

Adalimumab for Crohn's disease in New Zealand—a prospective multicentre experience

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Abstract

Aim Adalimumab is an effective treatment for Crohn's disease (CD). We aimed to describe the early patterns of use, efficacy and response to adalimumab in four regions of New Zealand.

Methods Prospectively collected CDAI data were used to examine adalimumab continuation rates in CD patients. Reasons for adalimumab cessation were determined and phenotypic characteristics of those remaining on adalimumab were examined.

Results 194 patients (100 female) from four centres were included. Indications for adalimumab included CDAI>300 (59.8%), extensive small intestinal disease (21.1%), stoma with active disease (4.6%), risk of short gut syndrome (7.7%) and other (6.7%). The mean follow-up was 20 months (252.8 patient years of data). Adalimumab continuation rates at 6, 12, 24 and 30 months were 92.7%, 87.3%, 76.6% and 67.4%, respectively. Patients with penetrating disease behaviour were more likely to continue on adalimumab ($p<0.005$). There was a significant reduction in mean CDAI from 357 to 110 ($p<0.0001$) over a 6-month period. The mean (range) number of days spent in hospital per patient in the year prior and after adalimumab initiation were 3.5 (0–38) days and 1.9 (0–67) days, respectively ($p<0.0001$).

Conclusions Adalimumab continuation rate in this multicentre CD population was higher than other populations. This may be due to adalimumab being used more commonly as the initial biologic drug in New Zealand.

Crohn's disease (CD) is an incurable chronic relapsing inflammatory enteropathy that leads to significant symptoms, morbidity and disability amongst those affected.¹ CD incidence is rising rapidly with high rates described in New Zealand and Australia and increasing rates in Asia.^{2–5} The treatment aims in CD are to induce and maintain clinical remission and subsequently prevent complications such as strictures, fistulising disease and surgery.

The treatment of CD includes a wide range of anti-inflammatory and immunosuppressive drugs, nutritional therapy and surgery. Over the last decade, biological drugs such as infliximab and adalimumab have been developed and shown to be effective at inducing and maintaining remission in patients with moderate to severe CD.^{6,7}

Adalimumab was first approved for use for moderate to severe CD in New Zealand in April 2007 while it became fully funded in September 2009 with specific criteria governing its use (Figure 1). These criteria were similar to those adopted in Australia,

although are more restrictive than the inclusion criteria used in clinical trials and in other jurisdictions.

Figure 1. Pharmac criteria used to approve adalimumab use in New Zealand

INITIAL APPLICATION

Applications only from a Gastroenterologist. Approvals valid for 3 months.

Patient has severe active Crohn's disease,

AND

Patient has a Crohn's disease Activity Index (CDAI) score of greater than or equal to 300

OR

Patient has extensive small intestinal disease affecting more than 50 cm of the small intestine

OR

Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection

OR

Patient has an ileostomy or colostomy, and has intestinal inflammation

AND

Patient has tried but has had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximal tolerated doses (unless contraindicated) and corticosteroids

AND

Surgery (or further surgery) is considered clinically inappropriate

RENEWAL

Applicant is a Gastroenterologist

OR

Applicant is a Practitioner and confirms that a Gastroenterologist has provided a letter, email or fax recommendation that the patient continues with adalimumab treatment

AND

The CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on adalimumab

OR

The CDAI score is 150 or less

OR

The patient has demonstrated an adequate response to treatment but CDAI score cannot be assessed

AND

Applicant to indicate the reason that CDAI score cannot be assessed

AND

Adalimumab to be administered at doses no greater than 40mg every 14 days

Adalimumab is a fully humanised immunoglobulin G Class 1 molecule targeting tumour necrosis factor- α (TNF- α). It is licensed for use in a number of inflammatory diseases including Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis. While clinical trials provide essential endpoints for drug registration, the real life experience of using these drugs is often different, particularly with regard to patient selection and efficacy.

