# Retention on anti-tumour necrosis factor therapy: the Waikato experience

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## ABSTRACT

**AIM:** To investigate the retention on anti-TNF agents used in a real-world setting, and determine the factors predicting retention on drug.

**METHOD:** Patients starting anti-TNF therapy were recorded prospectively on the departmental database. Medical records of all patients commenced on anti-TNF therapy between 2006 and 2013 at the Rheumatology Department, Waikato Hospital, Hamilton, were retrospectively reviewed to obtain details of their course on biologic therapy.

**RESULTS:** 183 patients were identified. 139 (76.5%) were commenced on adalimumab. The predominant indication was rheumatoid arthritis (52.5%). 60 patients (32.8%) discontinued their initial anti-TNF agent. Of these, 31.7% were due to primary failure, 36.7% due to secondary failure and 25% due to adverse events. At 5 years, retention on agents was: adalimumab (77.2%), etanercept (69.6%) and infliximab (16.7%). Retention on adalimumab was significantly higher than infliximab ($p<0.001$), but did not differ between adalimumab and etanercept, or etanercept and infliximab.

**CONCLUSION:** In a real-world setting, retention on infliximab was significantly lower than adalimumab.


The advent of biological disease-modifying anti-rheumatic drugs (bDMARDs) has revolutionised the management of chronic inflammatory arthropathies. In particular, tumour necrosis factor (TNF) antagonists are now recommended as first-line biological therapy for the management of rheumatoid arthritis (RA) recalcitrant to conventional DMARDs such as methotrexate.[1]

TNF, formerly TNF-α, is an inflammatory cytokine produced by both immune and non-immune cell types. At low concentrations, TNF exerts a beneficial effect through the initiation and augmentation of host defence mechanisms against local injury or infection.[2] In the context of autoimmune inflammatory diseases however, the high concentrations of TNF induced by unknown stimuli triggers a cascade of cellular responses which ends in apoptosis and up-regulation of inflammatory genes.[2] The importance of TNF in the pathogenesis of inflammatory diseases is evident through the broadening of indications for anti-TNF therapy, since their original development, to include psoriasis, inflammatory bowel disease, ankylosing spondylitis and anterior uveitis.

In New Zealand, three anti-TNF agents are subsidised by the Pharmaceutical Management Agency (PHARMAC) for use in the management of rheumatic disease. Adalimumab was first to become funded in 2006 for RA. The indications were extended in 2009 to include psoriatic arthritis and ankylosing spondylitis. Etanercept has been available since 2004 for juvenile idiopathic arthritis, with access widened in 2009 to include RA, psoriatic arthritis and ankylosing spondylitis. Infliximab became available in 2013, but had previously been approved for in-hospital use via individual District Health Board's medicines and therapeutics committees.

Infliximab and adalimumab are monoclonal antibodies directed against TNF, whereas etanercept is a fusion protein that binds both TNF and lymphotoxins (formerly TNF-β).[2] They differ in their pharmacokinetic properties, dosing regimens and route of administration. Of note, infliximab is

administered by intravenous infusion, while adalimumab and etanercept are administered as subcutaneous injections. Although no head-to-head randomised controlled trials are available, meta-analyses have failed to demonstrate any significant differences in efficacy between these three anti-TNF agents in the management of RA.[3,4] The incidence of adverse events associated with each anti-TNF agent has also not been shown to differ.[3] Accordingly, the European League against Rheumatism (EULAR) considers anti-TNF agents to have similar efficacy and safety in their latest recommendations.[1] Differences do exist in the treatment of other diseases however, with etanercept failing to demonstrate efficacy in the treatment of Crohn's disease compared to infliximab.[5]

In the absence of differences in risk-benefit profiles through randomised controlled trials, drug retention data can be used as an additional measure to aid clinical decisions on choice of initial anti-TNF agent. A recent study based on the Swedish Biologics Register between 2003 and 2011 found that 18.7% of patients discontinued their initial anti-TNF agent in the treatment of rheumatoid arthritis, primarily owing to inefficacy (51%) or adverse events (36%).[6] In this cohort, retention over up to 5 years' follow-up was greatest with adalimumab (81.2%), followed by etanercept (64.3%) and infliximab (49.7%).[6] These findings are consistent with those based on other European biologics registries, including those from the United Kingdom, Switzerland and Denmark.[7-9]

To date, no studies have been performed to assess the retention on anti-TNF agents in the management of rheumatic diseases in New Zealand. The initiation of adalimumab or etanercept for RA requires the presence of active erosive disease with intolerance or failure of methotrexate alone and in combination with sulphasalazine and hydroxychloroquine, followed by ongoing disease after a trial of at least 3 months of methotrexate in combination with leflunomide, cyclosporine or intra-muscular gold. For psoriatic arthritis, adalimumab and etanercept are available if disease activity persists despite a trial of methotrexate and either leflunomide or sulphasalazine. For ankylosing spondylitis, patients must have sacroiliitis, restricted spinal movement and on going disease activity after a trial of physiotherapy and two anti-inflammatory agents. Initiation of infliximab requires failure of adalimumab or etanercept secondary to intolerable side effects, or failure to meet the renewal criteria following at least 4 months' therapy. We set out to review our use of anti-TNF and to explore the factors that predicted retention on these agents.

