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A Systematic Review and Meta-analysis of the Efficacy and Adverse Events of Infliximab in Comparison to Corticosteroids and Placebo in Active Ulcerative Colitis

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Abstract: The proinflammatory cytokine tumor necrosis factor alpha (TNF- α) plays a major role in severity of Ulcerative Colitis (UC) and thus inhibition of TNF- α is used to control severe cases of UC. The present meta-analysis was performed to collect and review all the clinical trials that investigated the efficacy and tolerability of infliximab in order to determine whether infliximab is more effective than placebo or corticosteroids in inducing response and remission in UC. All bibliographic databases such as PubMed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials were searched for studies investigated the efficacy of infliximab for the management of UC. Data were collected from 1966 to September 2010. Three trials represented 57 patients with UC who were randomized to receive infliximab or corticosteroids and 5 trials represented 827 patients with UC who were randomized to receive infliximab or placebo were included in the analysis. The summary Relative Risk (RR) for clinical remission in comparison of infliximab with placebo was 1.93 with a 95% Confidence Interval (CI) of 1.62-2.3 and a significant RR ($p < 0.0001$). Summary RR for adverse events of infliximab comparing to placebo was 1.07 with a 95% CI of 0.99-1.14, a non-significant RR ($p = 0.0725$). The summary RR for serious adverse events of infliximab comparing to placebo was 0.83 with a 95% CI of 0.44-1.54 as a non-significant RR ($p = 0.5472$). The summary RR for clinical remission of infliximab comparing to corticosteroids was 1.07 with a 95% CI of 0.87-1.31 as a non-significant RR ($p = 0.5353$). Patients receiving infliximab were 1.93 and 1.07 times more likely to go to the remission as compared to those receiving placebo and corticosteroids, respectively. Meanwhile, the risk of adverse events in the patients receiving infliximab was 1.07 times more than placebo group. The risk of opportunistic infection was high in patients who have failed steroids and cyclosporine and were using infliximab. Although infliximab is more effective than corticosteroids in inducing clinical remission, we believe further trials are still needed to judge stronger in this respect.

Key words: Infliximab, ulcerative colitis, adverse events, serious adverse events, clinical response, clinical remission, meta-analysis, tumour necrosis factor, systematic review, corticosteroid

INTRODUCTION

Ulcerative Colitis (UC) is a chronic relapsing and remitting inflammatory disease that affects the mucosa of the colon with a wide range of severity. It could extend from the anus up to the cecum and from mild proctitis to extensive fulminant disease. Presenting symptoms include rectal bleeding, diarrhea, urgency, tenesmus and abdominal pain (Rahimi *et al.*, 2007a-c; Reinisch *et al.*, 2007; Gies *et al.*, 2010).

It is thought that infections and microbial agents (Rahimi *et al.*, 2006, 2007c), oxidative stress (Rezaie *et al.*, 2007) and immune system dysfunction (Hosseini-

Tabatabaei and Abdollahi, 2008) are involved in pathogenesis of UC. In UC, like other chronic inflammatory diseases, proinflammatory cytokines (Salari and Abdollahi, 2009), such as tumor necrosis factor alpha (TNF- α), Interleukin (IL)-1 β , IL-6 and NF- κ B (Esmaily *et al.*, 2010; Nakhai *et al.*, 2007) are thought to play a major role. TNF- α is found in increased concentration in the blood, saliva and colonic tissue of patients with both Crohn's Disease (CD) and UC (Jahanshahi *et al.*, 2004) and is mainly involved in induction of fistula (Nikfar *et al.*, 2010a). Therefore, inhibition of TNF- α which is an early activator of cytokine cascade is a potential target for therapeutic intervention.

Fortunately, with this belief new herbal drugs with anti-TNF characteristic (Baghaei *et al.*, 2010) or anti oxidative stress potential (Hasani-Ranjbar *et al.*, 2009) have been proposed for management of IBD.

Current goal of therapy of IBD include induction and maintenance of remission, prevention of the complications (disease-related and treatment-related) and to improve quality of life (Gies *et al.*, 2010). Therefore, standard medical treatment of UC involves sulfasalazine, aminosalicylates, corticosteroids and immunomodulators (Nikfar *et al.*, 2009; Rahimi *et al.*, 2009a) but they are limited with their adverse effects (Rahimi *et al.*, 2008b). As a last option in patients who fail to respond to current treatments, colectomy and ileal anal pouch anastomosis is done (Elahi *et al.*, 2008, 2009; Nikfar *et al.*, 2010b).

