Long-term Results of Adalimumab Treatment in Subjects with Moderately to Severely Active Fistulizing Crohn's Disease Who Have Failed Response or Showed Intolerance to Infliximab

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Abstract

INTRODUCTION: Adalimumab is a fully human monoclonal antibody anti-TNF.

AIMS & METHODS: This observational, open-label, multi-centre, prospective study evaluated the long-term efficacy and safety of adalimumab in the induction and maintenance of perianal fistula closure in subjects with fistulizing Crohn's disease (CD) who had lost response to or were intolerant of infliximab. Subjects were treated with subcutaneous adalimumab: 160 mg at Week 0, 80 mg at Week 2, then 40 mg eow for 52 weeks. Subjects were assessed for complete or partial, (≥50%, decrease in number of draining fistulas) fistula closure, PDAI score, and adverse events (AE).

RESULTS: In 24 subjects with fistulizing CD (CDAI<220; n=10) or luminal and fistulizing CD (CDAI≥220; n=14), the mean duration of CD was 8.7 ±6.4 years. At baseline, 79% of subjects were on AZA/6MP and 37% were on corticosteroids, 29.2% showed loss of response and 70.8% intolerance to infliximab, the PDAI score overall was 10.8 ±2.8, and the mean number of draining fistulas was 3.3 ±3.7. Long-term overall results are presented in the table.

PDAI and Fistula Closure Status Over Time in Subjects Treated with Adalimumab

	Basal (n=24)	Wk 4 (n=23)	Wk 12 (n=20)	Wk 20 (n=16)	Wk 42 (n=12)	Wk 52 (n=12)
PDAI	10.8	5.8	5.6	3.8	3.4	4.4
Number of draining fist.	3.3	0.86	1.21	0.47	0.27	1.0
Complete fist. closure %	–	20.8	16.7	20.8	29.2	29.2
Partial fist. closure %	–	41.7	37.5	37.5	41.7	41.7

ITT analysis

CONCLUSION: Adalimumab treatment maintains long-term reduction in PDAI levels and complete or partial perianal fistulae closure in subjects with fistulizing CD who had failed response or showed intolerance to infliximab. No new safety concerns were found compared with other adalimumab-treated populations.

Results continued

Figure 8. Evolution of Number of Draining Perianal Fistulas (All Fistulizing, n=24)

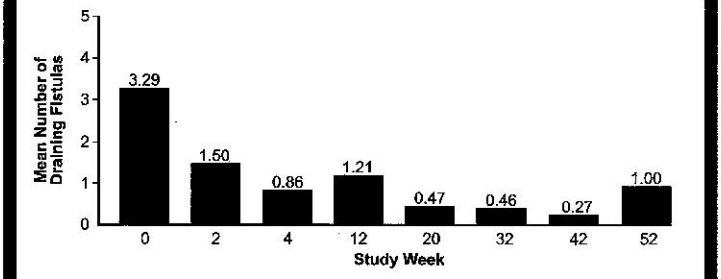
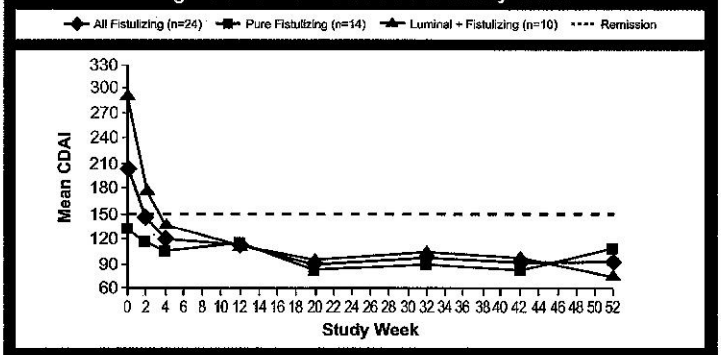


Figure 9. CDAI Evolution Per Study Week



Remission: CDAI<150.

Figure 10. CDAI/PDAI Evolution at Week 20 and Week 52 (All Fistulizing, N=24)

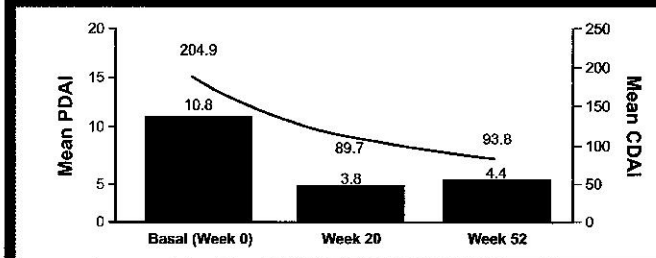


Table 2. Adverse Events (All Fistulizing, N=24)

Adverse Events	Events (patients)
Rash	3 (3)
Asthenia	2 (2)
Diarrhea	1 (1)
Upper respiratory tract infection	1 (1)
Myalgia	1 (1)
Injection site reaction	1 (1)
Maxillary sinus infection	1 (1)
Dizziness	1 (1)
Total	11 (11)

None of the events was severe.

