Use of mycophenolate mofetil in inflammatory bowel disease

Terrence Tan, Ian Craig Lawrence

Abstract

AIM: To assess the efficacy and safety of mycophenolate mofetil (MMF) prospectively in inflammatory bowel disease (IBD) patients intolerant or refractory to conventional medical therapy.

METHODS: Crohn’s disease (CD) or ulcerative colitis/IBD unclassified (UC/IBDU) patients intolerant or refractory to conventional medical therapy received MMF (500-2000 mg bid). Clinical response was assessed by the Harvey Bradshaw index (HBI) or colitis activity index (CAI) after 2, 6 and 12 mo of therapy, as were steroid usage and adverse effects.

RESULTS: Fourteen patients (9 CD/5 UC/IBDU; 8M/6F; mean age 50.4 years, range 28-67 years) were treated and prospectively assessed for their response to oral MMF. Of the 11 patients who were not in remission on commencing MMF, 7/11 (63.6%) achieved remission by 8 wk. All 3 patients in remission on commencing MMF maintained their remission. Ten patients were still on MMF at 6 mo with 9/14 (64.3%) in remission, while of 12 patients followed for 12 mo, 8 were in remission without dose escalation (66.7%). Three patients were withdrawn from the MMF due to drug intolerance. There were no serious adverse events attributed due to the medication.

CONCLUSION: MMF demonstrated efficacy in the management of difficult IBD. MMF appeared safe, well tolerated and efficacious for both short and long-term therapy, without the need for dose escalation. Further evaluation of MMF comparing it to conventional immunosuppressants is required.

© 2009 The WJG Press and Baishideng. All rights reserved.

Key words: Inflammatory bowel disease; Mycophenolate mofetil; Therapy; Crohn’s disease; Ulcerative colitis

INTRODUCTION

The natural history of both forms of the inflammatory bowel diseases (IBDs), Crohn’s disease (CD) and ulcerative colitis (UC), is characterized by a lifelong course of remissions and relapses and a proportion of these patients are steroid refractory or develop steroid dependence requiring maintenance immunosuppression. The most commonly used immunomodulatory medications are azathioprine (AZA), or its metabolite 6-mercaptopurine (6MP). Approximately 10% of patients, however, will be intolerant of these drugs, resulting in their withdrawal and the need for an alternative immunomodulator[1]. Up to 50% of CD and 20% of UC patients will also develop a severe acute episode of their disease requiring hospitalization[2] and almost half of these patients will require rescue therapy or surgery[3]. In severe steroid refractory UC, remission may be achieved through the use of cyclosporine or infliximab, but despite continued maintenance therapy for these patients with AZA/6MP, over 65% will relapse by 12 mo and 30% will require colectomy[4]. Thus, despite the advent of new biological agents, used in combination with AZA/6MP, efficacy is not universal so the need for other immunomodulatory medications remains imperative.

Mycophenolate mofetil (MMF) is a powerful...
immunosuppressant primarily indicated for prevention of solid organ transplantation rejection. It is an anti-metabolite with pharmacodynamic properties similar to AZA. MMF appears to be very safe and efficacious for this indication and is used as a first-line anti-rejection drug in many transplant centers. More recently, however, this immunosuppressant has been employed in the management of difficult IBD cases[5,6]. Its efficacy has primarily been assessed in small, uncontrolled case series with only a few small randomized trials[7-9]. They indicate that MMF may be effective in IBD, but its role is controversial. The problem arises primarily from observations that despite clinical remission and response achieved early in the course of treatment, a large proportion of patients ultimately flare and require biological agents or surgery. There is also a suggestion that the MMF dose needs to be increased over time in order to maintain an effect and some studies also suggest non-superiority of MMF to conventional immunosuppressants such as AZA[10,11].

Most of the early studies on MMF were undertaken in patients with chronic active CD who failed, or were intolerant to, AZA, and demonstrated good efficacy[7,9]. These findings, however, were not supported by later studies, with either a low response or high relapse rate[8,12]. The rate of treatment discontinuation due to side effects was also high[6,12,13] and studies comparing MMF to AZA yielded conflicting and inconsistent results[14]. In one study MMF was identified to be more likely to be effective in AZA intolerant, rather than refractory patients, and was not inferior to AZA in the management of UC for the induction or maintenance of remission at 6 mo[11]. Another study with longer term outcomes evaluating MMF in a cohort of AZA resistant/intolerant patients, however, observed that although MMF was initially effective, relapses were common[14].

