Anti-tumour necrosis factor-α treatment for perianal Crohn's disease in Australia

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ABSTRACT

Objective: To examine the prevalence of perianal Crohn's disease (PCD) and the eligibility of PCD patients to access anti-tumour necrosis factor-alpha (anti-TNFα) treatment under current Australian Pharmaceutical Benefits Scheme (PBS) guidelines.

Design, setting and participants: A retrospective study of patients with Crohn's disease (CD) and PCD attending four large adult inflammatory bowel disease (IBD) centres in Australia between January 2004 and May 2008. Patients for whom anti-TNFα therapy was clinically indicated were assessed to determine whether they satisfied PBS criteria for subsidised medication.

Main outcome measures: Prevalence of CD and PCD in patients attending different IBD centres; eligibility of PCD patients for PBS-subsidised anti-TNFα medication.

Results: Data were available on 3589 patients, representing about 6% of all patients with IBD in Australia. Of the 1815 patients with CD, 310 (17%) had PCD. Anti-TNFα therapy was deemed clinically indicated for 166 patients with PCD (54%), of whom 49 (30%) did not qualify for PBS-funded therapy.

Conclusion: Thirty per cent of patients with clinically significant PCD currently do not have access to PBS-subsidised optimal medical treatment. We believe that PBS criteria should be extended to include this subgroup of IBD patients.

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Perianal Crohn's disease (PCD) is a complication of Crohn's disease (CD)[1] that can significantly impair patients' quality of life.[2,3] Anti-tumour necrosis factor-alpha (anti-TNFα) treatment provides a significant advance in management of PCD-associated fistulae. The effectiveness of anti-TNFα therapy for alleviating PCD (including closing fistulae), first demonstrated by Present and colleagues[4] in a double-blind randomised controlled trial (RCT), has been confirmed and extended by two other double-blind RCTs: the ACCENT II Trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients with Fistulizing Crohn's Disease)[5] and the CHARM Trial (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance).[6] These trials demonstrate a reduction in hospitalisations and surgical procedures as well as improved health-related quality of life with anti-TNFα therapy.[5-8] They are the only medical therapies shown by double-blind RCTs to alleviate PCD-associated fistulae.

Currently, two anti-TNFα agents, infliximab and adalimumab, are listed on the Australian Pharmaceutical Benefits Scheme (PBS) for treating subgroups of CD patients with difficult active luminal disease, extensive small bowel disease, a short gut or a stoma (Box 1). Clinical criteria for PBS subsidy rely in large part on the Crohn's Disease Activity Index (CDAI)[9] as a measurement tool to assess eligibility. Other secondary measures of intestinal inflammation (raised platelet count, erythrocyte sedimentation rate, C-reactive protein level, stool lactoferrin or calprotectin level, and radiological testing) are considered for patients with small bowel disease, short gut syndrome, ileostomy or colostomy.

Unfortunately, the CDAI score, which was developed to measure luminal disease activity,[10] does not reflect PCD activity. Patients primarily affected by a draining fistula may have a relatively low CDAI score, as this contributes only 20 points to the overall CDAI score.[11] Hence, the PBS criteria potentially exclude patients with PCD from obtaining subsidised anti-TNFα medications, despite Level 1 evidence of clinical efficacy of these agents for PCD and the lack of adequate alternative therapies.

The aims of our study were to assess the prevalence of PCD among patients in four large Australian inflammatory bowel disease (IBD) centres and to determine the proportion of patients with clinically significant PCD who would qualify for subsidised anti-TNFα therapy under current PBS rules.