# Method

All patients commencing anti-TNF therapy at the Rheumatology Department, Waikato Hospital, Hamilton, were recorded in the department database. As specialist authority is required prior to commencement of bDMARDs for rheumatic indications, this database was deemed to be complete for those starting biologic therapy within the public health system.

The electronic and paper clinical records of each patient starting bDMARD between 2006 and 2013 were retrospectively reviewed. Data was collected on date of commencement on bDMARD, duration of therapy, reasons for cessation of therapy, indication for anti-TNF therapy, concurrent conventional DMARD use, as well as demographic variables. Primary failure was defined as lack of clinical improvement after 3 months, at the discretion of the rheumatologist. Secondary failure was defined as loss of efficacy on subsequent clinic visit following an initial response to anti-TNF therapy.

Kaplan-Meier analysis was used to evaluate discontinuation rates of each anti-TNF agent. Log-rank test was performed to analyse differences in discontinuation rates between different anti-TNF agents. Statistical analysis was performed using SPSS version 22. A p-value of $<0.05$ was considered statistically significant.

# Results

Demographic variables are presented in Table 1. A total of 183 patients had been commenced on anti-TNF therapy by rheumatologists at Waikato Hospital between 2006 and 2013. This cohort comprised 59% women with a mean age of 50.8 years (range 10 to 79 years). 10.4% were commenced

**Table 1:** Patient characteristics at initiation of anti-TNF therapy at Waikato Hospital, Hamilton (n = 183)

| Gender | n | % | Mean age (yr) | Range (yr) | |
|---|---|---|---|---|---|
| Male | 75 | 41 | 48 | 10-75 | |
| Female | 108 | 59 | 53 | 19-79 | |
| **Ethnicity** | **n** | **%** | **Location** | **n** | **%** |
| NZ European | 133 | 72.7 | Hamilton | 150 | 82 |
| Other European | 15 | 8.2 | Thames | 20 | 10.9 |
| Māori | 10 | 5.5 | Tokoroa | 5 | 2.7 |
| Indian | 5 | 2.7 | Te Kuiti | 5 | 2.7 |

**Table 2:** Indications for initiation of anti-TNF therapy

| | | Adalimumab | Infliximab | Etanercept | Total |
|---|---|---|---|---|---|
| **Indication** | **RA** | 82 | 2 | 0 | **96** |
| | **AS** | 27 | 12 | 7 | **46** |
| | **PsA** | 20 | 3 | 3 | **26** |
| | **JIA** | 1 | 0 | 5 | **6** |
| | **Other** | 6 | 2 | 1 | **9** |
| **Total** | | **139** | **19** | **25** | **183** |

RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; JIA, juvenile idiopathic arthritis

**Table 3:** Reason for discontinuation of initial anti-TNF agent. Data are presented as n (%)

| | | Primary failure | Secondary failure | Adverse event† | Difficult IV access | Patient request | Total |
|---|---|---|---|---|---|---|---|
| **Drug** | **Adalimumab** | 14 (10.1) | 13 (9.4) | 8 (5.8) | 0 (0) | 0 (0) | **35** (25.2) |
| | **Infliximab** | 2 (10.5) | 5 (26.3) | 5 (26.3) | 3 (15.8) | 1 (5.3) | **16** (84.2) |
| | **Etanercept** | 3 (12.0) | 4 (16.0) | 2 (8.0) | 0 (0) | 0 (0) | **9** (36.0) |
| **Total** | | **19** (10.4) | **22** (12.0) | **15** (8.2) | **3** (1.6) | **1** (0.5) | **60** (32.8) |

†Adverse events included: Recurrent infections (3), rash (3), palmoplantar pustulosis (2), anaphylaxis (1), breast cancer (1), headache (1), injection site reaction (1), miliary tuberculosis (1), peripheral neuropathy (1) and pneumonitis (1).

on infliximab as the initial anti-TNF agent, 13.1% etanercept and 76.5% adalimumab. The indications for initiation of anti-TNF therapy are presented in Table 2. The predominant diagnoses were rheumatoid arthritis (52.5%), ankylosing spondylitis (25.1%) and psoriatic arthritis (13.7%).