Exploring the efficacy and toxicity of adalimumab for CD patients in New Zealand provides a unique opportunity. Unlike most countries where both anti-TNF- α drugs (adalimumab and infliximab) are available equally for the treatment of luminal CD, this has not been the case in New Zealand.

The government drug-buying agency (Pharmac) negotiated a single supply deal with AbbVie (formerly Abbott Laboratories) to reimburse the cost of adalimumab for the treatment of severe CD with specific criteria (Figure 1).

While infliximab has remained available for the treatment of luminal CD, the use of infliximab for this indication has been very limited and at the financial discretion of individual hospitals.

Adalimumab, therefore, has become the first choice anti-TNF- α for the treatment of luminal CD in New Zealand. Furthermore, the use of this drug requires strict criteria to be met (Figure 1) with patients who are able to (i.e. those without a stoma) being required to complete a CDAI prospectively prior to the initiation of adalimumab and at six monthly intervals thereafter to confirm remission (CDAI<150) or CDAI 100 response.

In this uniquely controlled environment, we aimed to describe the early patterns of use, efficacy and response to adalimumab in four regions of New Zealand.

Materials and Methods

IBD services in four regions of New Zealand provided data on patients receiving adalimumab for CD. Each of these services supervised the application and renewal process for all CD patients receiving adalimumab for CD in their region. The regions were Canterbury (population 490,000), Otago (population 210,000), Auckland City (population 468,000) and Hutt Valley/Wairarapa (population 186,000).

Data were collected on each patient prospectively including date of birth, date of diagnosis, date of adalimumab commencement and date of cessation (and indication) or last follow up, sex, disease phenotype using Montreal classification,⁸ indication for adalimumab commencement (Figure 1), CDAI at adalimumab commencement, adverse drug reactions, days in hospital in the year before and the year after adalimumab commenced.

Data were analysed descriptively using SPSS Statistics Version 20 (IBM). Discrete variables were analysed using the Chi-squared test with the level of significance at $p < 0.05$. Kaplan Meier survival curves were constructed to show time to loss of response to adalimumab. A Mantel-Cox log rank test was used to compare the survival of phenotypic and other subgroups.

This study fulfilled the New Zealand Health and Disability Human Ethics Criteria for audit activity.

Results

The characteristics of the study population can be seen in Table 1. Most patients were from the Canterbury region and there were significant differences between the study groups with regard to age of diagnosis, disease location and behaviour and mean duration receiving adalimumab.