This study presents our experience in the use of MMF in the treatment of IBD patients in the short and long term. We prospectively assessed the efficacy of MMF in both the induction and maintenance of remission in patients who were intolerant of AZA/6MP and had previously failed courses of either methotrexate (MTX), antibiotics and/or infliximab. We particularly examined the need for dose escalation over time in patients who initially responded to the MMF as this has been a criticism of its long-term efficacy.

MATERIALS AND METHODS

All subjects were patients at the Centre for Inflammatory Bowel Diseases, Fremantle Hospital, which is a specialist IBD unit in a 450 bed tertiary institution that services the southern metropolitan region of Perth, Australia. Patients with IBD were classified as CD or ulcerative colitis/IBD unclassified (UC/IBDU) according to the “Montreal Classification” (a modification of the Vienna Classification). The diagnosis of IBD had to be definite, and was made in accordance with previously established criteria based upon clinical, endoscopic, histopathological and radiological findings. The diagnoses of CD or UC/IBDU were exclusive of infective enterocolitis (excluded by stool microscopy and culture, bacterial and amoebic serology, acid-fast staining of biopsies and mycobacterial cultures), Behcet’s disease and microscopic colitis. Patient demographics, disease status, infusion number, response and remission rates and adverse effects were recorded.

All patients were treated between Jan 2003 and July 2008. Patients treated with MMF received between 500 mg and 2000 mg twice a day with the dose optimized to maintain the white cell count (WCC) between 4 and 6 × 10^9/L, neutrophil count > 2.0 × 10^9/L and lymphocyte count at or just below the normal range of 1.1 × 10^9/L without side effects. A clinical response to the MMF in CD patients was determined by a reduction in the Harvey Bradshaw index (HBI) of greater than or equal to 3, with a remission defined as a HBI less than 5 off steroids. A clinical response to the MMF in the UC/IBDU patients was defined as a reduction of 4 or more points in the colitis activity index (CAI) and remission was considered to be CAI of less than or equal to 4 off steroids. The response and remission rates after 8 wk of therapy and long-term response to treatment with MMF were assessed.

Serious adverse effects (SAE) were analyzed. Serious adverse effects are defined as any adverse drug experience occurring that results in death, life-threatening adverse event, persistent or significant disability/incapacity, required in-patient hospitalization, or prolonged hospitalization or congenital anomaly or birth defect.

RESULTS

The primary indications for treatment were either steroid refractoriness, or dependence, and allergy, or intolerance, to AZA/6MP therapy. Patients were steroid dependant if they were unable to be withdrawn from steroids without a disease flare and patients were steroid refractory if they continued to suffer active inflammation whilst on steroids of 20 mg or greater per day. All patients with active disease were considered for treatment with MMF only after demonstrating failure of disease control or steroid dependency. Two CD and 1 UC/IBDU patients were in clinical remission at the time of commencing the MMF. One of these patients suffered from severe psoriasis in addition to her CD and was changed to MMF in consultation with the dermatologists in an attempt to control both the psoriasis and the CD. The second patient had undergone 3 terminal ileal resections with recurrent severe ileal inflammation occurring within 1 to 2 years after each surgery, but was allergic to AZA/6MP, while MTX and infliximab were ineffective. The third patient required 6MP to maintain remission, but was intolerant of this medication due to severe alopecia.

Patient Demographics

Fourteen patients (9 male, 5 female) were treated with MMF during the study period (Table 1). The ages at time of commencing the MMF ranged from 28-67 years (mean age 50.4 ± 12.9 years). Nine patients suffered from CD
and 5 had UC/IBDU. Of the CD patients, 77.8% (7/9) suffered from colonic inflammation, 22.2% (2/9) had ileal involvement alone, 11.1% (1/9) had jejunal CD, and 22.2% (2/9) suffered from perianal disease. Of the UC/IBDU patients, 2 had extensive colitis, while 2 suffered left-sided colitis and 1 patient had proctitis. The age of diagnosis was lower in the CD patients (mean 38.6 ± 13.3 years, range 19-54 years) compared to the UC/IBDU patients (mean 44.0 ± 12.7 years, range 30-63 years), but this was not statistically significant. Both the CD and UC/IBDU patient groups had similar disease duration at the time of the MMF therapy (mean 10.4 years and 9.8 years respectively). Four (44.5%) of the 9 CD patients had previously undergone at least one surgery (1 subtotal colectomy, 2 small bowel resections and 1 total colectomy and ileal surgery). C-reactive protein (CRP) levels were also elevated in 5 of the 9 CD patients and 4 of 5 UC/IBDU patients prior to commencement of the MMF.