CONCLUSIONS

- **Adalimumab treatment maintains long-term reduction in PDAI scores and complete or partial perianal fistulae closure in subjects with fistulizing CD who had failed response or showed intolerance to infliximab**
- **No new safety concerns were found compared with other adalimumab-treated populations**

Results continued

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oligo-, di- and monosaccharides and polyols) are rapidly fermented in the colon resulting in luminal distension, pain and bloating while high osmotic activity causes diarrhoea. Dietary FODMAP reduction in patients with FGD leads to significant symptom amelioration, but whether such intervention works in IBD is unknown.
AIMS & METHODS: We aimed to assessed the effect of dietary FODMAP reduction in patients with IBD patients without obvious active inflammation but poorly controlled symptoms.A retrospective audit of IBD patients who had seen a dietitian in our unit regarding gastrointestinal symptom reduction was performed. Patients gave consent before undergoing a structured telephone interview by a non-dietitian investigator. Primary endpoints were a significant improvement in overall or specific symptoms (defined as a >5 point improvement on a scale of −10 (change to worst symptoms possible) to +10 (change to absence of symptoms) in relation to a baseline score of 0 that represented the patient's symptoms at the time of dietary intervention). Assessment was made 3–6 months after dietary intervention Data were analysed descriptively.
RESULTS: 72 patients participated in the study (52 Crohn's disease (CD), 20 ulcerative colitis (UC)). At the time of intervention, the most common symptoms were diarrhoea (96%) bloating (81%) and abdominal pain (75%). Abdominal pain (CD $p < 0.0001$, UC $p = 0.016$), diarrhoea (CD $p < 0.0001$, UC $p = 0.0002$), bloating (CD $p < 0.0001$, UC $p = 0.0039$), and wind (CD $p = 0.0002$, UC $p = 0.0078$), were most likely to respond to dietary intervention. At least 50% of patients had a significant (>5 point) improvement in abdominal pain, diarrhoea and bloating. For CD patients, improvement in pain was associated with a positive hydrogen breath test for fructose malabsorption (OR = 5.14 [1.18–22]) and with adherence to a fructose-reduced diet (OR = 6.33 [1.44–28]).
CONCLUSION: Dietary FODMAP reduction IBD patients with FGD is effective in more than 50% of cases. As this is a commonly encountered clinical scenario, this study highlights the need for prospective controlled studies to be performed.
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MON-G-319 SYSTEMATIC CHEMOPREVENTION WITH MESALAMINE DURING REMISSIONS IN PATIENTS WITH LONGSTANDING ULCERATIVE COLITIS SEEMS TO PROTECT AGAINST COLORECTAL CANCER. PRELIMINARY RESULTS OF A RETROSPECTIVE STUDY

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INTRODUCTION: The aim of this retrospective study was to estimate if administration of 5-aminosalicylic acid derivatives (5-ASA) on a regularly base during remissions has any benefit in prevention of colorectal carcinoma (CRC) in patients with longstanding ulcerative colitis (i.e. more than 10 years after initial diagnosis has been made).
AIMS & METHODS: The study was performed between april 2000 and may 2006 and evaluated 406 patients with longstanding UC enrolled in our regional registry. Data collection showed that 219 of 406 patients (53.94±3.15%) were taking 5-ASA derivatives every day on a regularly base for more than 9 months/year. The mean duration of therapy was 12.34±3.47 years in this group and the extension of colitis has been stratified as follows: proctosigmoiditis: 43.12±3.54%, left-side colitis 34.23±1.25% and pancolitis (22.25%±5.73%). In average, each patient received a dose of 1.645±0.213 grams of 5-ASA per day.
RESULTS: At the end of study we found an overall incidence of CRC of 3.02±0.23%. Lower incidences of 1.44±0.13% were observed in the 5-ASA treated group, while in the non-5-ASA treated group a significantly higher incidence of 3.23±0.45% has been noticed ($p < 0.05$). The risk for CRC was higher in patients with pancolitis in both groups but those from the 5-ASA group has a significantly lower risk with an odds ratio of 0.51 (95% CI. 0.37–0.69) compared with 0.86 (95% CI. 0.71–0.92) for patients which did not followed chemoprevention.
CONCLUSION: Chemoprevention with 5-ASA derivatives seems to protect patients with UC from CRC, but the results are influenced by the extension and perhaps the duration of disease.
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MON-G-320 DAYS OFF WORK AND DAYS IN HOSPITAL ARE HIGH IN AN UNSELECTED COHORT OF ULCERATIVE COLITIS PATIENTS

