The role of anti-TNF therapy in practice

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Abstract

Biological therapy refers to agents that are derived from living sources, such as microorganisms, animals or humans and often represents state of the art medical research. One such biological drug class is the TNF inhibitors. Since infliximab became available nearly a decade ago, it has given new hope to patients with inflammatory diseases. These diseases, for example rheumatoid arthritis, may cause severe symptoms that have a significant impact on patient functioning and quality of life.

Two other TNF blockers are also available, and their characteristics, administration and therapeutic spectra differ from infliximab. Nonetheless, this drug class has been shown to be beneficial in a number of inflammatory conditions.

This article is the first in a series of two and will focus on the pathophysiology of inflammatory diseases, mechanisms to inhibit the inflammatory mediators, and the nomenclature and characteristics of the TNF inhibitors. Furthermore the clinical use of these drugs in various conditions is reviewed. In the follow-up article, the adverse effects of the TNF blockers will be discussed, as well as the issues around which drug to select and the appropriateness of switching from one to another.

Introduction

Advances in molecular biology have resulted in new therapeutic strategies in treating rheumatoid arthritis and other systemic inflammatory diseases associated with autoimmunity. One major breakthrough was the launch of infliximab, a TNF-alpha inhibitor, in the late 1990s.

Tumor necrosis factor alpha (TNF-alpha) is a key inflammatory mediator in the pathogenesis of many chronic inflammatory conditions, which include rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn’s disease and possibly ulcerative colitis. High levels of TNF-alpha lead to increasing levels of inflammation resulting in damage to cartilage, bone and bowel mucosa. TNF-alpha inhibitors bring about significant clinical improvement and reduction in objectively measured damage.

The three anti-TNFs currently registered in South Africa are:

- Adalimumab: Humira®
- Etanercept: Enbrel®
- Infliximab: Revellex®

These products are, however, significantly more expensive than conventional treatments for inflammatory diseases. In addition, there are concerns about serious adverse effects associated with them. The decision to implement TNF blocker therapy should therefore be taken with great care.

Pathophysiology of autoimmune diseases

In healthy persons, proinflammatory mediators and the nomenclature and characteristics of the TNF inhibitors. Furthermore the clinical use of these drugs in various conditions is reviewed. In the follow-up article, the adverse effects of the TNF blockers will be discussed, as well as the issues around which drug to select and the appropriateness of switching from one to another.

Mechanisms which inhibit inflammatory mediators

Diagram 1 denotes a simplified, yet typical inflammatory process involved in rheumatoid arthritis.

RA is considered a disorder of Th1 predominance, but tissue cytokine patterns may vary between patients. Furthermore, autoantibodies produced by B-cells under influence of Th2 lymphocytes play an important role in the pathogenesis of this disease. In addition, direct cytokine release from macrophages may also cause T-cell independent inflammation.

Diagram 1 denotes a simplified, yet typical inflammatory process involved in rheumatoid arthritis.

The anticytokine approach involves downregulation of two of the main inflammatory cytokines, interleukin-1 (IL-1) and TNF-alpha. Currently there are three types of molecules available to enhance the downregulation of these, namely:

- A soluble receptor antagonist, e.g. etanercept
- Monoclonal antibodies to cytokines or their receptors, e.g. infliximab and
Diagram 1: The role of the immune system and some inflammatory mediators in the pathogenesis of RA\textsuperscript{1,2,9,18,21,22,23}

- Infective agent/unknown stimuli in peripheral tissues
- Activation of innate immunity in genetically predisposed person
- Activation of macrophages
- Inflammatory mediators and cytokines released
  - Interleukin-1\textsuperscript{*}
  - TNF-\textalpha
- TNF-\textalpha attaching to receptors
- Target inflammatory, endothelial and immune cells in RA
- Production of additional inflammatory mediators (chemokines, prostaglandins), proteases, IL-1\textsuperscript{*}, growth factors, endothelial cells and adhesion molecules by TNF-\textalpha
- Tissue, cartilage and bone remodelling and damage
- IL-1 and TNF-\textalpha are capable of inducing synthesis of one another

- Migration of dendritic cells to lymph nodes
  - Activation of adaptive immunity in lymph node (T-cell activation)
  - Activated T-cells proliferate and migrate into the joint
  - Th2
  - Th1
  - B-cells
  - Production of proinflammatory cytokines
  - RF autoantibodies
  - Stimulation of macrophages, fibroblasts, chondrocytes and osteoclasts
  - Increase in activated macrophages and effector cells in synovial tissue and fluid

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adalimumab; certolizumab is a polyethylene glycolated monoclonal antibody, but is not available in South Africa.  

