METHOTREXATE IN PEDIATRIC ULCERATIVE COLITIS: A RETROSPECTIVE SURVEY AT A SINGLE TERTIARY REFERRAL CENTER

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**METHOTREXATE IN PEDIATRIC ULCERATIVE COLITIS: A RETROSPECTIVE
SURVEY AT A TERTIARY REFERRAL CENTER**

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ABSTRACT

BACKGROUND. Patients with ulcerative colitis (UC) often receive thiopurines as immunomodulators (IMs) to maintain remission and avoid corticosteroids (CS). If unresponsive or intolerant to these agents they are treated with methotrexate (MTX), an antimetabolite never assessed in pediatric UC.

AIM. To describe the experience with MTX in UC children

METHODS. Thirty-two patients (median age 13.9 years) received MTX. Pediatric Ulcerative Colitis Activity Index (PUCAI) and use of CS were the main outcomes evaluated baseline and at 3, 6 and 12 months.

RESULTS. Indications to MTX were azathioprine (AZA) unresponsiveness in 18, AZA intolerance/toxicity in 10 and spondyloarthropathy in 4. Response or remission were achieved in 72%, 63% and 50% of patients at 3, 6 and 12 months, respectively. Mean PUCAI was 49.5 ± 23.3 at baseline and 32.9 ± 21.9 , 29.5 ± 21.8 and 29.4 ± 19.9 at 3, 6 and 12 months, respectively ($p: 0.03$). At the beginning of MTX 16 patients (50%) received CS, that were discontinued in 13 of them (81%) by 6 months. At the end of the study 11 patients (33%) needed short courses of CS for disease relapse.

CONCLUSIONS. MTX may be useful in treating children with UC, although large, controlled trials are warranted to better define its effectiveness in pediatric UC.

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INTRODUCTION

Inflammatory bowel diseases (IBD), i.e. ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gut characterized by recurrent exacerbations intermingled with phases of quiescence (1,2). Most patients with active UC respond to aminosalicylates (5-ASA) or CS. The latter are highly effective in inducing remission, however, a considerable group of patients relapse when steroids are withdrawn (3). Moreover, children on long term CS exhibit serious adverse effects, among which linear growth delay, osteopenia, and infections are the most cumbersome (3,4). CS sparing while maintaining remission is a tricky therapeutic strategy in the management of IBD: for this purpose IMs have successfully been introduced into the therapeutic armamentarium of this disorder (5,6). The most commonly used IMs for IBD are thiopurine analogs such as azathioprine (AZA) and 6-mercaptopurine (6-MP) (7): however, serious adverse events may lead to cessation of therapy in up to 25% of patients, while unresponsiveness occurs in 15-20% of them (8,9). Thiopurine intolerant or unresponsive patients are usually treated with alternative IMs or biological therapy. Recently, there has been a great concern due to a reported increase in the risk of lymphoma in IBD patients chronically treated with AZA (10). The chronic use of thiopurine analogs has been also challenged following publication of cases of hepato-splenic T cell lymphoma in young adults receiving them in association with biologics (11). Thus, pediatric gastroenterologists not uncommonly consider alternative IMs.

Methotrexate (MTX), a potent folic acid antagonist, causes a decrease in purine production at the cellular level (12,13). A direct antiinflammatory effect of MTX (i.e. inhibition of cellular proliferation, decrease in the formation of antibodies and in the production of inflammatory mediators, induction of apoptosis) has also been demonstrated (13) leading to its use in several inflammatory disorders, such as psoriasis and rheumatoid arthritis (14,15). However, the role of MTX in IBD remains somewhat unclear, although it has been

shown to be effective both for induction and maintenance of remission in adults with CD (16-18). While very few reports have shown the effectiveness and safety of MTX in children with CD (19,20), reports in UC are lacking and confined to adult patients (21,23,24). Thus, the aim of this study was to report the experience of a tertiary referral Center for Pediatric Gastroenterology in the use of MTX in children with UC.

