Adverse effects and other issues with the use of anti-TNF therapy

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Abstract
In our previous article, we outlined the pathophysiology of inflammatory diseases and mechanisms to inhibit the inflammatory mediators, one of which is TNF-alpha. The nomenclature and characteristics of the TNF-alpha inhibitors, a biological class of drugs, were also reviewed. In addition, the clinical application of these drugs in various inflammatory conditions was discussed.

In this article, the second in the series, adverse effects and toxicities of the TNF blockers are investigated, in particular tuberculosis and the controversy over malignancy. Furthermore, we focus on the induction of autoimmunity caused by the anti-TNFs. Neutralising antibody formation, which may cause a decrease in the effectiveness of some of these drugs, is a specific problem, but may be reduced by various strategies.

Lastly, we look at issues around which anti-TNF drug to select, as well as the appropriateness of switching from one to another in patients where a particular TNF blocker does not show adequate or sustained clinical benefit.

Background
The causative factors for many autoimmune, inflammatory diseases are unknown, but it has been established that tumour necrosis factor alpha (TNF-alpha) is a key inflammatory mediator in the pathogenesis of most of these conditions.1 In the past 10 years much progress has been made with the development of TNF inhibitors and currently three such drugs are available in South Africa: adalimumab, etanercept and infliximab.2,3,4

The TNF blockers are biological drugs which show noteworthy clinical improvement in the signs and symptoms of conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.1,2,5,6,7,8,9,10,11 In addition, infliximab and adalimumab are also effective in inflammatory bowel disease (IBD), especially Crohn’s disease.1,5,6,12,13,14,15,16

These drugs are generally well tolerated,1,17 with a relatively quick onset of action and earlier relief of symptoms when compared to the standard disease modifying antirheumatic drugs (DMARDs) and immunosuppressive therapies used in the chronic inflammatory disorders.1 However, there are some concerns about rare, but serious adverse effects and toxicities associated with the TNF blockers.1,8,15,17,18,19 Furthermore, about a third of patients do not respond adequately to a TNF inhibitor, or some patients may respond initially and then lose benefit over time.5,15,17,20,21

Adverse Effects
Multiple adverse affects of anti-TNFs have been noted in both clinical trials and post–marketing surveillance.1,15,17,18,19 These include, but are not limited to the following:

Injection site reactions
Skin reaction is a common, yet minor problem at the site of medication injection and occurs more frequently with etanercept and adalimumab as compared to placebo.8 These reactions usually manifest during the first month of treatment and last for 3–5 days, but discontinuation of medication due to this is rare.19 In fact, the reactions may decrease in severity over time, most likely due to induced tolerance.17

Infusion reactions
These reactions are classified as one of two types, namely:

• Acute reactions develop within 24 hours and normally occur between 10 minutes and 4 hours after the start of infusion. The reactions sometimes relate to true allergies with anaphylactic events occurring in some patients treated with infliximab. However, the majority of the reactions with infliximab represent non-allergic reactions, not mediated by IgE.18

• Delayed reactions develop between 1 and 14 days after the infusion, but mostly occur after 5–7 days. These reactions are similar to serum sickness and may relate to mild type III (immune complex-mediated) reactions.18

Infusion reactions are associated with the presence of antibodies to infliximab and can be prevented by the use of antihistamines, prednisone, methotrexate, azathioprine or other immunomodulators.1,15,17,18,21,22,23,24

Infections
The cytokine TNF-alpha plays an important role in the immune system response to a variety of pathogens,1,17,18,19,24 Inhibition of TNF-alpha may therefore result in
an increased incidence of infections including tuberculosis, bacterial infections (particularly pneumonia), septic arthritis and opportunistic infections.\textsuperscript{1,8,19,24}

- **Tuberculosis (TB)**
  The risk of reactivation of latent tuberculosis and the progression of newly acquired infection to active TB is increased by the use of anti-TNF therapy.\textsuperscript{1,8,19} TB associated with TNF inhibitors more frequently involves extrapulmonary sites and more often presents as being diffused, compared to other TB causes.\textsuperscript{1,19} The risk of TB with use of anti-TNFs is increased in patients taking concomitant immunosuppressants, those with a history of active or latent infection, and those living in a TB-endemic region.\textsuperscript{19}

  The timing and risk of the TB vary from one anti-TNF agent to another.\textsuperscript{8,19,25} According to the FDA’s AERS the risk of TB is greater with infliximab than with etanercept and occurs sooner following initiation of therapy with infliximab. Less data is available for adalimumab, but estimates are that TB risk is intermediate compared to the other two TNF inhibitors.\textsuperscript{8,19}