- A cell surface receptor antagonist protein, e.g. anakinra, a recombinant antagonist of the IL-1 receptor (not available in South Africa).

Nomenclature and characteristics of the TNF-alpha inhibitors  

TNF-alpha inhibitors convey specific information relating to their structure by the abbreviations at the end of their generic names:1,2,9,16  

- Etanercept: ‘cept’ refers to the fusion of two p75 TNF receptors to the Fc part of the human IgG1 (thus a recombinant fusion protein)  
- Adalimumab: ‘mab’ indicates a monoclonal antibody (mAb) of human origin  
- Infliximab: ‘ximab’ indicates a chimeric (mouse and human components) monoclonal antibody (mAb)

Table 1 describes the main characteristics of the TNF blockers.

Rheumatoid Arthritis  

Rheumatoid arthritis (RA) is a debilitating inflammatory condition occurring worldwide, with 75% of people affected being women.2,24 It is a polyarthritis which is characterised by progressive bone erosion. Symptoms include tenderness, stiffness, pain and fatigue.2,21,22,24 Some patients also experience a spectrum of extraarticular manifestations, e.g. vascular, pulmonary fibrosis.2,24

In RA there is an increase in the number of synovial cells, infiltration of white blood cells and the formation of new blood vessels, resulting in enlargement of the synovium. The joint cavity is effused by synovial fluid. The synovium is inflamed and thickened, resulting in further synovial cell proliferation. The synovial fluid contains increased numbers of white blood cells, primarily neutrophils. The synovium is thickened and ischaemic, resulting in loss of synovial cell function.3,34,35,36 The disorder generally occurs in adults, with a third of patients presenting in their 30s.34,35,36 The disorder may reduce radiographic progression, but this issue is still much debated.1,15

Ankylosing Spondylitis  

Ankylosing spondylitis (AS) is a form of arthritis of the axial skeleton. It is a chronic, inflammatory disease characterised by back pain and progressive spinal stiffness due to fixation of the joints. Transient acute arthritis of the peripheral joints occurs in up to 50% of patients, with chronic changes occurring in 25% of patients. Other organs such as the eyes, lungs, and heart may also be affected. AS affects young adults with a peak age of onset between 20 and 30 years.17,32

The traditional DMARDs such as sulfasalazine, methotrexate or leflunomide are ineffective in patients with axial disease.3,32 Systemic cortisone is not recommended, but intraarticular injections may benefit some patients.32 There is some evidence that long term NSAIDs may reduce radiographic progression, but this issue is still much debated.1,15

Table 2 summarises the key information related to anti-TNFs in RA.

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Table 3 summarises the key information related to anti-TNFs in AS.

Plaque Psoriasis  

Psoriasis is a systemic, chronic inflammatory skin condition characterised by silvery, scaly erythematous plaques, but other manifestations may also be evident.34,35,36 The disorder generally occurs in adults, with a third of patients presenting with lesions at/before age 16.34,37 It can be physically scarring, leading to social stigmatisation, and psychological dysfunction.34,35,36 Mild to moderate disease usually responds to topical agents, such as tar, topical retinoids, calcipotriene and steroids. Severe disease however requires phototherapy and/or systemic therapy.

