South African National Department of Health
Tertiary and Quaternary Hospital Level
Annexure Document for Medicine Review

Adalimumab and infliximab in the management of patients with Crohn's Disease who are refractory to conventional therapies.

This document was developed to guide use of adalimumab and infliximab in practice for the approved indications of fistulising Crohn's Disease (Approval: NEMLC 14th March 2024) and Luminal / non-specific Crohn's Disease (Approval: NEMLC 16th May 2024).

The use of Infliximab and Adalimumab in clinical practice

Both infliximab (IFX) and adalimumab (ADA) are approved for the treatment of fistulising and luminal Crohn's disease (CD). Both are monoclonal antibodies targeting TNF-alpha, and as foreign proteins carry the risk of immunogenicity. Given its chimeric structure, the risk of anti-drug antibody formation is highest for IFX, and as such is invariably given in combination with a low dose immunomodulator (IMM) such as azathioprine or methotrexate. Although ADA is less immunogenic than IFX, many patients still develop anti-drug antibodies, and, in clinical practice, is also frequently administered in combination with an IMM. Anti-drug antibodies are associated with both primary non-response, secondary loss of response, and infusion reactions.

Once ADA and IFX are prescribed for Crohn's disease, patients should be monitored for response as per facility/clinic protocol. Patients who fail to respond or who have lost response should undergo reactive therapeutic drug monitoring (TDM) to optimise therapy. TDM involves the measurement of plasma anti-TNF trough levels (TLs) and anti-drug antibodies. There are 3 possible scenarios that are encountered:

1. **A low trough level (TL) with the absence of anti-drug antibodies**. This reflects an insufficient plasma concentration of the anti-TNF agent. Once adherence is assured, it is recommended that the anti-TNF dose be increased.
   - For infliximab (IFX) this can be achieved by either increasing the dose from 5mg/kg 8 weekly to 10mg/kg 8-weekly, or, alternatively, shortening the dosing interval from 8 weekly to 6 weekly.
   - For adalimumab (ADA) the dosing interval may be reduced from 2-weekly to once weekly (at a dose of 40mg SC).

2. **A low TL with positive high anti-drug antibody titre**. In this case the presence of anti-drug antibodies results in rapid and enhanced drug clearance and increasing the dose will not be effective. In this scenario the anti-TNF needs to be switched to a 2nd in-class alternative (e.g. IFX to ADA, or ADA to IFX). This strategy is effective as these antibodies are not cross-reactive.

3**. Therapeutic TLs (regardless of anti-drug antibody titre).** This scenario is termed mechanistic failure, whereby the inflammation is no longer mediated by TNF-alpha but rather through alternative cytokine pathways**.** Patients need to switch out of class to another advanced therapy. In these circumstances, patients should be referred back to their specialist centre and/or to the local Pharmaceutical Therapeutics Committee for further consideration.

Acknowledgment and declaration: Thanks to Dr Gillian Watermeyer (Department of Gastroenterology, Groote Schuur Hospital, and the Department of Medicine, University of Cape Town, Cape Town, Western Cape, South Africa). GM has no interests to declare but to note that she works with CD patients and uses TNF-inhibitors.