Abbreviations

Anti-TNFα	Anti-tumour necrosis factor-alpha
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
IBD	Inflammatory bowel disease
PBS	Pharmaceutical Benefits Scheme
PCD	Perianal Crohn's disease
PDAI	Perianal Disease Activity Index
RCT	Randomised controlled trial

METHODS

We conducted a cross-sectional cohort study of adults from four Australian IBD centres over the period January 2004 to May 2008, using an established AIBDA (Australian IBD Association) web-based database. AIBDA is one of three specialty interest associations within the Gastroenterology Society of Australia. Its members have an active clinical research focus on IBD. Data in

1 Eligibility criteria for PBS-subsidised anti-TNFα therapy

To be eligible for PBS-subsidised anti-TNFα therapy, a patient must have failed to achieve adequate response to prior systemic therapy, including 6 weeks' steroid therapy and more than 3 months' immunomodulatory therapy. Additionally, the patient must have:

- A Crohn's Disease Activity Index score of ⩾ 300; or
- Extensive small intestinal disease with radiological evidence of intestinal inflammation affecting more than 50 cm of the small bowel; or
- Diagnostic imaging or surgical evidence of short gut syndrome, or an ileostomy or colostomy with evidence of intestinal inflammation.

Anti-TNFα = anti-tumour necrosis factor-alpha. PBS = Pharmaceutical Benefits Scheme. ◆

the database are collected prospectively but voluntarily. Contributing centres were the Mater Health Services Adult Hospital, Brisbane, Queensland; the Royal Brisbane and Women's Hospital, Brisbane, Queensland; Fremantle Hospital, Fremantle, Western Australia; and Flinders Medical Centre, Adelaide, South Australia. Each of the contributing centres was asked to provide site statistics on:

- The total number of IBD and CD patients;
- The total number of PCD patients;
- The underlying luminal disease distribution in PCD patients;
- The number of PCD patients for whom anti-TNFα therapy was clinically indicated; and
- The number of patients with PCD who met the current PBS prescribing criteria.

For the purposes of our study, PCD was defined as "active fistulising perianal, vulvovaginal and/or penile disease". Patients with skin tags, haemorrhoids, fissures or isolated anorectal strictures were excluded. Luminal disease distribution was classified as ileal, colonic, ileocolonic or upper gastrointestinal, according to the Montreal disease classification.[12] In addition, there was a group of patients in which disease was confined to the perianal or genital regions without intestinal involvement. The treating physicians were asked to retrospectively assess eligibility for PBS-subsidised anti-TNFα therapy according to the current criteria for the CD subgroups (Box 1). Anti-TNFα therapy was deemed to be clinically indicated, irrespective of current PBS criteria, for patients with moderate or severe faecal or mucopurulent discharge from fistulating PCD[4] in spite of adequate conventional treatment (defined as at least 4 months' therapy with an adequate dose of thiopurine or methotrexate, with or without antibiotics).[4]

Statistical analysis

De-identified data were collated by the Mater site and analysed using a χ^2 test or Fisher exact test. Statistical significance was reported at $P < 0.05$, with the possibility of adjustment using the Bonferroni correction for multiple corrections. Analyses were performed using Stata software, version 9.2 (StataCorp, College Station, Tex, USA). Post-hoc power calculation using the outcome of PBS eligibility demonstrated a power of over 90%.

Ethics approval

The collection of demographic and clinical data for epidemiological research was approved by the human research ethics committees of each centre, and patients gave their informed consent for this purpose.

RESULTS

Complete data were identified for 3589 adult patients from the participating IBD centres (Box 2). Of these, 1815 (51%) had CD, and of those with CD, 310 (17%) had PCD.

Among patients with PCD, the largest group was those with ileocolonic disease (143 [46%]), followed by colonic disease (84 [27%]) and ileal disease (71 [23%]). Twelve patients (4%) had PCD in the absence of luminal disease. None of the PCD patients had isolated upper gastrointestinal CD.

Anti-TNFα therapy was deemed clinically indicated (as defined in the Methods section) for 54% of patients (Box 3). Seventy per cent of these patients met current PBS criteria for subsidised medication (113 on the basis of active luminal disease, three on the basis of short gut, ileostomy or colostomy, and one on the basis of extensive small bowel disease). There was variation between sites with regard to the proportion of patients with PCD requiring anti-TNFα therapy ($P < 0.001$) and the proportion of patients eligible for PBS-subsidised treatment ($P = 0.001$).

