of other cytokines, namely IL-1 and IL-6. In addition, it engages inflammatory cells into the joints and sets off the process of joint destruction. By targeting the very instigator of this inflammatory process through the use of a TNF blocker (antagonist or anti-TNF), the features of chronic inflammation are reduced.[6]

***Anti-TNF agents currently available in South Africa***

**Infliximab (Revellex®)** is indicated for[10]:
- the reduction of signs and symptoms
- prevention of structural joint damage
- improvement of physical function

in patients with active rheumatoid arthritis despite treatment with methotrexate (MTX).

**Adalimumab (Humira®)** is indicated for the treatment of moderate to severe rheumatoid arthritis in adult patients, including recently diagnosed patients not previously treated with methotrexate.
Adalimumab can be used in combination with methotrexate or as monotherapy, in the case of intolerance to methotrexate or when continued treatment with methotrexate is considered inappropriate.[11]

**Etanercept (Enbrel®)** is indicated[12]:
- as monotherapy or in combination with methotrexate for adults with rheumatoid arthritis when the response to one or more DMARDs has proven inadequate.
- for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

**Golimumab (Simponi®)** is indicated in combination with methotrexate for[13]:
- the treatment of active rheumatoid arthritis in adult patients when the response to DMARD therapy including MTX has been inadequate.
- the treatment of active rheumatoid arthritis in adult patients not previously treated with MTX.

**B-cell depleting agent**

CD20 is a molecule present on certain B-cells (B-lymphocytes) which develop into antibody-producing cells, necessary for the normal functioning of the immune system and in the inflammatory process in RA.

Rituximab targets this CD20 receptor and disrupts the inflammatory process involving B-cells.[2,14]

***B-cell depleting agent currently available in South Africa***

**Rituximab (MabThera®)** in combination with methotrexate is indicated for the treatment of adult patients with active rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs including one or more TNF inhibitor therapies.[15]

**Interleukin-6 inhibitors**

Interleukin-6 is a protein/cytokine that is most abundant in the rheumatoid joint involved in inflammation. By targeting IL-6, the inflammatory process is disrupted leading to improvements in symptoms of RA.

Tocilizumab is the only available biologic that targets IL-6 and is also able to improve fatigue by improving the anaemia associated with RA.[2]

***Interleukin-6 inhibitors currently available in South Africa***

**Tocilizumab (Actemra®)** IV or SC in combination with methotrexate is indicated for[16]:
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.
- the treatment of moderate to severe active rheumatoid arthritis in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more DMARDs or TNF antagonists.
- In these patients, tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

**T-cell co-simulators**

Co-simulation of the T-cells occur when the T-cell is activated to react to an antigen to promote inflammation, which leads to the damage in RA.

Abatacept blocks this activation of the T-cell to halt the development of inflammation at an early stage.[2]

***T-cell co-simulators currently available in South Africa***

**Abatacept (Orencia®)** Orencia® is indicated in adult patients with active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF-blocking agents.

Orencia® may be used as monotherapy or concomitantly with DMARDs other than TNF-blocking agents.[17]

## Notes for the pharmacist

Although the pharmacist may not be directly involved in managing patients with biological therapy, it is important for the pharmacist to be aware of certain considerations relating to the use of biologicals for RA.

### *Administration*

Biological therapies should be administered under the supervision of specialised medical practitioners.[10-13,15-17] For therapies where patients are taught to self-administer (under appropriate discretion of the treating physician), such as subcutaneous

tocilizumab, adalimumab or golimumab, the first few injections should be performed under the supervision of a qualified healthcare professional. Patients should be reminded that the recommended injection sites (abdomen, thigh and upper arm) should be rotated and injections should never be given into moles, scars, or other areas where the skin is tender, bruised, red, hard, or not intact.[11,13,18]

### *Immunosuppression*

Due to the way biological therapies work, there is a potential effect on the normal functioning of the immune system. Therefore, patients receiving biological therapies are at risk of immunosuppression and the consequences thereof.[7]

### *Risk of infection*

The presence of active infection is a contraindication to biological therapy. Owing to the immunosuppressive action of biological therapies, there is an increased risk of infection by bacterial, fungal and opportunistic pathogens.[7] Given the high prevalence of tuberculosis (TB) in South Africa, TB reactivation is a concern with biological therapies.[3] Therefore, screening for latent TB is a requirement before, during and after biological treatment. Patients who screen positive for TB should be given prophylactic therapy. Blood counts and infection markers should be monitored before, during and post treatment.[7] Interestingly, probiotics are not recommended for patients who have immunocompromising conditions or who are immunosuppressed because of a possible risk of infection.[19]

### *Prevention of infections*

Other infections that patients on biological therapy may be at risk of, carry a significant morbidity and mortality risk, such as vaccine-preventable infections. Ideally, patients should be vaccinated before starting biological therapy, as part of their screening and evaluation. Live vaccines against infections such as herpes zoster, varicella, measles, mumps and rubella should be administered at least four weeks before initiating biologics. Unlike live vaccines, inactivated vaccines do not pose a risk to immunosuppressed patients and patients with RA should be encouraged to be vaccinated against influenza (inactivated trivalent vaccine in South Africa) due to the high risk of complications from influenza in immunosuppressed patients. The pneumococcal vaccine (inactivated), given the increased risk of pulmonary infections in RA patients, should also be considered for these patients. Pharmacists are at the forefront to engage and encourage patients on measures of preventative care. Family and close contacts of patients on biological therapies should ensure they are up to date with their vaccines to avoid posing a risk of passing on an infection to the RA patient.[7,20,21]

### *Reactivation of Hepatitis B*

Hepatitis B reactivation has been reported in patients undergoing treatment with biologics. Therefore, patients should be screened for hepatitis immunity prior to starting biological therapy. Patients without evidence of immunity against hepatitis B should be vaccinated accordingly.[7,10-17]

### *Follow-up monitoring*

Due to the risks associated with the use of biologics, patient monitoring should be ongoing. Biologic-based treatments can affect blood counts. Therefore, the pharmacist is ideally positioned to remind patients with RA about the importance of follow-up appointments and blood tests to ensure ongoing monitoring of their well-being while on treatment.[7] Concerns of safety associated with biological therapies can be ameliorated by identifying toxicity early through routine laboratory monitoring of cardiovascular risk, serum lipid levels, liver function, kidney function and blood counts. Biological therapies for RA may increase the already present risks of co-morbid conditions in patients with RA or, by virtue of their side-effects, introduce new co-morbidities.[22]

### *Concomitant medication*

Patients on biologics should be made aware of the potential for exacerbated toxicity or drug interactions when taking other medication. Therefore, when seeking over-the-counter medication or other medication, this should be carefully evaluated.[7]

## Conclusion

Since managing a debilitating illness like RA involves a multidisciplinary approach, it is important for pharmacists to be up to date on developments in the treatment thereof. Treatment of RA is an area of ongoing research, with novel drugs being investigated and developed. It is necessary for pharmacists to offer patient education, support and ongoing motivation to be compliant with treatment and the overall management of their condition.

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