### Current and previous medical therapy

Conventional therapies had been tried in all patients (Table 2). Surgical options had been discussed in detail and were considered to be either medically inappropriate at that stage, or were declined by the patient. Of the 9 CD patients, 88.9% (8/9) were on 5-aminosalicylic acid (5ASA) and 77.8% (7/9) were dependent on, or maintained their disease remission. The other CD patient who was placed on MMF to prevent post-surgical recurrence was still in remission. All patients in non responders.

### Table 1 Demographics of the IBD patients using the Montreal classification

|                | CD patients | UC/IBDU patients |
|----------------|-------------|------------------|
| Gender: male   | 57.1% (8/14) | 57.1% (8/14)     |
| Age at diagnosis |             |                  |
| Mean ± SE (range) | 38.6 ± 13.3 yr (19-54) | 44.0 ± 12.7 yr (30-63) |
| A1-<16         | 0% (0/9)    | 0% (0/5)         |
| A2-17-40       | 44.4% (4/9) | 40% (2/5)        |
| A3->40         | 55.6% (5/9) | 60% (3/5)        |
| Disease duration |             |                  |
| Mean (range)   | 10.4 yr (1-26) | 9.8 yr (1-28)    |
| Crohn’s disease |             |                  |
| L1-terminal ileum | 22.2% (2/9) | 22.2% (2/9)      |
| L2-colon       | 33.3% (3/9) |                  |
| L3-ileocolonic  | 44.4% (4/9) |                  |
| L4-upper Gl    | 11.1% (1/9) |                  |
| P-perianal      | 22.2% (2/9) |                  |
| B1-inflammatory | 44.4% (4/9) |                  |
| B2-stricturing  | 33.3% (3/9) |                  |
| B3-perforating  | 22.2% (2/9) |                  |
| Ulcerative colitis/IBDU | 20% (1/5) |                  |
| E1-proctitis    | 20% (1/5)   |                  |
| E2-left sided   | 40% (2/5)   |                  |
| E3-extensive    | 40% (2/5)   |                  |
| Raised CRP     | 55.6% (5/9) | 80.0% (4/5)      |

### Table 2 Medications taken by study patients at time of the commencement of MMF therapy

|                | CD patients | UC/IBDU patients |
|----------------|-------------|------------------|
| Gender: male   | 57.1% (8/14) | 57.1% (8/14)     |
| Current        | 88.9% (8/9) | 100% (5/5)       |
| Steroids       | 55.5% (5/9) | 100% (5/5)       |
| Current        | 22.2% (2/9) | 0%               |
| Intolerant     | 33.3% (3/9) |                  |
| Intolerant     | 11.1% (1/9) | N/A              |
| AZA/6MP        | 88.8% (8/9) | 100% (5/5)       |
| Intolerant     | 33.3% (3/9) |                  |
| Antibiotics    | Ineffective |                  |
| Intolerant     | 11.1% (1/9) |                  |
| Infliximab     | Current     |                  |
| Ineffective    | 44.4% (4/9) | 40% (2/5)        |
| Ineffective    | 22.2% (2/9) | 0%               |

### Table 3 Response and remission rates at 8 wk and CRP levels with MMF therapy

|                | CD patients | UC/IBDU patients |
|----------------|-------------|------------------|
| Remission      | 66.7% (6/9) | 80% (4/5)        |
| Response       | 66.7% (6/9) | 80% (4/5)        |
| Intolerant     | 22.2% (2/9) | 20% (1/5)        |
| Ineffective    | 11.1% (1/9) | 0% (0/5)         |
| Raised CRP     | In responders | 0% (0/6)      |
| In non responders | 33.3% (1/3) | 100% (1/1)       |

N/A: Not applicable.