PATIENTS AND METHODS

This is a retrospective longitudinal study conducted at a single tertiary referral Center for Pediatric Gastroenterology. The Department database was screened for all children diagnosed with UC by 2004, and those treated with MTX were identified. Diagnosis of UC was based on widely agreed endoscopic and histological criteria (25), after excluding infectious and systemic disease, food allergies and malabsorption syndromes. All patients underwent ileocolonoscopy with a pediatric videocolonoscope (Olympus, PCF Q 180 I) following conscious sedation with i.v. pethidine (1-2 mg/Kg) and midazolam (0.1 mg/Kg) or under general anesthesia. Endoscopic criteria for UC were diffuse continuous inflammation extending from the rectum proximally and characterized by granularity, friability, small diffuse superficial ulcers superimposed on a background of loss of vascular mucosal pattern and normal appearing distal ileal mucosa. Histological features for UC were a continuous intense mixed acute and chronic inflammatory infiltrate of the lamina propria, distortion of crypt architecture and/or crypt atrophy, basal plasmacytosis, cryptitis and crypt abscesses, Paneth cell metaplasia distal to the ascending colon. The behavior of disease activity, measured through PUCAI (26) and the use of corticosteroids (evaluated baseline and at 3, 6, 12 months post-MTX) were the main outcomes. PUCAI is a validated, noninvasive, multi-item measure of disease activity with established cut-off values for remission (<10 points), mild (10–34 points), moderate (35–64 points), and severe disease (65–85 points), developed in 2007 (26,27,28). Clinical remission was defined as a PUCAI

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score < 10 and clinical response as a decrease in the PUCAI of at least 20 points as compared to baseline (26). Medical records of patients evaluated before 2007 were retrospectively reviewed by an experienced physician unaware of medical therapy and PUCAI sub-domain scores were attributed. The use of CS, adverse effects and surgical procedures during the study period were the secondary outcomes recorded. Thiopurine intolerance was defined as a requirement to discontinue thiopurine because of side effects. Thiopurine refractoriness was defined as no clinical improvement to a trial of at least 12 weeks therapy. MTX was given weekly by intramuscular injection at the dose of 15 mg/m² body surface area. All children received 5 mg of intramuscular folic acid weekly, 6 hours after MTX. To detect potential hepatic, renal or haematological side effects of MTX therapy, patients were monitored every 2 weeks during the first 2 months and every 8 to 12 weeks thereafter (29). Laboratory tests included full blood count, inflammatory, renal and liver function parameters, serum albumin, electrolytes, lipase and amylase. Liver ultrasound was performed if liver function tests were abnormal, while chest x-ray was performed in all patients before starting MTX to rule out pulmonary fibrosis.

Statistical analysis for the comparison of the qualitative variables was carried out by χ^2 test or Fisher's exact test (where appropriate). Continuous variables were compared using the Mann-Whitney nonparametric *U* test. A p value less than or equal to 0.05 was considered as significant. Data were given as median (and ranges) and as mean $\pm$ SD.

RESULTS

Of the 38 children with active UC treated by MTX with a follow-up of at least 12 months, 32 (16 males) provided complete data on all items of the PUCAI with a valid total score (median age: 14.0 years; range: 8.3–19.8; IQR 12.5). The mean age at diagnosis of UC was 10 $\pm$ 4.3 years, and MTX was commenced 23.4 $\pm$ 12.3 months after diagnosis. The Table summarizes baseline clinical characteristics of the patients. At the introduction of

MTX, an extensive colitis (pancolitis) was present in 24 (75%), a left-sided colitis in 5 (16%), and a proctitis in 3 (8%). AZA had been introduced in all but 4 patients as first-line IM agent. Thiopurine therapy was discontinued because of primary nonresponse or relapse in 18 patients (56%), and intolerance/toxicity in 10 (31%). In 4 patients MTX had been introduced as the first-line IM because of coexisting joint disease (spondyloarthropathy). MTX was administered parenterally in all patients with a mean dose of MTX for patient of 13.7 ± 3.6 mg/m²/week. All patients were on chronic treatment with mesalazine (75-100 mg/Kg/day) that was maintained in addition to MTX during all the observation period.