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INTRODUCTION: In order to determine the unmet needs of chronic ulcerative colitis (UC) patients and determine cost-effectiveness of new therapies, we require accurate information on quality of life, hospitalization and surgery rates in patients treated with conventional anti-inflammatory and immunosuppressive therapies. We undertook this prospective study to characterise a cohort of UC patients under follow up regarding their disease status, time off work, hospitalization and surgery rates as well as their quality of life (IBDQ).
AIMS & METHODS: 302 unselected UC patients (128 men), average age 48years, responded to a questionnaire regarding their disease status and quality of life (82% response rate). The answers to the questionnaires were then validated against their case records.
RESULTS: 22% of patients complained of diarrhoea of 4 or more per day at the time of the questionnaire and 34% complained of diarrhoea of 4 or more per day during the past 3 months. 16% of patients complained of bloody stools often or most of the time and 14% of patients complained of faecal incontinence often or most of the time during the past 3 months. 302 patients were hospitalized for a total of 491 days (average 1.6 days per patient) over the past 12 months and 6 patients had colectomy. Over the past 3 months, the patients were admitted as day cases for 47 days. 302 patients took 550 days of sick leaves because of UC (average 1.8 days per patient) during the past 3 months. Average IBDQ of this cohort was 169; 38% of patients had IBDQ below 170, 16% had IBDQ below 140 and 10% of patients had IBDQ below 120.
CONCLUSION: In a cohort of UC patients treated with conventional anti-inflammatory and immunosuppressive therapies, the burden of disease is high, with a high inpatient days and considerable time off work due to UC. Better therapies and therapeutic strategies are required.
*The study was supported by an unrestricted educational grant from Schering Plough Ltd.
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MON-G-321 LONG-TERM RESULTS OF ADALIMUMAB TREATMENT IN SUBJECTS WITH MODERATELY TO SEVERELY ACTIVE FISTULIZING CROHN'S DISEASE WHO HAVE FAILED RESPONSE OR SHOWED INTOLERANCE TO INFLIXIMAB

F. Gomollon[1], J. Hinojosa[2], P. Nos[3], M. Penate[4], D. Ceballos[5], M.A. Gassull[6]. [1]*Gastroenterology, Hospital Clinico Lozano Blesa, Zaragoza,* [2]*Gastroenterology, Hospital Sagunto,* [3]*Gastroenterology, Hospital La Fe, Valencia,* [4]*Gastroenterology, Hospital Insular Las Palmas,* [5]*Gastroenterology, Hospital de Gran Canaria Dr. Negrin, Las Palmas,* [6]*On behalf of GETECCU, Hospital Germans Trias I Pujol, Barcelona, Spain*

INTRODUCTION: Adalimumab is a fully human monoclonal antibody anti-TNF.
AIMS & METHODS: This observational, open-label, multi-centre, prospective study evaluated the long-term efficacy and safety of adalimumab in the induction and maintenance of perianal fistula closure in subjects with fistulizing Crohn's disease (CD) who had lost response to or were intolerant of infliximab. Subjects were treated with subcutaneous adalimumab: 160 mg at week 0, 80 mg at week 2, then 40 mg eow for 52 weeks. Subjects were assessed for complete or partial, (≥50%, decrease in number of draining fistulas) fistula closure, PDAI score, and adverse events (AE).
RESULTS: In 24 subjects with fistulizing CD (CDAI < 220; n = 10) or luminal and fistulizing CD (CDAI > 220; n = 14), the mean duration of CD was 8.7±6.4 years. At baseline, 79% of subjects were on AZA/6MP and 37% were on corticosteroids, 29.2% showed loss of response and 70.8% intolerance to infliximab, the PDAI score overall was 10.8±2.8, and the mean number of draining fistulas was 3.3±3.7. Long-term overall results are presented in the table.

