

Monoclonals against TNF are a major advance in the treatment of Crohn's disease

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract that results from a dysregulated immune response to commensal gut bacteria. In health there is a state of mucosal immune tolerance to our gut bacteria. There is a complex interaction between the epithelial cell and the T lymphocyte in the lamina propria. This "cross-talk" is mediated by cytokines such as TNF-alpha (TNF- α), IL12 and IL23.

TNF-alpha is central to the inflammatory response in Crohn's disease promoting other inflammatory cytokines and upregulating the expression of adhesion molecules on vascular endothelial cells.¹

Monoclonal antibodies that target specific molecules (often called biologicals) have been a major advance in the treatment of Crohn's disease. The first target proposed was TNF-alpha (tumour necrosis factor) and this has proven to be a major success story. Monoclonal antibodies bind to TNF receptors on activated T cells and monocyte/macrophages causing blockade of activity but more importantly cause apoptosis and cell cycle arrest. The details of the inflammatory response in Crohn's disease have become much more important in the biological era in the search for other potential targets for inhibitory antibodies.

Infliximab was the first anti-TNF agent and continues to be widely used for Crohn's disease and many other inflammatory conditions. This drug needs to be given by infusion every 8 weeks—this limits acceptability but does ensure compliance.

Adalimumab is a humanised monoclonal to TNF-alpha that is given subcutaneously every 2 weeks. The review of adalimumab use in New Zealand (NZ) by Thomas et al, in this issue of the *Journal*, adds to the literature confirming effectiveness of these agents for moderate to severe Crohn's disease.²

Treatment options before the advent of anti-TNF monoclonal were limited. Corticosteroids have an initial effect but lose effect partly because these drugs do not lead to mucosal healing. Crohn's disease is a transmural inflammation that will lead to complications such as structuring, perforation and fistula if left unchecked.

Immunosuppressant treatment has been helpful, particularly azathioprine, which has been the favoured drug in NZ and in many parts of the world. It is an old drug that is being used as well as possible with new data on appropriate dosing determined by monitoring of blood levels of metabolites.

Surgery is required to deal with complicated disease but Crohn's disease will often reoccur and repeated operations quickly lead to major issues with nutrition and reduced quality of life.

Adalimumab and infliximab are approved and funded in NZ for use in moderate to severe Crohn's disease. Most clinical trials and the current PHARMAC criteria use

the Crohn's disease activity index (CDAI) to define severity of the disease. This is a somewhat cumbersome tool that is not used routinely in clinical practice.

The current criteria in NZ for adalimumab use a relatively high CDAI of 300 (compared to the enrolment criteria of CDAI of 220 for many of the pivotal clinical trials). It is often apparent that "real world" experience is different from clinical trials. The continuation rates in this NZ review (87.3% and 76.6% at 1 and 2 years respectively) are higher than would be expected from clinical trial data. However it should be emphasised that high rates of continuation do not equate directly with response or remission as defined in clinical trials.

Data from the CHARM study showed that complete remission (defined as a CDAI less than 150) occurred in only 36% at 52 weeks and response (defined as a >100 points fall in CDAI) occurred in 41% of patients.⁴ Open label and single centre retrospective studies have shown response rates between 60–75% at 1 year. There are several possible reasons for the high rates of continuation in this study.

Firstly, patients that are naïve to previous anti-TNF treatment have higher response rates. The CARE study showed 61% in remission at 20 weeks for infliximab naïve patients compared with 52% for those previously exposed to anti-TNF treatment.³ It is likely, as the authors suggest, that the rate of previous infliximab use was low in this NZ audit but this data is not presented apart from stating that 7% had "grandfathering", that is, transferring from infliximab to adalimumab, mainly for the convenience of subcutaneous dosing, expecting to maintain remission.⁷

Secondly, patients with objective signs of inflammation (mucosal lesions and raised CRP) may do better with anti-TNF treatment.⁸ Patients in this review may have been treated earlier with more inflammatory disease and less complicated disease. Thirdly, there are several indications for starting treatment in NZ where the continuation rules are not based on CDAI (40% in this study) and therefore patients may continue treatment without achieving a strict definition of response.