Table 1. Characteristics of the study population

Variables	Canterbury	Auckland City	Otago	Hutt/Wairarapa	Total population
Total	117	30	19	28	194
Female	59 (50.4)	15 (50)	8 (42.1)	18 (64.3)	100 (51.5)
Age*					
<17	16 (13.9)	11 (36.7)	0 (0)	4 (14.3)	31 (16.1)
17–40	83 (62.4)	18 (60)	15 (78.9)	17 (60.7)	133 (69.3)
>40	16 (13.9)	1 (3.3)	4 (21.1)	7 (25)	28 (14.6)
Location**					
Ileal	24 (20.9)	8 (26.7)	13 (68.4)	5 (17.9)	50 (26)
Colonic	36 (31.3)	15 (50)	3 (15.8)	5 (17.9)	59 (30.7)
Ileocolonic	55 (47.8)	7 (23.3)	3 (15.8)	18 (64.3)	83 (43.2)
Behaviour#					
Inflammatory	68 (61.3)	12 (40)	13 (68.4)	11 (39.3)	104 (55.3)
Stricturing	30 (27)	12 (40)	1 (5.3)	8 (28.6)	51 (27.1)
Penetrating	13 (11.7)	6 (20)	5 (26.3)	9 (32.1)	33 (17.6)
Perianal disease	32 (27.4)	15 (50)	5 (26.3)	10 (35.7)	62 (32)
Disease duration (mean)	8.5 years	8.4 years	8.3 years	11.5 years	8.9 years
ADA indication					
Elevated CDAI	68 (58.1)	19 (63.3)	10 (52.6)	19 (67.9)	116 (59.8)
Extensive small bowel disease	26 (22.2)	6 (20)	5 (26.3)	4 (14.3)	41 (21.1)
Stoma	5 (4.3)	1 (3.3)	0 (0)	3 (10.7)	9 (4.6)
Grandfathered	9 (7.7)	0 (0)	2 (10.5)	2 (7.1)	13 (6.7)
Short gut	9 (7.7)	4 (13.3)	2 (10.5)	0 (0)	15 (7.7)
Duration of disease prior to ADA (mean)**	19.3 months	22.5 months	15.1 months	25.5 months	20.3 months
Duration on ADA (mean)#	1.2 years	1.4 years	1.1 years	1.9 years	1.3 years
Cessation due to ADR	5 (4.3)	2 (6.6)	0 (0)	1 (3.6)	8 (4.1)
Cessation due to loss of response	24 (20.9)	3 (9.9)	4 (21)	2 (7.1)	33 (17.1)
Cessation due to pregnancy	1 (0.8)	0 (0)	2 (10.5)	0 (0)	3 (1.5)
Cessation during the study period	30 (26)	5 (16.5)	6 (31.5)	3 (10.7)	44 (23.7)

*P<0.005, **P<0.01, #P<0.05.

The most common cause for cessation was loss of response followed by adverse drug reactions and voluntary cessation due to pregnancy. Adverse drug reactions leading to cessation included neurological symptoms [paraesthesia (1), pins and needles (1)], tiredness (1), allergic reaction (1), cardiomyopathy (1), neutropaenia (1) and psoriaform reaction (2). These adverse effects occurred over 252.7 years of patient follow-up.

There was no statistically significant difference between centres with regard to continuation rates. Combined adalimumab continuation rates at 6, 12, 24 and 30 months after initial prescription were 92.7%, 87.3%, 76.6% and 67.4%, respectively.

There were no significant differences in adalimumab continuation rates between sexes, disease locations, the presence of perianal disease, disease duration and indication for commencing adalimumab (Figures 2–4). Patients with penetrating disease behaviour were more likely than those with stricturing or inflammatory behaviour to continue on adalimumab (Figure 5, $p < 0.005$).

In those patients who were prescribed adalimumab for severe active Crohn's disease with a CDAI > 300 , there was a significant reduction in mean CDAI from 357 to 110 (Figure 6, $p < 0.0001$).

Admission rates in patients prescribed adalimumab were compared before and after the commencement of adalimumab. The mean (range) number of days spent in hospital per patient in the year prior and the year after the initiation of adalimumab was 3.5 (0–38) days and 1.9 (0–67) days, respectively ($p < 0.0001$).

Figure 2. Cumulative probability of remaining on adalimumab treatment for Crohn's disease between disease location