Of the 32 children on MTX a clinical improvement (response or remission) was seen in 72%, 63%, and 50% at 3, 6, and 12 months respectively (Figure): this included 6 of 10 with AZA intolerance or toxicity, and 14 of 18 with AZA refractoriness. Remission was observed in 10 patients at 3 months, and in 9 at both 6 and 12 months; response was observed in 13, 11 and 7 patients at 3, 6, and 12 months, respectively. Mean PUCAI 6 months before the introduction of MTX was 40.5 ± 23.6 (moderate disease), 49.5 ± 23.3 at the introduction of MTX, and 32.9 ± 21.9 , 29.5 ± 22.8 , 29.4 ± 25.9 (mild disease) at 3, 6 and 12 months post-MTX, respectively (p: 0.03). At the beginning of MTX 16 patients were receiving oral prednisolone with a mean dose of 1.24 mg/Kg/day (range 0.2-3.2 mg): tapering of CS was possible in 14 (87.5%), with complete discontinuation in 11 (68.7%) within the first 3 months, and in other 2 patients after 6 months of MTX. At 12 months, 8 children were receiving short courses of CS because of disease relapse. At the end of the study period 8 patients had a sustained steroid-free clinical remission.

No surgery was performed during the observation period. There were adverse reactions in 8 patients within the first 3 months of therapy: asymptomatic elevation of alanine aminotransferase (ALT 3 to 4 times the upper limit of normal) in 4, with normalization in all after dose reduction of MTX, whereas 4 needed to discontinue the drug because of

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intractable nausea. No haematological or infectious complications were observed in this case series.

DISCUSSION

The natural history of UC is characterized by phases of remission intermingled with recurrent flare-ups, that occur in an unpredictable fashion and impair the quality of life of the patients. The main goals in the management of pediatric UC are to control disease exacerbations and avoid prolonged use of CS (1). The classical medical armamentarium for UC includes anti-inflammatory drugs, CS and IMs. While CS have a short-term clinical efficacy, they do not change the disease natural history and cause a number of troublesome side effects. The IMs are considered as steroid sparing agents, when a long-term remission is attainable (30). Although thiopurines are the most commonly used IMs, some patients exhibit unresponsiveness or intolerance to them and MTX has been proposed as an alternative immunomodulatory therapy (1,2). Whereas there are few retrospective reports on MTX in patients with CD, there are no data on the effectiveness and safety of MTX in pediatric UC. Our study shows that children with UC may benefit from MTX, both to induce and to maintain remission, as well as in reducing CS exposure. Of the 32 treated patients, we observed an overall clinical improvement in 23, 20 and 16 at 3, 6 and 12 months, respectively. Comparable high response rates are reported in adult studies. A recent retrospective study in 32 adults nonresponsive or intolerant to thiopurines reported a clinical response of 68% using either oral or parenteral MTX at an induction dose of 25 mg/week (31). Previously, a response rate of 72% and a remission rate of 42% had been reported in adults with active UC formerly treated with thiopurines (24). The evidence for using MTX in UC is restricted to observational studies, while the only randomized, placebo-controlled trial in adults found no efficacy, however it was underpowered and a low oral dose of MTX (12.5 mg weekly) was used (21). In our study

the majority of patients started MTX during a flare-up of the disease, thus it is conceivable that a “regression to the mean phenomenon” might contributed to the clinical response to the therapy, leading to a lower disease activity just by chance. However, as shown by longitudinal assessment of disease activity, our patients had highly active disease already six months before starting MTX (i.e. medium PUCAI 40.5 ± 23.6), thus reducing the likely impact of this phenomenon.

We gave MTX intramuscularly since it has previous shown that this way of administration may be more useful due to the variable oral bioavailability of the drug (22). Subcutaneous injection is as an alternative method of parenteral administration: as compared to intramuscular injection it produces similar pharmacokinetics, and leads to greater patient comfort by reducing local complication rate at the injection site (23). The majority of our patients improving on MTX achieved clinical remission within 10-12 weeks (range, 6–12), this indicating that MTX is clinically efficacious earlier than thiopurines, which have a delayed onset of action, usually 2 or 3 months after commencement of administration (30). The anti-inflammatory effect of MTX at low-doses has not clearly been defined. Whereas MTX at high doses has an antiproliferative and cytotoxic effect, by inhibiting the enzyme dihydrofolate reductase and leading to defective DNA synthesis and cell death (12), at low-doses it acts mainly as an IM (32). The immunomodulatory effect of MTX is poorly understood but it involves increased concentrations of adenosine (33), inhibition of cellular proliferation and induction of apoptosis (34), and decreased production of inflammatory mediators, such as interleukins and eicosanoids (13).