Eligibility criteria for public healthcare funding are such that all patients must have inadequate disease control in spite of conventional therapy. 66.1% received concomitant conventional DMARDs through the course of their anti-TNF therapy. Of these, 39.9% were receiving therapy with a single agent. Mean retention on anti-TNF therapy with concomitant DMARD was 145 weeks, compared to 127 weeks when administered without. However, this did not reach statistical significance.

Reasons for discontinuation of initial anti-TNF agent are presented in Table 3. Overall, 60 patients (32.8%) discontinued their first anti-TNF agent. Across the three agents, 19 (31.7%) discontinuations were due to primary failure, 22 (36.7%) due to secondary failure, and 15 (25%) due to adverse events. Of note, the rates of primary and secondary failure were almost equal. Within each agent, rates of secondary failure and adverse events were greatest for infliximab (26.3%, 26.3%), as compared to adalimumab (9.4%, 5.8%) and etanercept (16%, 8%).

**Figure 1:** Retention of anti-TNF agent by year

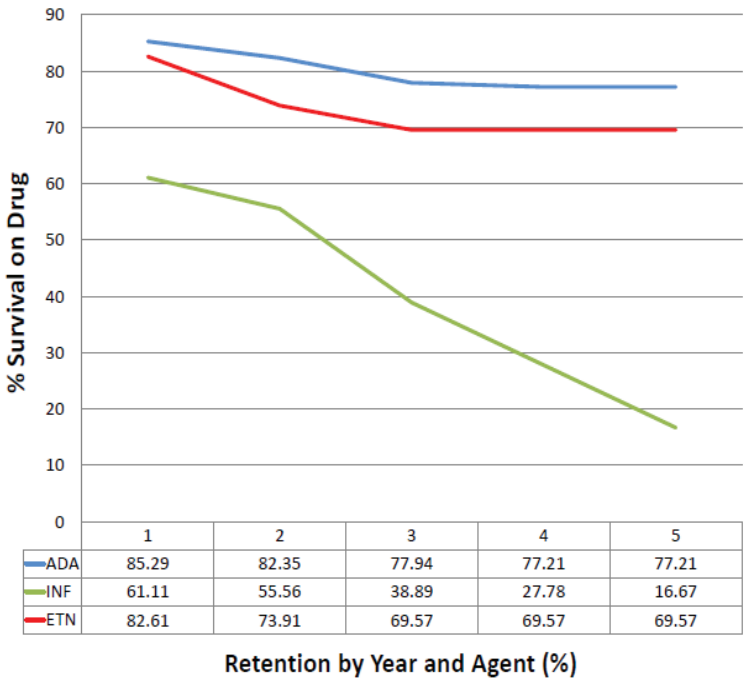


**Figure 2:** Kaplan-Meier analysis of retention on anti-TNF agent. Retention on adalimumab was significantly higher (p<0.001) than etanercept or infliximab.

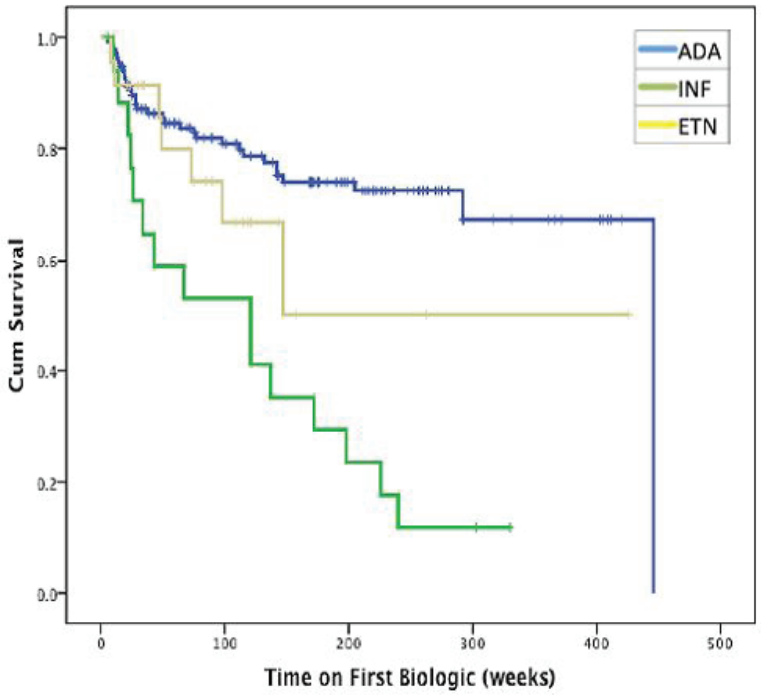


**Table 4:**
Pairwise comparison of retention between anti-TNF agents assessed by Log-rank test.

| First anti-TNF agent | Adalimumab | | Infliximab | | Etanercept | |
|---|---|---|---|---|---|---|
| | $X^2$ | p | $X^2$ | p | $X^2$ | p |
| **Adalimumab** | | | 24.6 | <0.001 | 1.29 | 0.256 |
| **Infliximab** | 24.6 | <0.001 | | | 3.13 | 0.077 |
| **Etanercept** | 1.29 | 0.256 | 3.13 | 0.077 | | |

For those experiencing primary failure, the mean time until discontinuation was 34.5 weeks, compared to 147.2 weeks for those experiencing secondary loss of effect. At 52 weeks, retention of individual anti-TNF agents was 61.1% for infliximab, 82.61% for etanercept and 85.29% for adalimumab (Figure 1). This trend was maintained at 5 years, with retention rates of 16.7%, 69.6% and 72.2% respectively (Figure 1).