NF blocking agents as monotherapy have been shown to reduce inflammatory parameters, reduce symptoms and improve quality of life. Time to maximal response may however be as much as 6 weeks and patients with advanced disease may be less likely to respond to these drugs.32 Use of TNF blockers may retard radiographic progression to a degree, but does not halt it.3,32

Table 3 summarises the key information related to anti-TNFs in AS.
A strong genetic component is apparent and T-cell dysfunction is believed to be an important mediator. Not surprisingly, trials with TNF inhibitors have shown significantly reduced disease severity, less fatigue and depression, as well as noteworthy improvement in overall health related quality of life in patients with moderate to severe psoriasis.

TNF blocking agents are suggested as alternatives in the systemic treatment of moderate-severe disease in patients who also have psoriatic arthritis, as well as in patients with a history of melanoma or extensive non-melanoma skin cancer.

Table 4 summarises the key information related to anti-TNFs in Plaque Psoriasis.

Psoriatic Arthritis
Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis. It affects both women and men equally. Per definition patients must have evidence of psoriasis, thus diagnosis is simplified when arthritis appears after the onset of skin lesions. The disease is characterised by pain and stiffness in the affected joints. However, joints of patients with PsA tend to be less tender than those of patients with RA. Consequently patients may present with joint deformity without a significant degree of pain. Standard therapy includes NSAIDs and DMARDs (e.g. methotrexate, sulfasalazine, leflunomide, cyclosporine, gold), but neither of these seem to prevent radiologic progression.

TNF and other inflammatory cytokines released via the T-cell pathway is implicated in the cause of PsA. Infliximab and etanercept have been shown to improve symptoms, as well as patient function and quality of life. In addition, there is evidence that progression of the arthritis is limited by all three TNF blockers.

Table 5 summarises the key information related to anti-TNFs in PsA.

Crohn’s Disease
Crohn’s disease (CD) is an idiopathic, chronic condition characterised by segmental transmural inflammation and granulomatous lesions of the bowel. The typical signs and symptoms of CD include fatigue, prolonged diarrhoea with abdominal pain, weight loss and fever with or without gross bleeding. Approximately one third of patients develop fistulas, which represent a serious complication of the disease. The fistulas may be enterocutaneous, i.e. extending through the abdominal wall or into the perineum, or they may be internal, for example from bowel to bowel, bowel to bladder or rectovaginal.

Patients with CD are treated with 5-Amino-Salicylic-Acid derivatives (5-ASAs, e.g. sulfasalazine, mesalamine), or immunomodulators such as methotrexate and azathioprine, and often require antibiotics, prolonged courses of corticosteroids or repeated surgery. Bowel healing may be achieved with methotrexate and azathioprine, but the fistulas are difficult to treat.

Since the discovery of increased levels of TNF-alpha in the intestinal mucosa and stools of CD patients, neutralisation of the biologic activity of TNF-alpha has become an attractive intervention. However, since etanercept is not effective in IBD, it is likely that the benefit of infliximab and adalimumab in CD relates to the destruction of activated effector cells through apoptosis (cell death) and/or other mechanisms. Treatment with these two agents results in a remarkable decrease in disease activity and steroid use; clinical remission and closure of fistulas have also been achieved in some patients.

Table 6 summarises the key information related to anti-TNFs in CD.
Ulcerative Colitis

Ulcerative colitis (UC) is a condition characterised by mucosal ulceration, rectal bleeding, diarrhoea and abdominal pain. The recurring episodes of inflammation is limited to the mucosal layer of the colon. Management of the condition has centered around 5-ASAs, corticosteroids and immunosuppressants, e.g. methotrexate, azathioprine and cyclosporine. Treatment with 5-ASA and steroids may heal the bowel mucosa, but not all patients respond to these drugs.

The cytokine TNF-alpha is found in large amounts in the blood, colonic mucosa, stool and urine of patients with UC, but its role in the pathogenesis of UC has been debated. Nonetheless, infliximab treatment has resulted in a reduction in disease activity and steroid use, as well as in clinical remission and mucosal healing in patients unresponsive to conventional therapy. Adalimumab has been used successfully in a few patients with intolerance or loss of response to infliximab, but its benefits have to be evaluated in randomised, double-blind, placebo-controlled trials.