In responders:

### Efficacy at 8 wk

After 8 wk of MMF therapy, 63.6% (7/11) of patients (3 CD and 4 UC/IBDU) who were not in remission at commencement of MMF responded and went into remission, while 71.4% (10/14) went into remission or maintained clinical remission (Tables 3 and 4) as determined either by the HBI or CAI. The 2 patients who had AZA/6MP ceased and MMF commenced due to concurrent severe psoriasis and severe alopecia, maintained their disease remission. The other CD patient who was placed on MMF to prevent post-surgical recurrence was still in remission. All patients in remission at 8 wk also had normal CRP levels. Three of the 14 patients (2 CD and 1 UC/IBDU) were intolerant to MMF and took the medication for 1 mo or less. In only 1 patient was MMF ineffective after 8 wk of therapy, with the patient undergoing surgery 6 mo after commencing the MMF. The surgical pathology
demonstrated chronic active inflammation and fibrosis of the previous ileocolonic anastomosis.

**Efficacy at 6 mo**

Of the 10 patients on MMF who responded or were in remission at 8 wk, all were still on MMF at 6 mo. Only one patient suffered a disease flare in that 6-mo period. This patient flared 10 wk after commencing the MMF and required further steroids and a single dose of infliximab to induce remission, but continued on the MMF with subsequent successful withdrawal of the steroids and no further need for infliximab therapy. None of the other patients required an increase in their dose of MMF over the 6-mo period in order to maintain their remission. The patient who was on the MMF for recurrent inflammation following previous terminal ileal resections for uncontrolled CD inflammation underwent a colonoscopy at 6 mo, which demonstrated no ileal or colonic CD inflammation.

**Efficacy at 12 mo**

Ten patients (Table 4) had been on MMF for more than 6 mo (mean 18.1 ± 12.1 mo, max 48 mo) with 8 patients taking MMF for 12 mo or more. Of the 10 patients, 1 flared at 8 mo and was withdrawn from MMF due to lack of efficacy. One of the patients died 12 mo after commencing the MMF from an unrelated cause while in remission from his CD. One patient who flared after 30 mo of MMF was withdrawn and commenced on adalimumab with good effect. A total of 12 patients were followed for 12 mo or more and of these 8 were in remission (66.7%). All the 8 patients on MMF maintained their remission without the need for dose escalation.

**Adverse effects**

There was one serious adverse event (SAE) in this patient cohort. This patient died from decompensated alcoholic liver disease. He had previously denied any significant alcohol consumption on numerous occasions and had been on a stable dose of MMF for over 10 mo. The patient presented to hospital jaundiced with ascites and blood results consistent with an acute hepatitis. The MMF was ceased and the patient was subsequently diagnosed with acute severe alcohol-induced hepatitis. His condition deteriorated over a 2-wk period and he died from liver failure. This SAE was considered to be ‘unlikely related’ to the MMF use. Adverse events that resulted in cessation of the medication occurred in 3 (21.4%) patients (2 CD and 1 UC/IBDU). These were GI disturbances (nausea and vomiting) and severe headaches. There were no other adverse events that required modification of the MMF dose.

**DISCUSSION**

The treatment of refractory IBD has always been one of the most challenging aspects in the clinical practice of luminal gastroenterology. MTX has been the primary alternative therapy for CD patients who are treatment refractory or intolerant to AZA/6MP. Although MTX has demonstrated efficacy in CD, the rate of adverse events at the higher doses often required to achieve clinical response/remissions has limited its use[18]. At low doses, however, MTX is often ineffective[15] and definitely less effective than AZA/6MP[16] with longer-term studies demonstrating a frequent loss of efficacy over time[17]. A systematic review of 5 trials identified only one large randomized trial that recommended high dose parenteral MTX to induce clinical remission[18]. The remaining studies using oral forms have disappointing results[15] and because of its route of administration MTX is not acceptable to many patients. Despite some evidence justifying the use of MTX in UC[19], and fistulising CD[20], data remains limited and confined to retrospective chart reviews. AZA/6MP, therefore, has been the mainstay of immunosuppressive maintenance therapy in IBD. The use of MMF has, therefore, been proposed as an alternative immunosuppressive therapy for patients who either are refractory or intolerant to AZA/6MP.