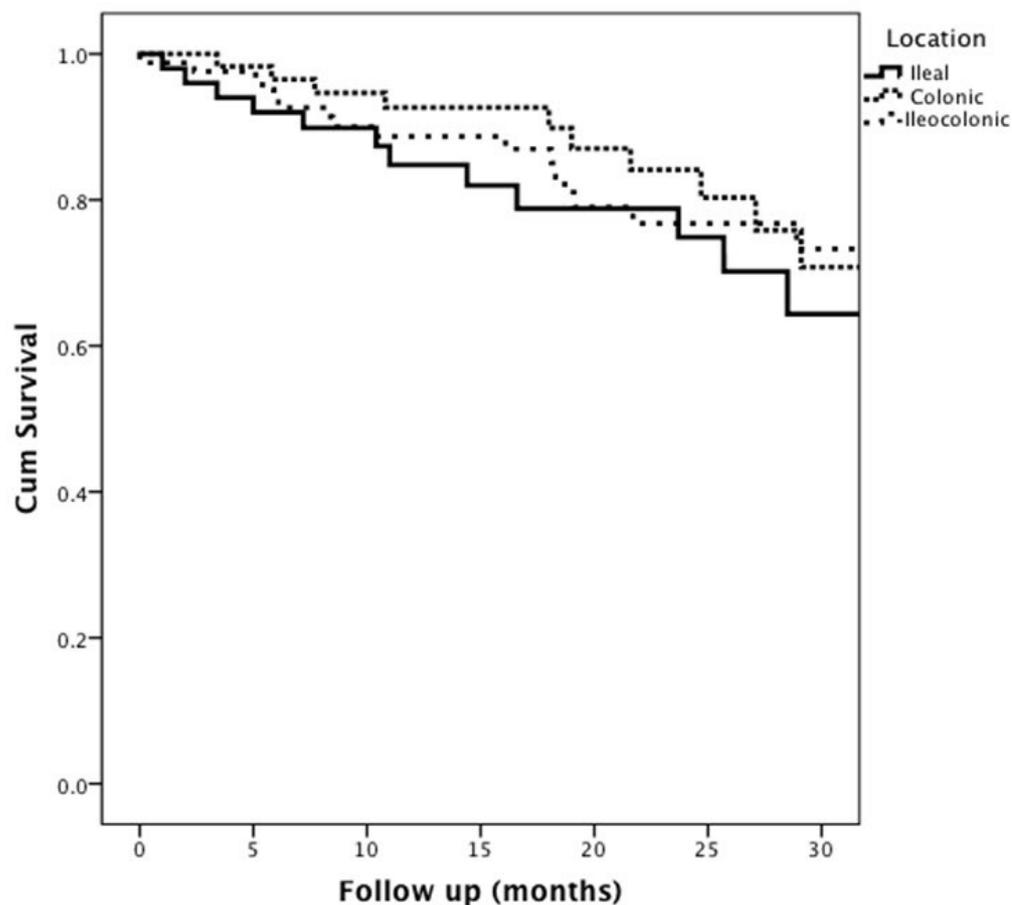


Figure 3. Cumulative probability of remaining on adalimumab treatment for Crohn's disease in those with and without perianal disease

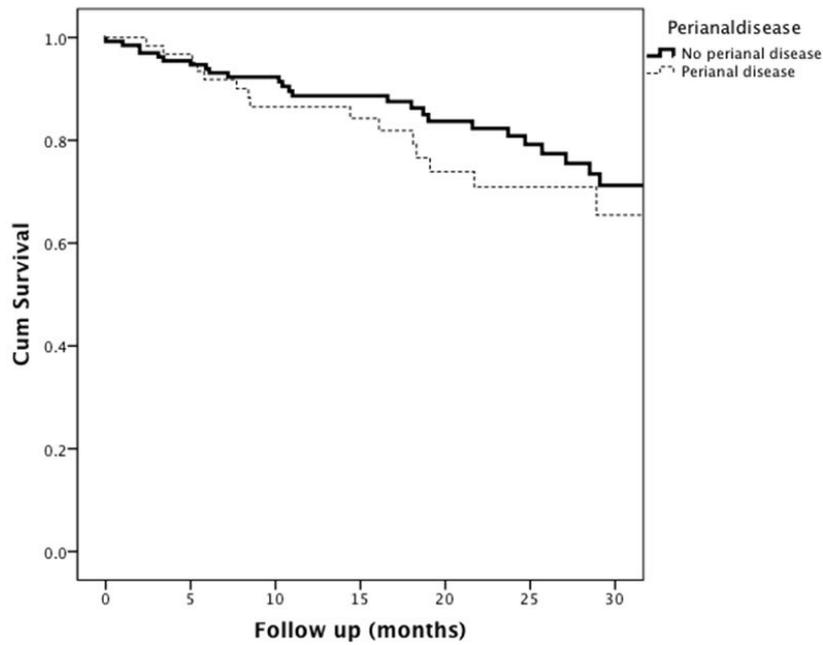


Figure 4. Cumulative probability of remaining on adalimumab treatment for Crohn's disease in those with different indications for adalimumab therapy