Of the variables considered, choice of initial agent was the only statistically significant factor predicting anti-TNF therapy survival ($p<0.001$ by log-rank test) (Figure 2). Pairwise comparisons between agents demonstrates a significant difference in retention only between adalimumab and infliximab ($p<0.001$) (Table 4). Demographics, indication and concomitant use of conventional DMARDS were not significant in this cohort.

# Discussion

This retrospective cohort study has demonstrated a statistically significant difference in survival of the three anti-TNF agents publically funded in New Zealand, when prescribed for rheumatic indications. As the initial anti-TNF agent, infliximab has the poorest retention rate as compared to adalimumab and etanercept.

Our real world data has shown longer retention rates on biologics than reported in other biologics registries. Arora et al recently published a systematic review of European national drug registers.[10] They reported 60-month pooled drug retention rates in biologic-naïve rheumatoid arthritis patients as adalimumab 47.5%, etanercept 52.2% and infliximab 37.1%. Our corresponding figures at 60-months were 77.2%, 69.6% and 16.7%. Shorter drug retention on anti-TNF agents in Europe may reflect ease of access to a greater number of bDMARDs, and consequently, a lower threshold to discontinue and change therapy. In support of this, a Swiss study noted that retention on anti-TNF agents was inversely associated year of initiation, possibly due to the greater availability of alternative therapy being developed and marketed.[8] Additionally, longer retention on leflunomide compared to international data has also been previously demonstrated in an environment where biologic therapy was not yet available.[11]

Consistent with a number of European drug registries, our findings highlight that infliximab has a significantly lower retention compared to adalimumab.[6-10] Our data did not find a statistically significant difference between retention on infliximab and etanercept, perhaps reflecting the relatively low numbers of patients receiving these agents. Previous studies postulate the higher retention on the subcutaneous agents may be due to infliximab's dosing regimen, potentiated by its mode of administration by infusion, which produces greater serum concentrations and heightens risk of an infusion reaction. The rate of infusion reactions, a well described adverse effect of infliximab, is reported to occur in up to 8.6% of infusions.[12] However, as no patients discontinued as a result of infusion reaction, this explanation does not appear applicable to our cohort. It may be that the availability of other agents available by subcutaneous mode of administration and greater patient convenience may also be a driving factor.

An alternative explanation for infliximab's inferior survival is its greater immunogenic potential. Infliximab is a chimeric antibody, which is more immunogenic than the humanised antibodies like adalimumab.[13] However, the clinical significance of the formation of anti-drug antibodies remains unclear. Anti-infliximab antibodies have been reported in up to 11% of patients who discontinued therapy within 30 weeks.[14] Paradoxically, an even greater number of patients (28%) receiving adalimumab developed anti-adalimumab antibodies after 3 years in a prospective cohort study which found a statistically significant association between anti-adalimumab antibody and failure to sustain adequate disease control.[15] No commercial tests for these anti-drug antibodies are available and it is not possible to assess this in our cohort.

The development of anti-drug antibodies is reduced with concurrent immunosuppressive therapy such as methotrexate.[13] Indeed, multiple studies have reported superiority of combination therapy with anti-TNF agent and methotrexate, compared to anti-TNF agent alone, for both clinical

and radiographic outcomes.[16] In our cohort, use of concomitant conventional DMARD extended the mean survival of anti-TNF agent by 18 weeks, although this did not reach statistical significance.

To our knowledge, this is the first study investigating the survival of anti-TNF agents in a New Zealand cohort. As an observational study, it has merits in considering the use of bDMARDs in a 'real world' setting with an extended follow-up period. However, the main limitations are the retrospective nature of the data collection and the lack of a standardised protocol definition of primary and secondary failure of the medications.

We conclude that in this regional cohort of biologic-naïve patients, significant differences in the survival of initial TNF antagonists were observed. Treatment retention was shorter for patients commenced on infliximab than those commenced on adalimumab or etanercept. These findings are in keeping with those of European drug registries, but cannot be accounted for by infusion reactions unique to infliximab's intravenous administration, as postulated by previous studies.

**Competing interests:** Nil

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