Over the past decade new treatments based on novel aspects of pathogenesis have become available like phosphodiesterase inhibitors (Salari-Sharif and Abdollahi, 2010), probiotics (Rahimi *et al.*, 2008a, c), antibiotics (Rahimi *et al.*, 2006, 2007b), infliximab (Rahimi *et al.*, 2007a, b) and compounds come from traditional medicine (Rahimi *et al.*, 2010, 2009b). Infliximab is a chimeric monoclonal antibody that can neutralize TNF- α effects by blocking soluble and membrane-bound forms of TNF- α . Blocking of TNF is associated with suppression of NF- κ B and further control of disease (Esmaily *et al.*, 2010; Miroliaee *et al.*, 2011).

Our previous meta-analysis on the efficacy of infliximab on UC published in 2007 (Rahimi *et al.*, 2007a) indicated that infliximab is effective in inducing response and remission in patients with UC when administered in combination with corticosteroids. In the present systematic review meta-analysis, we firstly aimed to show how infliximab is more effective than corticosteroids and then to update current knowledge on the efficacy and tolerability of infliximab in inducing response and remission in UC.

MATERIALS AND METHODS

Data sources: The PubMed, Scopus, Web of Science and Cochrane Central Register of Controlled Trials were searched for studies that investigated the efficacy of infliximab for the management of UC. Data were collected from 1966 to September 2010. The search terms were: “ulcerative colitis” and “infliximab” and “clinical trial”. The reference lists from retrieved articles were also evaluated to make sure all applicable studies have been included. Abstracts found from Scopus and Web of Science were also reviewed. Clinical improvement (clinical response or clinical remission) and adverse events were the key outcome of interest.

Study selection: Randomized, placebo-controlled trials investigating the efficacy of infliximab in induction of

Table 1: Quality score of included studies

Study	Factors and Jadad score			Total Jadad score
	Randomization	Blinding	Withdrawals and dropouts	
Armuzzi <i>et al.</i> (2004)	1	0	0	1
Sands <i>et al.</i> (2001)	1	2	0	3
Probert <i>et al.</i> (2003)	2	2	1	5
Rutgeerts <i>et al.</i> (2005)	2	2	1	5
Ochsenkuhn <i>et al.</i> (2004)	2	0	0	2
Gavalas <i>et al.</i> (2007)	0	0	0	0
Jamerot <i>et al.</i> (2005)	2	2	1	5

response and maintaining remission of active UC were considered. Three reviewers independently reviewed the title and abstract of each article to eliminate duplicates, reviews, case studies and uncontrolled trials and those published in languages other than English. Trials were disqualified if their outcome was not remission and those whose target groups were not patients with UC (patients with CD or pouchitis) were excluded from meta-analysis. The data on patients’ characteristics, therapeutic regimens, dosage, sample size, trial duration and outcome measures were extracted. Disagreements between reviewers were resolved by discussion.

Assessment of trial quality: The methodological quality of included trials was assessed using the Jadad score which judges of the descriptions of randomization, blinding and dropouts (withdrawals) in the trials (Jadad and Enkin, 2007) (Table 1). This is summarized as follow: (a) whether randomized or not (yes = 1 point, No = 0); (b) whether randomization was described appropriately or not (yes = 1 point, No = 0); (c) double blind (yes = 1 point, No = 0); (d) was the double blinding described appropriately (yes = 1 point, No = 0) and (e) whether withdrawals and dropouts described or not (yes = 1 point, No = 0). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3.

Statistical analysis: Data from selected studies were extracted in the form of 2x2 tables. All included studies were weighted and pooled. Data were analyzed using Statsdirect (2.7.8). Relative Risk (RR) and 95% Confidence Intervals (95% CI) were calculated using the Mantel-Haenszel and Der Simonian-Laird methods. The Cochran Q test was used to test heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as publication bias indicator.

RESULTS

The electronic searches yielded 673 items; 115 from PubMed, 17 from Cochrane Central, 241 from Web of

Science and 1460 from Scopus. Of those, 10 articles were scrutinized in full text. Two reports were considered ineligible because they were cohort studies (Fidder *et al.*, 2009; Gies *et al.*, 2010). Thus, 8 studies remained where one article consisted of two trials (Rutgeerts *et al.*, 2005). Three trials represented 57 patients with UC who were randomized to receive infliximab or corticosteroids (Armuzzi *et al.*,

2004; Ochsenkuhn *et al.*, 2004; Gavalas *et al.*, 2007) and 5 trials represented 827 patients with UC who were randomized to receive infliximab or placebo were included in the analysis (Sands *et al.*, 2001; Probert *et al.*, 2003; Jarnerot *et al.*, 2005; Rutgeerts *et al.*, 2005). Patients' characteristics, dosage of infliximab and duration of treatment for each study are summarized in Table 2 and 3.

