TNFα Inhibitors Therapeutic Drug Monitoring
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Introduction
Tumour necrosis factor alpha (TNFα) is a pro-inflammatory cytokine involved in the pathogenesis of several chronic inflammatory conditions. The introduction of monoclonal antibody derived “biologic” drugs targeting TNFα has redefined the treatment of multiple chronic inflammatory diseases (see Figure 1) and has led to considerable improvement in clinical outcomes for patients with these conditions.

TNFα inhibitors (TNFi)
These biologic drugs are monoclonal antibodies of various designs (see Figure 2). Infliximab (Revellex®) was the first TNFα inhibitor to be approved for the treatment of inflammatory bowel disorders. Infliximab is a chimeric monoclonal IgG1 antibody composed of a murine variable region and a constant human region. Alternative tradenames for many of these monoclonal antibody drugs exist because “biosimilars” produced by other manufacturers, after the patent of the original drug has expired, have entered the market. Biosimilars contain a similar version of the active substance of an original biological medicinal product and are very close to the reference product in terms of quality characteristics, biological activity, safety, and efficacy based on comprehensive comparability studies done before registration of the product as well as phase 4 effectiveness studies.

Figure 1. Spectrum of chronic inflammatory diseases in which TNFα inhibitors are used

Figure 2. Schematic representation of the structure of a few common TNFα inhibitors
TNFα therapeutic drug monitoring

The management of patients receiving TNFα inhibitors has until recently been empirical, with dose adaptations based on various complex clinical measures and derived scales that have been developed to quantitate patient symptoms, and which may include both objective and subjective measures of improvement. Recent technological advances have made therapeutic drug monitoring (TDM) of TNFα inhibitors possible. Consequently treatment with these very costly biologicals can now be more personalised for the individual patient, and ultimately more cost-effective.

Multiple clinical studies have demonstrated a link between trough concentrations of infliximab (IFX), the concentration of the drug just before administration of the next dose, and clinical response in patients with inflammatory bowel disease (IBD). Low or undetectable concentrations correlated with poor response and adequate trough levels are associated with a sustained response to IFX. In rheumatoid arthritis (RA), the use of a biologic disease-modifying anti-rheumatic drug (DMARD) or the targeted kinase inhibitor tofacitinib is recommended for patients with moderate or high disease activity despite monotherapy with a conventional (non-biologic) DMARD. The most commonly used biologics in these patients are the TNFα inhibitors etanercept, adalimumab, and infliximab. Newer TNFi (e.g. certolizumab pegol and golimumab) are also used, but less frequently.

For any patient on TNFi biological therapy, treatment failure may occur and it can be either primary or secondary. Primary failure occurs in approximately 30% of patients who are refractory to, and do not improve clinically while on induction therapy with TNFα inhibitors. Secondary treatment failure, defined as decreased or lack of response in a previously responsive patient, may also occur. Table 1 outlines the most common reasons for secondary treatment failure on TNFi, which may occur in up to 50% of IBD/RA patients that responded initially.

The production of anti-drug antibodies (ADA), which neutralise and accelerate the clearance of the particular TNFα inhibitor, results in reduced drug availability. ADA may occur transiently in some patients, which are of no clinical consequence. High levels of ADA that influence treatment outcomes may also occur. The point prevalence of ADA is approximately 60% in episodic treatment with TNFi and 6 – 25% in scheduled treatment. Most patients that develop ADA do so within the first 12 months of treatment.

Table 1 also outlines the major adverse events that can occur in patients on biologicals. Especially important are allergic reactions to the drug, increased risk for the development of active tuberculosis, major bacterial and viral infections, as well as various malignancies.

Table 1. Common causes of treatment failure and complications of TNFα inhibitors

<table>
<thead>
<tr>
<th>Causes of treatment failure</th>
<th>Complications</th>
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<tbody>
<tr>
<td>Severity of disease</td>
<td>Allergic reactions to drugs, e.g. urticaria, difficulty swallowing or breathing, joint pain, fever or chills, swelling of the face or hands</td>
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<tr>
<td>Duration of disease</td>
<td>Serious viral or bacterial infections, incl. tuberculosis, especially in people aged &gt; 65 years</td>
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<tr>
<td>Smoking</td>
<td>Skin reactions, incl. psoriasis (red scaly patches), rashes, skin lesions, ulcers and hives, swollen face and lips</td>
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<tr>
<td>High BMI</td>
<td>Worsening of pre-existing cardiac condition</td>
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<tr>
<td>Pharmacokinetics – drug elimination</td>
<td>Increased cancer risk, e.g. lymphoma</td>
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<tr>
<td>Drug binding</td>
<td>Liver inflammation</td>
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<td>Anti-drug antibodies</td>
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<tr>
<td>Alternative non-TNFα mediated disease pathways</td>
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<td>Concomitant treatment with immunosuppressants</td>
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<td>Prior treatment failure with another TNFα inhibitor</td>
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Multiple studies and cost effectiveness analyses provide guidance on the use of TNFi in patients with IBD. Locally guidance is provided by the South African Gastroenterology Society (SAGES), which mostly uses the approach of the TAXIT study in their guidelines. Similarly EULAR/SARAA recommendations exist for the use of TNFα inhibitors in rheumatological conditions. Figure 3 outlines a symptomatic approach to IFX TDM for inflammatory bowel diseases.

Lancet Laboratories is using an ELISA based system that detects levels of infliximab and its biosimilars with a reportable range of 0.5 – 48 μg/mL, and anti-drug antibodies (ADA) with a reportable range of 2.5 – 1 000 ng/mL. These particular assays were chosen because of their superior performance compared to other TNFα inhibitor immunoassays available in the market, in particular their ability to detect both infliximab and its biosimilars, as well as increased sensitivity to detect anti-drug antibodies.

Soon to be introduced is an adalimumab (ADM) assay with anti-ADM antibodies as well as more rapid TDM systems for both infliximab and adalimumab (Humira®) and its biosimilars.

References

Figure 3. Symptom-guided approach to TNFα inhibitor and drug antibody monitoring