DISCUSSION

Our study sampled a large population of IBD patients, which we estimate (on the basis of a 2007 report on CD[13]) to be 6% of all adult and paediatric patients with IBD in Australia. Patients with CD made up slightly over half of our study population. The prevalence of PCD (17%) was consistent with prevalences reported elsewhere.[14,15] Nearly a third of PCD patients in our study who had a clinically indicated need for anti-TNFα therapy did not meet PBS criteria and therefore could not receive subsidisation for these high-cost drugs. This occurred despite Level 1 evidence demonstrating the efficacy of anti-TNFα therapy for fistulising CD and the lack of effective alternative therapies.[4-8]

Eligibility for PBS subsidy is strongly influenced by the CDAI score, but the score is a poor measure of quality of life. Inadequacy of the CDAI for scoring PCD severity may explain why many patients for whom anti-TNFα therapy is clinically indicated are ineligible for PBS subsidy. This was highlighted by a recent Australian study described during Australian Gastroenterology Week.[16] The study found that in a cohort of patients with active PCD resulting in significant impairment to quality of life, the mean CDAI score was only 236, with individual scores rarely exceeding the threshold of 300 needed to comply with PBS criteria.

Several methods have been devised to quantify PCD severity. In our study, we employed a "fistula drainage assessment" of moderate or severe faecal or mucopurulent discharge to define clinical severity. This assessment tool, used in the first infliximab double-blind RCT,[4] has the advantages of being simple, easy to use retrospectively (because the presence or absence of an actively discharging fistula is recorded in our database assessment field), and clini-

2 Disease characteristics, by IBD centre

	IBD	CD	PCD
Hospital	*n*	*n* (% of IBD)	*n* (% of CD)
MHSAH	975	407 (42%)	66 (16%)
RBWH	1135	520 (46%)	110 (21%)
FH	650	425 (65%)	74 (17%)
FMC	829	463 (56%)	60 (13%)
Total	*3589*	*1815 (51%)*	*310 (17%)*

CD = Crohn's disease. FMC = Flinders Medical Centre. FH = Fremantle Hospital. IBD = inflammatory bowel disease. MHSAH = Mater Health Services Adult Hospital. PCD = perianal CD. RBWH = Royal Brisbane and Women's Hospital. ◆

3 PBS eligibility of PCD patients for whom anti-TNFα therapy was clinically indicated

	PCD	Anti-TNFα therapy indicated*(TI)	PBS ineligible†
Hospital	*n*	*n* (% of PCD)	*n* (% of TI)
MHSAH	66	32 (48%)	14 (44%)
RBWH	110	42 (38%)	3 (7%)
FH	74	61 (82%)	22 (36%)
FMC	60	31 (52%)	10 (32%)
Total	*310*	*166 (54%)*	*49 (30%)*

Anti-TNFα = anti-tumour necrosis factor-alpha. FMC = Flinders Medical Centre. FH = Fremantle Hospital. MHSAH = Mater Health Services Adult Hospital. PCD = perianal Crohn's disease. PBS = Pharmaceutical Benefits Scheme. RBWH = Royal Brisbane and Women's Hospital. * $P < 0.001$ for between-centre differences. † $P = 0.001$ (based on the Fisher exact test) for between-centre differences. ◆

cally relevant to anti-TNFα treatment. The more comprehensive assessment tool, the Perianal Disease Activity Index (PDAI),[17] which scores five subcategories (discharge or drainage; pain; restriction of sexual activity; type and number of perianal lesions; and induration), is not fully clinically validated and is difficult to equate with meaningful clinical remission.[10] Furthermore, anti-TNFα treatment can be contraindicated if there is induration (the fifth subcategory of the PDAI).