Table 2: Characteristics of trials comparing infliximab and corticosteroids

	Number of patients		Remission		AE		Withdrawal	
	IFX (f/m)	Corticosteroids (f/m)	Infliximab	Corticosteroids	IFX	Corticosteroids	IFX	Corticosteroids
Armuzzi <i>et al.</i> (2004)	20		9/10	8/10	-	-	-	-
Ochsenkuhn <i>et al.</i> (2004)	13		After 3 weeks (therapy success)		1*	8*	1	1
			5/6	6/7				
	3/3	4/3	After 13 weeks (remission)					
			3/6	5/7				
Gavalas <i>et al.</i> (2007)	24		IFX: complete response in 11 and partial in 3 and partial in 2	Methylprednisolone: complete long-term response in 5	-	6/8	-	-
	16	8						

IFX: Infliximab; *All reported; AE: Adverse Event

Table 3: Characteristics of trials comparing infliximab and placebo

	Number of patients			Remission			Serious AE			Any AE			
	IFX (f/m)	Placebo (f/m)		Infliximab	Placebo		IFX	Placebo		IFX	Placebo		
Probert <i>et al.</i> (2003)	43			9/23	6/20		-	2/20		-	-		
				Open label infusion at week 6									
				3/11	1/9								
Sands <i>et al.</i> (2001)	11			At week 2			2/3		2/8		-		
	1/2	2/6		0/3	4/8								
Rutgeerts <i>et al.</i> (2005)	364			At week 8			26	29	31	106	111	103	
	43/78 (5 mg IFX)	50/72 (10 mg IFX)	50/72 (placebo)	84/121	75/122	45/121							
Rutgeerts <i>et al.</i> (2005)	364			At week 8			13	11	24	99	96	90	
	45/76 (5 mg IFX)	52/68 (10 mg IFX)	52/71 (placebo)	78/121	83/120	36/123							
Jarnerot <i>et al.</i> (2005)	45			Induction of remission			-		3/21		9/24		8/21
	8/16	13/8		17/24	7/21								
				Remaining in remission (after 3 months)									
				6/15	2/6								

IFX: Infliximab; AE: Adverse Event

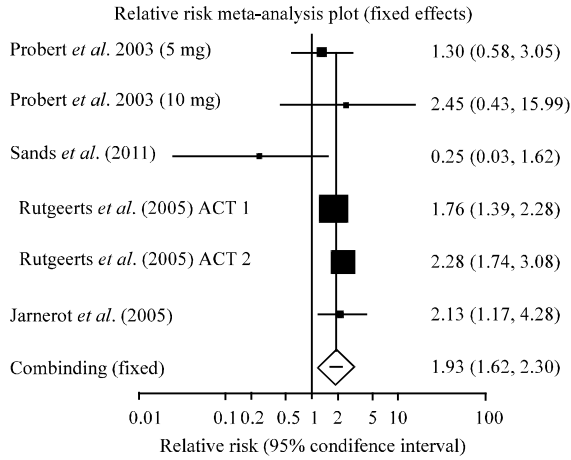


Fig. 1a: Individual and pooled relative risk for the outcome of remission in the studies considering Infliximab vs. placebo therapy

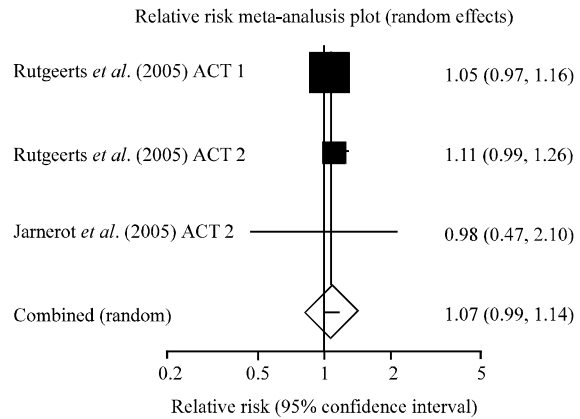


Fig. 2a: Individual and pooled relative risk for the outcome of adverse events in the studies considering Infliximab vs. placebo therapy