Table 1. PDAI and Fistula Closure Status Over Time in Subjects Treated With Adalimumab

	Basal (n = 24)	Week 4 (n = 23)	Week 12 (n = 20)	Week 20 (n = 16)	Week 42 (n = 12)	Week 52 (n = 12)
PDAI	10.8	5.8	5.6	3.8	3.4	4.4
Number of draining fist.	3.3	0.86	1.21	0.47	0.27	1.0
Complete fist closure (%)	-	20.8	16.7	20.8	29.2	29.2
Partial fist closure (%)		41.7	37.5	37.5	41.7	41.7

ITT analysis

CONCLUSION: Adalimumab treatment maintains long-term reduction in PDAI scores and complete or partial perianal fistulae closure in subjects with fistulizing CD who had failed response or showed intolerance to infliximab. No new safety concerns were found compared to other adalimumab-treated populations.
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MON-G-322 AZATHIOPRINE TOXICITY IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE: OUTPATIENT CLINIC EXPERIENCE OF SEVEN YEARS

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INTRODUCTION: Azathioprine is frequently used in the treatment of inflammatory bowel disease (IBD). Toxicity can result in drug discontinuation.
AIMS & METHODS: The aim of this study is to determine the incidence and the causes of withdrawal and dose reduction of azathioprine in patients with IBD. Patient charts of IBD patients followed in our IBD outpatient clinic from 1999 to 2006 were reviewed for side-effects of azathioprine.
RESULTS: 590 IBD patients (including 21 with Behçet's syndrome) were treated between 1990 and 2006. Among these, 151 received azathioprine (66 female 85 male, mean age 36.3±11.3 years). The diagnosis of these patients was Crohn's disease (n = 100), ulcerative colitis (n = 36), and Behcet syndrome with gastrointestinal involement (n = 15). The mean disease duration was 3.2±3.9 years and the mean AZA dose was 1.9±0.4 mg/kg. The mean Crohn disease activity index, Seo index and CRP levels were 168.7±97.9, 148±55.3 and 30.4±44.9 mg/dl respectively. The mean duration of treatment was 23.8±19.6 months. These patients had 2.1±1.5 visits/month during their follow-up. Drug toxicity was observed in 26 of 151 (17.2%) patients who received azathioprine. In 13 (13/151, 8.6%) of these patients, azathioprine treatment was discontinued. The causes of drug withdrawal were hepatotoxicity (n = 3), pancreatitis (n = 2), leukopenia (n = 1) and gastrointestinal intolerance (n = 7). Leukocyte count was below 3000/μL in 3 patients and one of them had accompanying fever which was controlled with antibiotic therapy. The mean azathioprine dose in these patients was not significantly different from those who did not experience toxicity (1.8±0.4 mg/kg versus 1.9±0.4 mg/kg p = 0.76). The current drug dose in patients who are using azathioprine is 2.1±0.4 mg/kg.

Table 1: Types of toxicity and mean time to toxicity appearance

Type of Toxicity (Diagnosis)	N (female/male)	%	Mean time to appearance Days (range
Leukopenia (7CD, 4UC, 1BS)	12 (8/4)	7.9	282.2 (56–875
GI intolerance (9CD)	9 (4/5)	5.9	7.6 (1–16)
Hepatotoxicity (2CD,1UC)	3 (1/2)	1.9	218 (7–264
Pancreatitis (2CD)	2 (2/0)	1.3	57.5 (56–59

CD: Crohn's disease UC: Ulcerative colitis BS: Behçet syndrome GI: Gastrointestinal

CONCLUSION: Although azathioprine therapy is considered to be relatively safe in IBD, toxicity was observed in 17.2% and permanent discontinuation of the drug was necessary only in half of this patients. Pancreatitis and gastrointestinal intolerance appears earlier than hepatotoxicity. Although all toxicities appear less than 1 year after starting of AZA, as a rarest cause of AZA discontinuation, leukopenia may appear some years after. Azathioprine dose does not seem to be responsable for the side effects.
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MON-G-323 OUTCOME OF 6-MERCAPTOPURINE TREATMENT IN AZATHIOPRINE INTOLERANT PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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INTRODUCTION: Adverse drug reactions is a significant reason for therapy failure when treating inflammatory bowel disease (IBD) patients with thiopurines. Some smaller series in azathioprine (AZA) intolerant IBD patients have shown that a shift to 6-mercaptopurine (6-MP) may be successful in many of these patients.
AIMS & METHODS: The aim of this study was to assess the tolerability of 6-MP therapy in AZA-intolerant IBD patients. The medical records of all AZA intolerant IBD patients shifted from AZA to 6-MP at three hospitals were reviewed. 6-MP doses were recalculated into AZA equivalent doses by a conversion factor of 2.0. Results are presented as medians with interquartile ranges.

SUPPLEMENT NO III VOL 56

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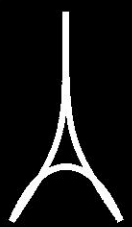

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