UC can ultimately be cured by a colectomy, but this has its own complications. It is uncertain whether infliximab can prevent this outcome, especially in those patients with severe and refractory disease. Patients may be exposed to the risk and the high cost of this treatment, while not preventing colectomy. The need for colectomy may however be delayed with infliximab treatment. Overall, the benefits of anti-TNF treatment in severely ill, hospitalised patients are not clear.

Table 7 summarises the key information related to anti-TNFs in UC.

Summary

TNF inhibitors are an innovative class of drugs which show significant clinical improvement in signs and symptoms of chronic inflammatory and rheumatic conditions. While infliximab currently has the broadest range of clinical applications, it has to be administered intravenously. Efficacy data for adalimumab is accumulating and the drug can be given subcutaneously. Etanercept is also administered subcutaneously, but is not effective in IBD.

The decision of how to treat patients involves detailed knowledge of the available treatment options as well as categorising the suitable patient who would need intense treatment with TNF-inhibitors. It must also be noted that many important clinical outcomes are still unidentified, or poorly quantifiable, such as consistent evidence of disease modification and reduction in disability with use of these expensive agents.

Table 5: The use of anti-TNF agents in Psoriatic Arthritis

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Not registered in South Africa; Off label: 40 mg SC fortnightly*</td>
<td>25 mg SC twice weekly</td>
<td>Not registered in South Africa; Off label: 5 mg/kg IV infusion at week 0, 2 and 6; then 8 weekly#</td>
</tr>
<tr>
<td>International approval</td>
<td>FDA, EU, UK</td>
<td>FDA, EU, UK</td>
<td>FDA, EU, UK</td>
</tr>
<tr>
<td>Use with DMARD</td>
<td>With/without methotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place in therapy</td>
<td>Failure of 2 standard DMARDs at therapeutic dose (NICE*)</td>
<td></td>
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* NICE = The National Institute for Health and Clinical Excellence
# Not yet registered by the MCC for PsA at the time of going to press

Table 6: The use of anti-TNF agents in Crohn’s Disease

<table>
<thead>
<tr>
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<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
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<tbody>
<tr>
<td>Dosage</td>
<td>Not registered in South Africa. Off label: 160 mg SC at week 0 followed by 80 mg at week 2 and maintenance dose of 40 mg every other week beginning at week 4*</td>
<td>Not registered in South Africa</td>
<td>5 mg/kg as an IV infusion initially at week 0, 2 and 6; additional maintenance on 8-weekly basis at 5–10 mg/kg</td>
</tr>
<tr>
<td>International approval</td>
<td>FDA, EU</td>
<td>No</td>
<td>FDA, EU, UK</td>
</tr>
<tr>
<td>Use with DMARD/immuno-suppressant</td>
<td>Immunomodulators do not enhance remission or response rates</td>
<td>–</td>
<td>Should be used with methotrexate or azathioprine; immunosuppressant may decrease development of antibodies; patients with inflammatory disease – initial response more likely in those using immunosuppressants; patients with fistulas – no difference in response whether immunosuppressants are used or not</td>
</tr>
<tr>
<td>Place in therapy</td>
<td>Moderate-to-severe disease in patients who have an inadequate response to conventional therapies (failure of cortisone, methotrexate and azathioprine) and in whom surgery is inappropriate</td>
<td>Not effective in IBD</td>
<td>Moderate-to-severe disease in patients who have an inadequate response to conventional therapies (failure of cortisone, methotrexate and azathioprine) and in whom surgery is inappropriate (SAGES*; NICE**)</td>
</tr>
</tbody>
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* SAGES = South African Gastroenterology Society
** NICE = The National Institute for Health and Clinical Excellence
# Not yet registered by the MCC for CD at the time of going to press

References:
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<td><strong>Dosage</strong></td>
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<td><strong>Use with DMARD/immunosuppressant</strong></td>
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<td><strong>Place in therapy</strong></td>
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* ADA = American Gastroenterology Association

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68. Lewis JD. Anti-TNF Antibodies for Crohn’s disease - In Pursuit of the Perfect Clinical Trial. NEJM 2007;357:296-298