This study shows a higher use of adalimumab in Canterbury. This is probably due to early enthusiasm and early uptake of treatment in this region but this variation between different centres may change over time with increasing use in centres outside of Canterbury. Community funding of adalimumab is a much better model than prescribing through gastroenterology departments which resulted in major regional differences in prescribing rates.

There is a gradual loss of response to anti-TNF monoclonal treatment that is approximately 15% per year (17% in this study over mean follow-up of 1.3 years). The falling continuation rates over 3 years in this study are consistent with this trial data.

Many clinical trials allowed an increase to weekly dosing if there was non-response or loss of response. Clinical trials and open label experience for first year show that approximately 15–20% require a dose increase to 40 mg weekly but this option is not available in NZ at present.^{3–6}

There is another anti-TNF monoclonal antibody called certolizumab which can offer another choice if there is loss of response to the other two agents but this is not available in NZ.

The cost of adalimumab in 2013 for the treatment of Crohn's disease was \$11 million. This represents a significant increase in treatment costs for Crohn's disease. It is legitimate to ask what is the benefit over standard treatment?

Gastroenterologists who treat these patients have no doubt that lives have been transformed by this medication but accurate data is required to answer critics of the increasing drug costs. This benefit may be less quantifiable than increased months of survival for cancer treatment but may be more valuable for our community. This study has shown that days spent in hospital after 1 year of treatment is reduced. This is a crude indicator but it is very encouraging to find a significant difference in hospital stay over a relatively short period of treatment. Improved quality of life, return to employment and long-term avoidance of significant surgery are other important goals of treatment.⁹

The costs of treatment will decrease over time although it is likely that the proportion of patients treated with biologicals will gradually increase over time. There were 31 patients (16%) in this NZ audit who were 16 years or less. Children and adolescents do well with this treatment. The resulting improvement in overall wellbeing gives these young people hope to face the future, to complete studies, gain employment and start relationships with confidence.⁶

There are many debates in the field of anti-TNF treatment. The most difficult question is the use, in combination, of immunomodulators such as azathioprine. There is good evidence of better response rates for combination treatment, higher rates of mucosal healing and probably less problems with loss of response over time.¹⁰

The concern with combination treatment is with regards to long-term safety. The risk of infection is increased and there is an increased risk of lymphoma with long-term use of thiopurines—this may be a 3-fold increased risk of this rare cancer.¹¹ Combination treatment is favoured in NZ (data not presented in this study) but the potential risks need addressed with our patients.

When to stop anti-TNF treatment is another difficult question. Some patients achieve “deep remission” with no discernible disease activity, normal inflammatory markers and complete mucosal healing. It is likely that some of these patients will have a sustained response after stopping treatment.¹² Preventing postoperative recurrence is another potential use for adalimumab that is not yet funded. Under the current criteria patients need to have a significant clinical relapse and the opportunity to prevent further surgery may have been missed.

Monitoring of response with faecal calprotectin and serum levels of infliximab or adalimumab with appropriate changes in dose or dosing interval is likely to become part of routine management.¹³ There will be a trend to earlier prescribing in the course of the disease to prevent irreversible gut damage. There is good data showing a better response with early treatment.¹⁴

Biologicals should be started early with an aggressive disease phenotype—this is onset at a young age, poor response to corticosteroids (or early relapse after stopping) and early onset of complicated disease such as fistula (including perianal fistula).

The use of biologicals for ulcerative colitis (UC) has not been the same success story. There is some activity of anti-TNF treatment for UC but this is not considered cost-

effective in NZ at present. Infliximab can be used for severe ulcerative colitis. Other biologicals in development may be more effective for UC.

The future involves optimising the dosing of existing agents and looking to having more options available when there is loss of response. Crohn's disease affects young people and the real test will be the long-term success of biologicals over 10–15 years not just the first 12 months.

Competing interests: Nil.

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