The safety of MTX has been extensively studied in patients with chronic inflammatory diseases such as rheumatoid arthritis and psoriasis. In the short term, the most common side effects are of gastrointestinal type, in particular nausea, vomiting and diarrhea, and asymptomatic elevation of transaminases. Longer-term safety concerns include bone marrow suppression, opportunistic infection due to immune suppression, pneumonitis,

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3 teratogenicity, and cirrhosis (30). The supplementation of folates during MTX therapy
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5 seems to reduce the risk of cytopenia and the severity of gastrointestinal symptoms
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7 without reduction in efficacy and bioavailability of the drug (35). The majority of our
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9 patients preferred folic acid intramuscularly despite the latter is widely know to be very
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11 effective by oral route (36).
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15 In our study MTX was well tolerated and safe. Four children needed to discontinue the
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17 drug due to intractable nausea unresponsive to folic acid and antiemetics; in 4 patients
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19 there was a transient abnormality in liver function tests, that resolved with MTX dose
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21 reduction. Due to the rarity of severe chronic liver disease related to MTX therapy and
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23 according to recent recommendations (37,38) a conservative approach was done and no
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25 patient underwent liver biopsy.
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29 It is still unsettled whether MTX may be considered as a first-line IM agent in the treatment
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31 of UC. Indeed, there are no head-to-head studies comparing MTX and AZA in IBD and no
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33 data are available on MTX as first-line therapy while its is commonly reported in patients
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35 unresponsive or intolerant to thiopurines. In our study only 4 patients with UC and
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37 spondyloarthopathy received MTX as first-line IM agent: they improved both in intestinal
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39 and articular symptoms without adverse reactions.
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43 Although this study has some limitations such as the small sample size, the lack of
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45 controls and the retrospective nature, however it suggests that MTX can be a useful agent
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47 for the management of pediatric UC patients, unresponsive or intolerant to thiopurines.
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49 Large, controlled prospective trials are warranted to better define the role and the place of
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51 MTX in the treatment of pediatric UC.
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Table. Clinical characteristics of 32 pts with UC treated with methotrexate

Age (yrs)	Median	14.0
	Range	8.3 – 19.8
Sex		12M,12F
Age at diagnosis (yrs)	Mean±SD	10±4,3
	Proctitis	3 (8%)
Disease location	Left-sided colitis	5 (16%)
	Pancolitis	24 (75%)
Previous therapy with AZA		28 (87%)
Indication to MTX therapy	AZA intolerance/toxicity	10 (31%)
	Nonresponse/ relapse on AZA	18 (56%)
	Spondyloarthropathy	4 (12%)
CS at the introduction of MTX		16 (50%)

REFERENCES

1. Grossman AB, Baldassano RN. Specific considerations in the treatment of pediatric inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2008;2:105-24.
2. Sauer CG, Kugathasan S. Pediatric inflammatory bowel disease: highlighting pediatric differences in IBD. *Med Clin North Am.* 2010;94:35-52.
3. Hyams J, Markowitz J, Lerer T et al. The natural history of corticosteroid therapy for ulcerative colitis in children. *Clin Gastroenterol Hepatol* 2006;4:1118-23.
4. Leonard MB. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. *Pediatrics* 2007;119:S166-72.
5. Rufo PA, Bousvaros A. Current therapy of inflammatory bowel disease in children. *Paediatr Drugs* 2006;8:279-302.
6. Punati J, Markowitz J, Leret T, et al. Effect of early immunomodulator use in moderate to severe pediatric Crohn's disease. *Inflamm Bowel Dis* 2008;14:949-54.
7. Braus NA, Elliott DE. Advances in the pathogenesis and treatment of IBD. *Clin Immunol* 2009; 132:1-9.
8. Homan M, Baldassano RN, Mamula P. Managing complicated Crohn's disease in children and adolescents. *Nat Clin Pract Gastroenterol Hepatol* 2005;2:572-9.
9. Akoberg AK. Crohn's disease: current treatment options. *Arch Dis Child* 2008;93:787-792.
10. Kandiel A, Fraser AG, Korelitz BI, Brensinger C, Lewis JD. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;54:1121-5.
11. Cucchiara S, Escher J, Hildebrand H, Amil-Dias J, Stronati L, Ruemmele FM. Pediatric inflammatory bowel disease and risk of lymphoma: should we revise our treatment strategies? *J Pediatr Gastroenterol Nutr* 2009;48:257-67.
12. Jolivet J, Cowan KH, Curt GA, Clendeninn NJ, Chabner BA. The pharmacology and clinical use of methotrexate. *N Engl J Med* 1983;309:1094-1104.
13. Cronstein BN. The mechanism of action of methotrexate. *Rheumat Dis Clin North AM* 1997;23:739-755.
14. Feely MG, Erickson A, O'Dell JR. Therapeutic options for rheumatoid arthritis. *Expert Opin Pharmacother* 2009;10:2095-106.