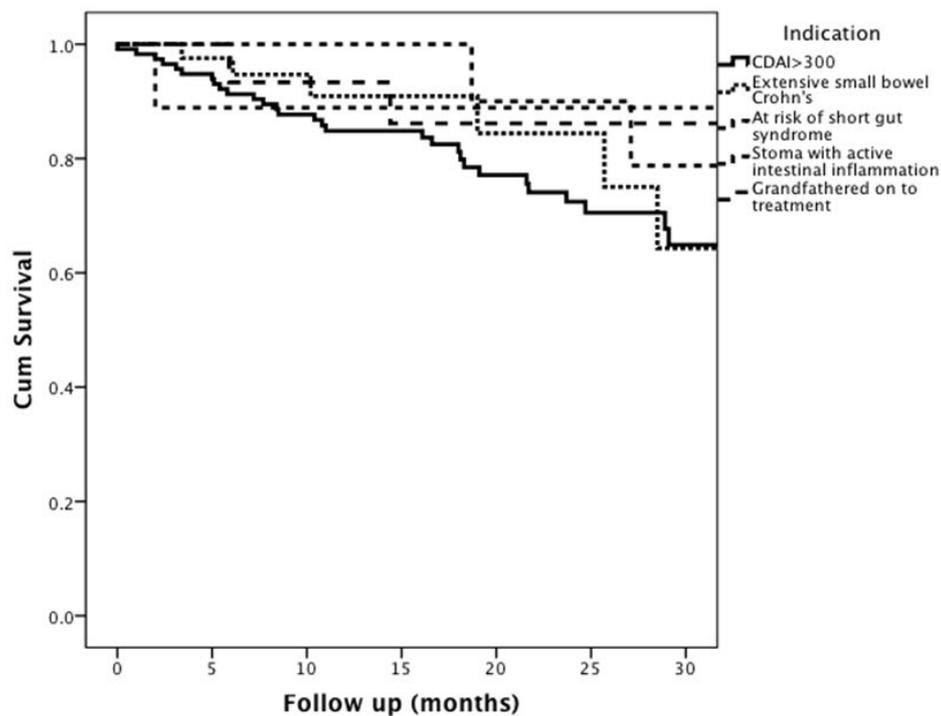


Figure 5. Cumulative probability of remaining on adalimumab treatment for Crohn's disease in those with different disease behaviour