There was significant variability among patients in our study with regard to clinical indication for anti-TNFα therapy and eligibility for PBS-subsidised therapy (Box 3). While this is perhaps not surprising, given that this is a real-life post-marketing study based on information from a voluntarily maintained database, the causes of variability require some explanation. First and foremost, the large subjective component involving functional assessment of diarrhoea, pain and wellbeing contributing to the CDAI score may lead to significant variation or even manipulation of the CDAI score with regard to eligibility. Other factors that may contribute to variability include different referral patterns within Australian states and individual prescriber thresholds for failure of conventional therapy.

The total cost to the government of anti-TNFα therapy in the financial year 2007–2008 in Australia was $174 397 235,[18] most of which was expended on rheumatoid arthritis. Expenditure on CD was $14 125 377. Based on prevalence data, it is estimated that the anti-TNFα expenditure on all PCD in 2007 was about $2 400 000. This cost should be compared with the cost of not providing PBS-subsidised anti-TNFα treatment for PCD. According to a recent Australian study, CD patients with fistulising disease incur a significantly higher annual health care utilisation cost (exclusive of medications) than CD patients without fistulae.[19] This includes hospitalisation for local surgery (eg, drainage or repair of fistulae) and more radical surgery (eg, ileostomy). Importantly, from the patient perspective in this predominantly young population, anti-TNFα therapy can help to alleviate faecal incontinence and to reduce awkwardness around sexual activity. We believe that the cost of expanding the PBS criteria to include all patients with clinically significant PCD would be well justified, given the proven clinical benefit of anti-TNFα therapy in this group of CD patients.

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COMPETING INTERESTS

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REFERENCES

1 Tarrant KM, Barclay ML, Frampton CMA, Gearry RB. Perianal disease predicts changes in Crohn's disease phenotype — results of a population-based study of inflammatory bowel disease phenotype. *Am J Gastroenterol* 2008; 103: 3082-3093.
2 Kamm MA, Ng SC. Perianal fistulizing Crohn's disease: a call to action. *Clin Gastroenterol Hepatol* 2008; 6: 7-10.
3 Kasparek MS, Glatzle J, Temeltcheva T, et al. Long-term quality of life in patients with Crohn's disease and perianal fistulas: influence of fecal diversion. *Dis Colon Rectum* 2007; 50: 2067-2074.
4 Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; 340: 1398-1405.
5 Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; 350: 876-885.
6 Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; 132: 52-65.
7 Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalisation and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008; 135: 1493-1499.
8 Loftus EV, Feagan BG, Colombel JF, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008; 103: 3132-3141.
9 Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; 70: 439-444.
10 Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003; 125: 1508-1530.
11 Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002; 122: 512-530.
12 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; 19 Suppl A: 5-36.
13 Access Economics. The economic costs of Crohn's disease and ulcerative colitis. Melbourne: Access Economics for the Australian Crohn's and Colitis Association, 2007. http://www.accesseconomics.com.au/publicationsreports/search.php?searchfor=disease (accessed Feb 2010).
14 Hellers G, Bergstrand O, Ewerth S, et al. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. *Gut* 1980; 21: 525-527.
15 Schwartz DA, Loftus EV Jr, Tremaine WJ, et al. The natural history of fistulising Crohn's disease in Olmstead County, Minnesota. *Gastroenterology* 2002; 122: 875-880.
16 Wilson JL, Brown SJ, Elliot PR, et al. Poor health related quality of life in patients with fistulising perianal Crohn's disease [abstract]. *J Gastroenterol Hepatol* 2008; 23 Suppl 4: A191.
17 Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. *J Clin Gastroenterol* 1995; 20: 27-32.
18 Medicare Australia. Pharmaceutical Benefits Schedule item reports. https://www.medicareaustralia.gov.au/statistics/pbs_item.shtml (accessed Feb 2010).
19 Gibson PR, Weston AR, Shann A, et al. Relationship between disease severity, quality of life and health-care resource use in a cross-section of Australian patients with Crohn's disease. *J Gastroenterol Hepatol* 2007; 22: 1306-1312.

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