### Table 4: Individual patient data of disease extent, age at treatment, duration of MMF therapy and response

| Sex | Diagnosis | Age at diagnosis | Age at MMF | Indication for MMF | Disease extent | Duration of MMF (mo) | Response after 8 wk | Steroids continued at 8 wk |
|-----|-----------|------------------|------------|-------------------|----------------|----------------------|----------------------|--------------------------|
| 1 M | CD        | 27               | 28         | Steroid dependant | Pancolitis     | 30                   | Remission            | Ceased                   |
| 2 M | CD        | 54               | 55         | Steroid dependant | L.Sided colitis/fistula | 12           | Remission            | Ceased                   |
| 3 F | CD        | 50               | 67         | Severe Psoriasis  | Ileocolonic disease | 48           | Remission            | N/A                      |
| 4 M | CD        | 41               | 56         | Steroid dependant | Ileocolonic disease | 12           | Remission            | Ceased                   |
| 5 M | CD        | 53               | 63         | Recurrent TI resections | Recurrent ileal disease | 15           | Remission            | N/A                      |
| 6 F | CD        | 32               | 58         | Steroid intolerant | Colectomy/2x TI resection/ recurrent ileal disease | < 1         | Intolerant            | Continued                 |
| 7 F | CD        | 19               | 28         | Steroid dependant | Subtotal colectomy/recurrent ileal disease/fistula | < 1         | Intolerant            | Continued                 |
| 8 M | CD        | 21               | 48         | Steroid dependant | Ileal disease   | 6         | Ineffective           | Surgery                   |
| 9 F | UC/IBDU   | 43               | 50         | Steroid dependant | Pancolitis      | 12           | Remission            | Ceased                   |
| 10 M | UC/IBDU  | 31               | 33         | Steroid dependant | L.Sided colitis | 9         | Remission            | Ceased                   |
| 11 M | UC/IBDU  | 53               | 64         | Steroid dependant | L.Sided colitis | 22           | Remission            | Ceased                   |
| 12 F | CD        | 50               | 50         | Recurrent flares  | Pancolitis      | 12           | Remission            | Ceased                   |
| 13 M | UC/IBDU  | 63               | 63         | Steroid dependant | Pancolitis      | 8         | Remission            | Ceased                   |
| 14 F | UC/IBDU  | 30               | 58         | Steroid dependant | Subtotal colectomy/proctitis | < 1         | Intolerant            | Continued                 |
The aim of our study was to prospectively evaluate the short and long-term efficacy and safety of MMF in patients who were either steroid refractory, or dependent, as well as intolerant or allergic to AZA/6-MP therapy. We also wanted to examine the need for dose escalation of MMF over time as this has been suggested as a problem with the use of MMF by some studies. As with many of the other published data on MMF, ours was a small cohort of IBD patients with open-label use of MMF. Our patients, however, were assessed at numerous time points and were followed for over a year. The patients in our cohort were also medication resistant, with two thirds failing anti-TNF-\( \alpha \) therapy, suggesting a more difficult-to-treat population of patients compared to some other studies. Despite this the results were encouraging. Overall the response rate observed was 71% of patients achieving or maintaining a complete clinical remission after 8 wk of therapy. Excluding the 3 patients who were in remission and off steroids at the time of commencing the MMF, the response/remission rates were still 63.6% at 8 wk. These findings are in contrast with current literature, which reports short-term response rates of only between 25%-40%.

A proportion of MMF-treatment failures in previous studies have been attributed to discontinuation secondary to significant adverse effects. In our study MMF was generally well tolerated, but discontinuation of the MMF secondary to adverse effects was still 21.4%, similar to the 30% observed in other studies. This does not explain the difference, however, in the overall response rates and the reasons behind the difference remains unclear. Relapses over time have also been previously reported as common. Early relapse in our cohort, however, was not commonly observed and even after 12 mo of MMF therapy, 57.1% (8/14) of our IBD patients were still in remission. Of particular note is the lack of dose escalation required over time in our patients responding to MMF. None of the 8 patients on MMF in remission at 12 mo had their dose of MMF increased in the previous 6 mo.

In our experience, the efficacy of MMF appears to differ in some aspects to the published data. Our data demonstrate that MMF can be efficacious and well tolerated in treating refractory IBD patients who are intolerant to AZA/6-MP. Problems of lack of long-term efficacy and early disease flare as well as the need for dose escalation over time did not eventuate. Our findings support the use of MMF in the management algorithm of resistant IBD, but its role needs further clarification in larger randomized, double-blind studies comparing it to conventional immunosuppressants. Long-term efficacy would appear to be demonstrated in our study and our current experience suggests that MMF can and should be considered in patients who have failed conventional immunosuppressive therapy.