  Patients who potentially qualify for anti-TNF therapy should be screened for LTBI (Latent Tuberculosis Infection) by performing a tuberculin skin test and chest X-ray before they commence therapy.\textsuperscript{1,8,19,24} If patients are diagnosed with LTBI they should be treated with standard preventative therapy, most often isoniazid.\textsuperscript{1,19} It has been suggested that anti-TB therapy should commence at least one month prior to starting anti-TNF therapy and should continue for at least 9 months. Patients who develop TB during anti-TNF therapy, should stop this therapy and may only resume it once TB has improved on antituberculosis treatment.\textsuperscript{19}

- **Neurological Diseases**
  There have been cases which may suggest a potential link between TNF inhibitors and optic neuritis, transverse myelitis, multiple sclerosis and demyelinating-like syndromes.\textsuperscript{1,8,18} These effects have been reported more often with etanercept than with infliximab, but seem to disappear after the withdrawal of the TNF inhibitors.\textsuperscript{8,18} These agents are best avoided in patients with an established neurological disease such as multiple sclerosis and should be discontinued immediately if a demyelinating-like disorder or optic neuritis occurs.\textsuperscript{8,18,25}

- **Heart Failure**
  Data gathered from post-marketing surveillance by the FDA, as well as randomised clinical trials, show heart failure (HF) as a possible adverse effect.\textsuperscript{8,18,24,25} This effect mostly occurs with high-dose regimens, e.g. infliximab at doses > 5mg/kg.\textsuperscript{8,25}

  Based on evidence to date it is recommended that in patients with symptomatic HF, strategies other than TNF inhibitors ought to be used.\textsuperscript{18} Anti-TNF therapy is contra-indicated in patients with NYHA class III or IV HF.\textsuperscript{25} Targeted TNF inhibition may however be considered for patients with refractory RA and mild HF (NYHA class I or II), but these patients should be closely monitored and high doses of anti-TNFs should be avoided.\textsuperscript{8,18,25} If patients develop HF while on TNF inhibitors, therapy should be stopped and a drug-induced cause should be suspected.\textsuperscript{8,25}

- **Malignancy**
  TNF was initially recognised for its capability of lysing tumors in a variety of study models. This elicits the possibility that TNF blockade might increase the risk of cancer.\textsuperscript{26} There have been some reports of malignancies, for example lymphoma, related to the TNF inhibitors, as recorded from studies and post-marketing surveillance.\textsuperscript{8,25} Clinical data regarding risk of solid tumors and lymphomas are however mixed.\textsuperscript{8,24,25,26}

  Currently there are a number of challenges in determining the true severity of risk (if any) in the development of malignancy with the use of TNF-alpha inhibitors, namely:
  - A heightened predisposition to cancer based on underlying condition e.g. high disease activity in rheumatoid arthritis and ulcerative colitis.\textsuperscript{1,8,26}
  - The concomitant use of medication, especially cyclophosphamide and azathioprine, that may increase malignancy risk. It is recommended not to use cyclophosphamide together with TNF inhibitors.\textsuperscript{26}
  - Rigorous clinical trials with anti-TNFs and monitoring of their adverse effects, as opposed to limited data gathering on conventional DMARDs, resulting in an increased likelihood of malignancies being reported for TNF inhibitors.\textsuperscript{26}

  The effect of anti-TNF therapy on pre-malignant conditions, such as cervical dysplasia, large bowel polyps and Barrett’s oesophagus is also unknown, and caution is advised in these individuals.\textsuperscript{25}

- **Induction of autoimmunity**
  The use of TNF inhibitors may result in the production of neutralising antibodies, which may lead to allergic reactions or loss of efficacy.\textsuperscript{15,17,18,21,22,23,24} Autoantibody formation is another complication, but it is not clear if this directly results in the manifestations of secondary autoimmune disorders.\textsuperscript{8,15,25} The risk of antibody formation varies with the specific type of TNF inhibitor,\textsuperscript{15} as described below and summarised in Table 1.

<table>
<thead>
<tr>
<th>Drug origin/composition</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humanised monoclonal antibody</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Soluble receptor antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chimeric (human and mouse) monoclonal antibody</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Human anti-chimeric antibodies (HACA)</td>
<td>Yes</td>
<td>No</td>
<td>Not known</td>
</tr>
<tr>
<td>Human antihuman antibodies (HAHA)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antinuclear antibodies (ANA)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibodies to dsDNA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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Antinuclear antibodies (ANA) and antibodies to dsDNA have also been reported with all three TNF blockers, but are more common with infliximab. Autoimmune diseases such as Lupus-like syndrome, have been reported with infliximab and adalimumab. Interstitial lung disease, vasculitis and uveitis have also been recorded. 