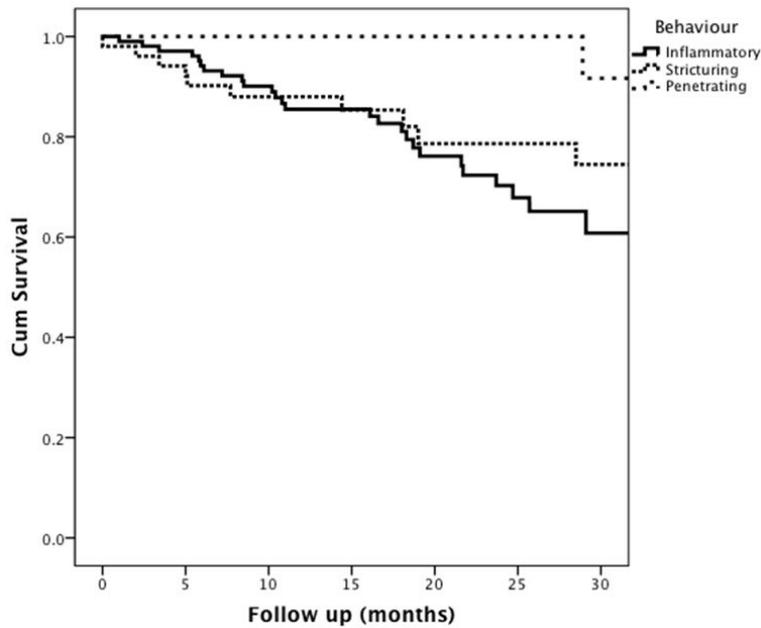
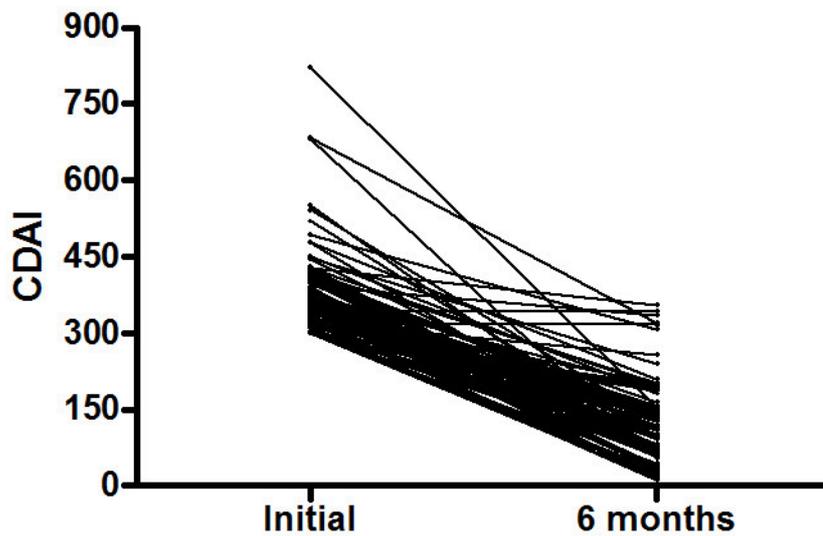


Figure 6. Changes in CDAI in patients with severe active Crohn's disease following initiation of adalimumab



Discussion

Adalimumab has been shown to be effective for the treatment of moderate to severe Crohn's disease in clinical trials.^{7,9} However, the experience of efficacy and toxicity of a drug in the real world may differ from clinical trials where many patients are

excluded.¹⁰ Furthermore, some patients who received adalimumab in clinical trials would not be eligible to receive it in some jurisdictions. The present study demonstrates high rates of adalimumab continuation compared with clinical trials. At 30 months after initiation of adalimumab, over three-quarters of all patients remained on the drug. Furthermore, the rates of adverse reactions leading to cessation of the drug were low (4.1%) and a small number of patients voluntarily stopped the drug after finding that they were pregnant (1.5%).

Compared with other published case series of adalimumab continuation rates, the present study suggests high rates of efficacy. Data from a multicentre retrospective study from Madrid of 174 CD patients with luminal disease followed for a mean of 40 weeks showed a response rate of 70% at 6-month follow up. However, 59% of the cohort had previously been treated with infliximab.¹¹

A retrospective study from the Mayo Clinic (Rochester) of 118 CD patients revealed a cumulative probability of complete or partial response at one year of 81.3%. However, 96% of the patients had received prior infliximab and almost half were receiving systemic corticosteroids at the commencement of adalimumab. Furthermore, dose escalation to weekly adalimumab was required in 54% of patients by 1 year.¹²

A further retrospective study of 55 Swiss patients revealed a remission rate at 12 months of 44.7%.¹³ An early series prospectively describing 38 CD patients using adalimumab from Western Australia demonstrated response and remission rates of 81.8% and 63.6% at 12 weeks.¹⁴

Unlike the present study, 15 of these patients were secondary non-responders to infliximab. Finally, a Scottish nationwide retrospective study of 98 CD patients receiving adalimumab with 100.5 patient follow-up years revealed a clinical remission rate of 60% at 1 year but dose escalation in 30% by this time.¹⁵