REFERENCES

1. Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001; 121: 255-260
2. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974; 1: 1067-1070
3. Järnerot G, Rolny P, Sandberg-Gertzén H. Intensive intravenous treatment of ulcerative colitis. *Gastroenterology* 1985; 89: 1005-1013
4. Campbell S, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. *Eur J Gastroenterol Hepatol* 2005; 17: 79-84
5. Hafraoui S, Dewit O, Marteau P, Cosnes J, Colombel JF, Modigliani R, Cortot A, Lémann M. [Mycophenolate mofetil in refractory Crohn's disease after failure of treatments by azathioprine or methotrexate] *Gastroenterol Clin Biol* 2002; 26: 17-22
6. Ford AC, Towler RJ, Moayyedi P, Chalmers DM, Axon AT. Mycophenolate mofetil in refractory inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; 17: 1365-1369
7. Neurath MF, Wantischke R, Peters M, Krummenauer F, Meyer zum Büschenfeld KH, Schlaak JF. Randomised trial of mycophenolate mofetil versus azathioprine for treatment of chronic active Crohn's disease. *Gut* 1999; 44: 625-628
8. Fellermann K, Steffen M, Stein J, Raedler A, Hämling J, Ludwig D, Loesche R, Stange EF. Mycophenolate mofetil: lack of efficacy in chronic active inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; 14: 171-176
9. Fickert P, Hinterleitner TA, Wenzl HH, Aichbichler BW, Petrisch W. Mycophenolate mofetil in patients with Crohn's disease.
disease. *Am J Gastroenterol* 1998; 93: 2529-2532

10 **Miehsler W**, Reinisch W, Moser G, Gangl A, Vogelsang H. Is mycophenolate mofetil an effective alternative in azathioprine-intolerant patients with chronic active Crohn's disease? *Am J Gastroenterol* 2001; 96: 782-787

11 **Orth T**, Peters M, Schlaak JF, Krummenauer F, Wanitschke R, Mayet WJ, Galle PR, Neurath MF. Mycophenolate mofetil versus azathioprine in patients with chronic active ulcerative colitis: a 12-month pilot study. *Am J Gastroenterol* 2000; 95: 1201-1207

12 **Hassard PV**, Vasiliauskas EA, Kam LY, Targan SR, Abreu MT. Efficacy of mycophenolate mofetil in patients failing 6-mercaptopurine or azathioprine therapy for Crohn's disease. *Inflamm Bowel Dis* 2000; 6: 16-20

13 **Palaniappan S**, Ford AC, Greer D, Everett SM, Chalmers DM, Axon AT, Hamlin PJ. Mycophenolate mofetil therapy for refractory inflammatory bowel disease. *Inflamm Bowel Dis* 2007; 13: 1488-1492

14 **Wenzl HH**, Hinterleitner TA, Aichbichler BW, Fickert P, Petrirsch W. Mycophenolate mofetil for Crohn's disease: short-term efficacy and long-term outcome. *Aliment Pharmacol Ther* 2004; 19: 427-434

15 **Din S**, Dahele A, Fennel J, Aitken S, Shand AG, Arnott ID, Satsangi J. Use of methotrexate in refractory Crohn's disease: the Edinburgh experience. *Inflamm Bowel Dis* 2008; 14: 756-762

16 **Ardizzone S**, Bollani S, Manziomma G, Imbesi V, Colombo E, Bianchi Porro G. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003; 35: 619-627

17 **Domenech E**, Mañosa M, Navarro M, Masnou H, Garcia-Planella E, Zabana Y, Cabrè E, Gassull MA. Long-term methotrexate for Crohn's disease: safety and efficacy in clinical practice. *J Clin Gastroenterol* 2008; 42: 395-399

18 **Alfadhli AA**, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev* 2005; CD003459

19 **Nathan DM**, Iser JH, Gibson PR. A single center experience of methotrexate in the treatment of Crohn's disease and ulcerative colitis: a case for subcutaneous administration. *J Gastroenterol Hepatol* 2008; 23: 954-958

20 **Soon SY**, Ansari A, Yaneza M, Raoof S, Hirst J, Sanderson JD. Experience with the use of low-dose methotrexate for inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2004; 16: 921-926