15. Kalb RE, Strober B, Weinstein G, Lebowitz M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol*. 2009;60:824-37.
16. Kozarek RA, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989;110: 353–6.
17. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate in the treatment of Crohn's disease. *N Engl J Med* 1995; 332:292–7.
18. El-Matary W, Vandermeer B, Griffiths AM. Methotrexate for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2009.
19. Uhlen S, Belbouad R, Nareski K, Goulet O, et al. Efficacy of Methotrexate in pediatric Crohn's disease: a french multicenter study. *Inflamm Bowel Dis* 2006;12:1053-1057.
20. Weiss R, Lerner A, Shapiro R, et al. Methotrexate treatment in pediatric Crohn's disease patients intolerant or resistant to purine analogues. *J Pediatr Gastroenterol Nutr* 2009;48:526-30.
21. Oren R, Arber N, Odes S, et al. Methotrexate in chronic ulcerative colitis: a double blind, randomised, Israeli multicentre trial. *Gastroenterol* 1996;110:1416-21.
22. Cummings JRF, Herrlinger KR, Travis SPL, et al. Oral methotrexate in ulcerative colitis. *Aliment Pharmacol Ther* 2005;21:285-9.
23. Patel V, Macdonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009.
24. Paoluzi OA, Pica R, Marcheggiano A, et al. Azathioprine or methotrexate in the treatment of patients with steroid dependent or steroid resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002;16:1751-9.
25. Justinich CJ, Hyams JS. Inflammatory bowel disease in children and adolescence. *Gastrointest Endosc Clin N Am*, 1994;4:39-54.
26. Turner D et al. Development, validation and evaluation of a Pediatric Ulcerative Colitis Activity Index: a Prospective Multicenter Study. *Gastroenterol* 2007;133:423-432.
27. Turner D, Seow CH, Greenberg GR, et al. A systematic prospective comparison of noninvasive disease activity indices in ulcerative colitis. *Clin Gastroenterol Hepatol*. 2009;7:1081-8.

28. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis*. 2009;15:1218-23.

29. Kremer JM, Alarcn GS, Lightfoot RW, et al. Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *American College of Rheumatology. Arthritis Rheum* 1994;37: 316-28.

30. Markowitz J, Grancher K, Kohn N, Daum F. Immunomodulatory therapy for pediatric inflammatory bowel disease: changing patterns of use, 1990-2000. *Am J Gastroenterol*. 2002;97:928-32.

31. Wahed M, Louis-Auguste JR, Baxter LM, et al. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine/mercaptopurine. *Aliment Pharmacol Ther* 2009; 30:614-20.

32. Ravikumara M, Hinsberger A, Spray CH. Role of methotrexate in the management of Crohn's disease. *J Pediatr Gastroenterol Nutr* 2007;44:427-30.

33. Morabito L, Montesinos MC, Schreiber DM, et al. Methotrexate and sulfasalazine promote adenosine release by a mechanism that requires ecto-5'-nucleotidase-mediated conversion of adenine nucleotides. *J Clin Invest* 1998;101:295-300.

34. Genestier L, Paillot R, Fournel S, et al. Immunosuppressive properties of methotrexate: apoptosis and clonal deletion of activated peripheral T cells. *J Clin Invest* 1998;102:322-8.

35. 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;23:954-8.

36. Pavy S, Constantin A, Pham T, Gossec L, Maillefert JF, et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. *Joint Bone Spine*. 2006;73:388-95.

37. Aberra FN, Lichtenstein GR. Monitoring of inflammatory bowel disease. *Aliment Pharmacol Ther* 2005;21:307-19.

38. Siegel CA, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. *Aliment Pharmacol Ther* 2005;22:1-16.

Figure. Rate of clinical remission/response and relapse/intolerance to MTX in pts with UC over the 1-year study period
254x190mm (72 x 72 DPI)