A large database study using US Medicare data from 2006–2010 revealed that 47% of patients commenced on adalimumab continued on the drug at 26 weeks. Similar rates were found for infliximab continuation with no significant difference between the two drugs with regard to need for surgery or hospitalisation.¹⁶

The present study differs from other published studies that used retrospective assessments of disease activity, included high rates of infliximab experienced patients and included frequent dose escalations.^{14,15,17–20}

The present study is one of the only prospective studies where adalimumab is used as a first line biologic drug. These differences may be the major reasons for the high rate of continuation in the present study compared with other published studies. It is clear from a number of studies that the rate of response and remission to a second biologic drug is less than that for the first biologic drug,²¹ an observation that may reflect more severe disease in those who fail a biologic, or increased drug clearance.

The cohort of patients included in this study represents those with the most severe Crohn's disease from the centres that provided data. In addition to the continuation rates being high, there is a significant CDAI reduction in those prescribed adalimumab for active luminal disease. These data were recorded prospectively and show a significant reduction in CDAI from a mean of 357 to 110.

Crohn's disease patients in New Zealand must have a CDAI greater than 300 and have failed immunomodulators to access adalimumab. To remain on adalimumab they must either enter remission (CDAI <150) or have a 100-point reduction in CDAI from baseline. These criteria for commencing adalimumab represent patients with more severe disease than the clinical trials where a CDAI of greater than 220 was required and many patients did not receive immunomodulators.^{7,9}

The reduction in CDAI has also translated into a reduction in Crohn's disease related hospitalisation which, in this group of patients, reduced in the year after commencing adalimumab from a mean of 3.5 to 1.9 days in hospital per patient. Reductions in hospitalisation have been seen in randomised controlled trials where patients receiving adalimumab are hospitalised significantly less than those receiving placebo.²² Long-term effects on hospitalisation and surgery have also been seen in open label studies.²³

There is heterogeneity between the populations from each of the study centres. Canterbury patients comprise the majority of patients but also represent the largest population with a high prevalence and incidence of Crohn's disease.^{2,24} It is known that some patients from the Auckland City region were not recruited, particularly those who are cared for in the private sector. The phenotype of patients receiving adalimumab in each of the centres was also different, with Canterbury and Otago having higher proportions of patients with inflammatory disease behaviour while Auckland City and Hutt Valley/Wairarapa having higher proportions of patients with complicated disease behaviour.

There were no significant differences in adalimumab continuation rates between other disease phenotypic or drug indication characteristics except for higher rates of drug continuation amongst those who had penetrating disease behaviour. This observation is somewhat surprising given that patients with penetrating disease have a higher risk of requiring surgery and failing medical therapy than patients with inflammatory disease.^{25,26} One explanation for this observation may be that these patients were more likely to have already undergone surgery prior to commencing adalimumab, or that they were more likely to have been prescribed adalimumab for non-CDAI indications such as active disease in a patient with a stoma, or active disease in those with a high risk of developing short gut syndrome.

The adverse events noted in this study are consistent with the published literature. Interestingly infections did not comprise a significant number of adverse reactions leading to adalimumab cessation. Other centres in Australasia have also reported relatively low rates of infections in patients receiving biological drugs²⁷ although one must always be vigilant for infections in this group of patients.²⁸

In summary, we report high continuation rates of adalimumab therapy in a large prospectively recruited cohort of CD patients. Unlike other studies, these patients received adalimumab as a first line biologic drug for CD after failing standard immunomodulator therapy. These high rates of continuation are likely to reflect the use of adalimumab as the first biologic drug in these patients. Furthermore, the prospective collection of data confirms the efficacy of adalimumab for severe Crohn's disease and demonstrates a significant impact on short-term hospitalisation. No new or unexpected adverse events have been identified.

Competing interests: Nil.

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