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Focus

Monitoring Anti-TNF-α Therapies in Chronic Inflammatory Disorders: Infliximab and Adalimumab

Anti-tumour necrosis factor (anti-TNF) therapy has, since the 1990s, become an important part of the management of several chronic inflammatory diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondylitis and severe psoriasis. The first anti-TNF drug to be approved for clinical use was infliximab; since then several more have been developed including adalimumab, golimumab, and etanercept.

Mechanisms of Action

Although all of these so-called biologicals work by neutralizing TNF-α, they do so by different mechanisms. The two main strategies used to neutralize TNF-α involve monoclonal IgG antibodies (infliximab, adalimumab, golimumab) and soluble TNF-α receptor (etanercept). Infliximab is a humanized mouse monoclonal antibody; adalimumab and golimumab are fully human monoclonal antibodies, and etanercept is a construct comprising two human p75 TNF-α receptors coupled to the Fc portion of of a monoclonal human antibody.

These structural differences help explain the many differences seen between these drugs *in vitro* and *in vivo*. Infliximab binds both monomeric (inactive) and trimeric (active) forms of TNF, whereas etanercept binds the more active trimeric form. In addition, infliximab forms stable complexes whereas etanercept tends to form relatively unstable complexes, allowing dissociation and the potential to form a reservoir for binding TNF-α. Also, infliximab and adalimumab, but not etanercept, fix complement, and therefore can lyse cells which express surface TNF-α. Since TNF-α is initially expressed on the cell surface before being cleaved by TNF-α converting enzyme, cells such as T-cells may be susceptible. A decrease in absolute numbers of CD4+ T-cells is seen in the peripheral blood in patients with ankylosing spondylitis treated with infliximab, but an increase with etanercept.

VRE *In vivo*, not all drugs are similarly effective in all inflammatory diseases. For example, in RA all are highly effective, in Crohn's disease there is a clear clinical benefit with infliximab and adalimumab but not with etanercept.

Side Effects

There are also subtle differences in side-effects of TNF-α therapies. All are associated with an increase in infection, but patients taking infliximab and adalimumab appear in some studies to have a higher risk of infection by histoplasmosis and coccidioidomycosis, or reactivation of tuberculosis (TB). Etanercept does not have these side-effects.

The reasons for these differences are not clearly understood, but some may be related to the drugs' ability to fix complement and interfere with granuloma formation (beneficial in Crohn's disease, detrimental in the reactivation of tuberculosis).

Differing Responses to Drugs

In addition to drug-related differences in disease response, individual patients with a given disease show differing responses to a given drug. A patient who does not respond to one anti-TNF-α drug may well benefit from another.

Finally, there are many cases in which an initial favourable response to a given anti-TNF-α drug is lost over time (see below).

Although anti-TNF-α therapy has revolutionized the treatment of chronic inflammatory disorders, side-effects are a significant risk and empiric therapy may be disappointing. For these reasons, careful pre-therapy assessment and monitoring of treatment response are required, both clinically and by laboratory tests.

Pre-treatment Assessment for Infliximab and Adulimumab

Exclusion criteria include current sepsis or infection, pregnancy or breastfeeding, moderate to severe heart failure, and active or latent tuberculosis. These should be assessed by a comprehensive history and examination, including chest X-Ray, Mantoux or Quantiferon Test, and serological tests for HIV, hepatitis B and C, VZV, and herpes simplex. Vaccines for VZV, HPV, pneumococcus, influenza and hepatitis B should be given as appropriate.

Monitoring of Infliximab and Adalimumab Therapy

Despite the substantial improvement in outcomes that anti-TNF agents have provided for patients with IBD and other chronic inflammatory processes, response is not universal. More than one third of patients do not respond to induction therapy (primary non-responders), and response wanes over time in 20 – 60% of patients who showed a good initial response (secondary non-responders).

Hypotheses for treatment failure include:

- Inadequate serum levels of the anti-TNF agent
- Consumption of the drug by a high inflammatory disease burden
- The development of immunogenicity (formation of antibodies to the anti-TNF drug)

Immunogenicity is a strong predictor of loss of response to infliximab and adalimumab:

- About 50% of IBD patients may eventually experience a loss of response to infliximab or adalimumab, requiring dose modification or a switch to an alternative treatment[1,3,4]
- Up to 72% of patients who have antibodies to infliximab (ATI) experience a loss of response to infliximab[5]
- Up to 44% of patients who lost response to adalimumab had antibodies[1,6-8]

Measuring drug levels of infliximab or adalimumab is important; detectable infliximab/adalimumab serum concentrations are associated with:

- Better remission rates in CD and UC[2,10,12]
- Endoscopic improvement in CD and UC[7,10,12]
- Lower CRP levels in CD patients[6,7,10]
- Lower risk of colectomy in UC[12]

An empiric treatment strategy may lead to unnecessary and costly drug intensification in patients who:

- Have clinical symptoms which may not correlate with active IBD[11,13]
- Have antibodies to infliximab or adalimumab[9,11]
- Exhibit therapeutic levels of drug, but whose inflammation is not TNF-driven[11,13]

Feagan *et al* (2012) analysed 1487 serum infliximab (IF samples from patients on maintenance IFX in four prospectiv randomized clinical trials showing[14]

- IFX concentrations ≥ 3 μg/mL were predictive of lower disease activity (CRP)
- The benefits of IFX were diminished in the presence of antibodies to IFX, despite optimal drug concentration: CRP levels remained similar in ATI-positive samples despite optimal drug concentration
- Therefore, measuring both IFX and ATI concentrations may help guide patient management

Similarly, in two cross-sectional studies, Velayos et al analysed serum from 54 patients and Yarur et al analysed serum from 66 CD and UC patients on adalimumab (ADA) and showed[6,7]

- That ADA concentrations ≥ 5 μg/mL were predictive of significantly lower disease activity (CRP)
- That detectable antibodies to ADA were positively associated with an elevated CRP independent of drug concentration

Finally, measuring both serum drug and antibody levels has been shown to be more cost-effective than empiric management[15].

Biomnis Ireland Offers the Following Tests:

1. Infliximab drug level and anti-infliximab antibodies
   Sample type: 1mL Serum frozen
   TAT: 2 weeks
2. Adalimumab drug level and anti-adalimumab antibodies:
   Sample type: 1mL Serum frozen
   TAT: 2 weeks
3. Quantiferon :
   Sample type: whole blood in Quantiferon TB Gold Kit
   TAT: 5 working days

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