Paradoxically, new-onset psoriasis has been noted in patients with rheumatoid arthritis receiving TNF inhibitors — in a UK register, the risk with adalimumab was 4 times higher than with etanercept and 3 times higher than with infliximab. Similarly, new-onset and flare of IBD have been observed in ankylosing spondylitis patients receiving these drugs. Infliximab may prevent IBD activity, but more data are required for adalimumab. In both scenarios, the clinical significance of differences between the three TNF blockers must still be clarified.

These autoimmune manifestations however normally resolve once the TNF blocker is stopped.

Choice of agent and switching of anti-TNF therapy

There are currently no direct comparative trials of the 3 TNF-inhibitors, and it is unlikely that such trials will be done. Based on indirect comparison, the available agents are regarded as similarly effective within their approved indications.

At least a third of patients do not attain clinical benefit from anti-TNF treatment used for any of the approved indications. This could be due to: Diverse pathogenetic mechanisms in different subjects; Different mediators of disease development and progression in various stages of the disease; Genetic make up of individuals; Specific properties of the TNF blocker used.

Considering the difference in the mechanisms of action of the monoclonal antibodies (infliximab and adalimumab) and the soluble fusion protein (etanercept), it would make clinical sense to switch to a different anti-TNF agent (within its registered use), in certain conditions where a particular TNF inhibitor has failed.

Several studies have been done to determine whether patients benefit clinically from switching over to a different anti-TNF agent. Most of these studies involved the switching over of adalimumab/ infliximab to etanercept and vice versa, with considerable improvement.

Furthermore, in the GAIN trial (n=325), patients with Crohn’s disease who had symptoms despite receiving infliximab therapy were switched to adalimumab or placebo; 21% of patients on adalimumab achieved remission versus 7% on placebo.

In the ReACT study (n = 6610), it was concluded that response to adalimumab was lower in rheumatoid arthritis patients who previously received another TNF-alpha blocker, than in those who were TNF-alpha inhibitor naive. On the other hand, response was better in those who lost response to their initial TNF blocker over time, than in those who were primarily non-responders to the first agent.

More trials have yet to be done in order to confirm the benefits and cost-effectiveness of switching TNF-inhibitors, but preliminary findings indicate that failure of one TNF-inhibitor does not exclude response to another.

Despite this, the National Institute for Health and Clinical Excellence (NICE) preliminary guidance of April 2008 does not recommend the use of an alternative anti-TNF drug if a patient has experienced inadequate response to an initial TNF-blocker, but the British Society of Rheumatology (BSR) has challenged this decision. NICE has subsequently announced that the decision will be reconsidered. The South African Rheumatism and Arthritis Association (SARAA) follows the European guidelines and does not place restrictions on switching of TNF blockers.

Conclusion

While the TNF-alpha inhibitors have proved to be a major advance in the treatment of many inflammatory disorders, some potentially serious side effects and unexpected toxicities have been found. Examples include tuberculosis and heart failure, as well as autoimmunity and demyelinating diseases. The issue around an increased possibility of malignancy due to use of these drugs is not yet resolved and further vigilance is warranted.

However, these risks must be viewed in relation to the potential benefits and adverse effects of conventional treatment with DMARDS and immunomodulators — toxicities of which are also significant. Further studies and patient registries will hopefully provide more information on the efficacy and toxicity of the biological drugs.

Neutralising antibody formation is a concern with infliximab, as these may lead to allergic reactions or loss of efficacy. Adalimumab has a lower potential for development of these antibodies, while...
such antibodies have not been noted with etanercept.15

The choice of agent is ultimately decided based on the patient’s unique risk profile and the characteristics of individual TNF blockers.8,16-25 Where one agent in this drug class has failed, a patient may sometimes be treated successfully with another.8,30

Physicians need to consider all these factors, as well as significant costs associated with anti-TNF therapy, when deciding on the best treatment approach for their patients.8,36

References:
1. Nash PT, Florin THJ. Tumor necrosis factor inhibitors. MJA 2005;183(4):205-208
28. Lewis JD. Anti-TNF Antibodies for Crohn’s disease - In pursuit of the perfect clinical trial. NEJM 2007;357:296-298

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