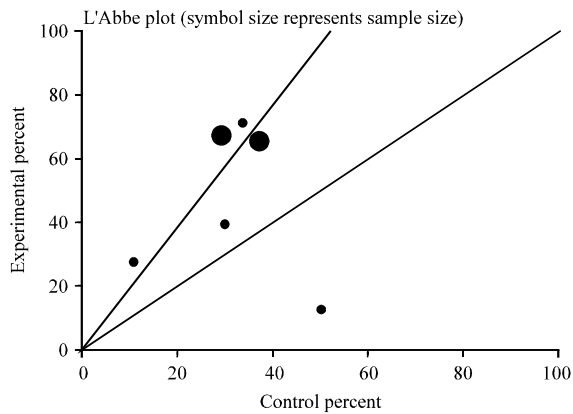


Fig. 1b: Heterogeneity indicators for the outcome of “remission” in the studies considering Infliximab vs. placebo therapy

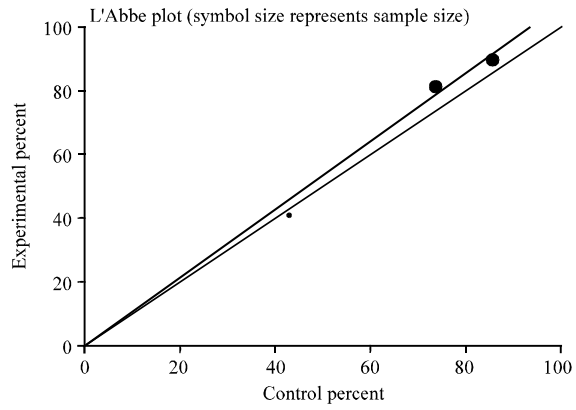


Fig. 2b: Heterogeneity indicators for the outcome of “adverse events” in the studies considering Infliximab vs. placebo therapy

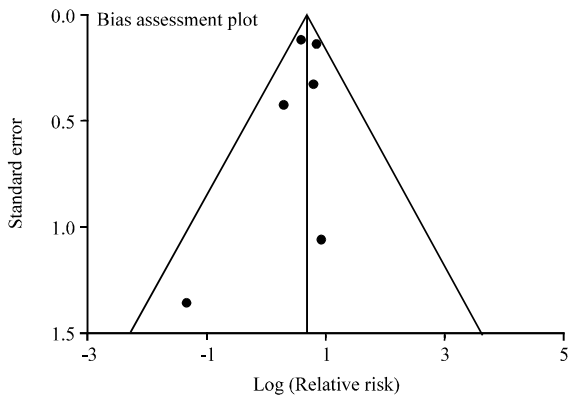


Fig. 1c: Publication bias indicators for the outcome of “remission” in the studies considering Infliximab comparing to placebo therapy

Efficacy of infliximab comparing to placebo: The summary RR for clinical remission in five trials (Sands *et al.*, 2001; Probert *et al.*, 2003; Jarnerot *et al.*, 2005; Rutgeerts *et al.*, 2005) was 1.93 with a 95% CI of 1.62-2.3 and a significant RR ($p < 0.0001$, Fig. 1a). The Cochran Q test for heterogeneity indicated that the studies are not heterogeneous ($p = 0.4113$, Fig. 1b) and could be combined. Thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for remission among infliximab vs., placebo therapy was -0.658588 (95% CI = -2.541893 to 1.224718 , $p = 0.3866$) and Kendall's test on standardized effect vs., variance indicated $\tau = -0.333333$, $p = 0.2722$ (Fig. 1c).

Adverse events of infliximab comparing to placebo:

Summary RR for adverse events in three trials (Jarnerot *et al.*, 2005; Rutgeerts *et al.*, 2005) was 1.07 with a 95% CI of 0.99-1.14, a non-significant RR ($p = 0.0725$, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are homogenous ($p = 0.7641$, Fig. 2b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for adverse events among infliximab vs. placebo therapy could not be calculated because of too few strata.

Serious adverse events of infliximab comparing to placebo:

The summary RR for serious adverse events in three trials (Sands *et al.*, 2001; Rutgeerts *et al.*, 2005) was

0.83 with a 95% CI of 0.44-1.54 and a non-significant RR ($p = 0.5472$, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies are homogenous ($p = 0.0561$, Fig. 3b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for serious adverse events among infliximab vs. placebo therapy could not be calculated because of too few strata.

Efficacy of infliximab comparing to corticosteroids:

The summary RR for clinical remission in three trials (Armuzzi *et al.*, 2004; Ochsenkuhn *et al.*, 2004; Gavalas *et al.*, 2007) was 1.07 with a 95% CI of 0.87-1.31 and a non-significant RR ($p = 0.5353$, Fig. 4a). The Cochrane Q test for heterogeneity indicated that the

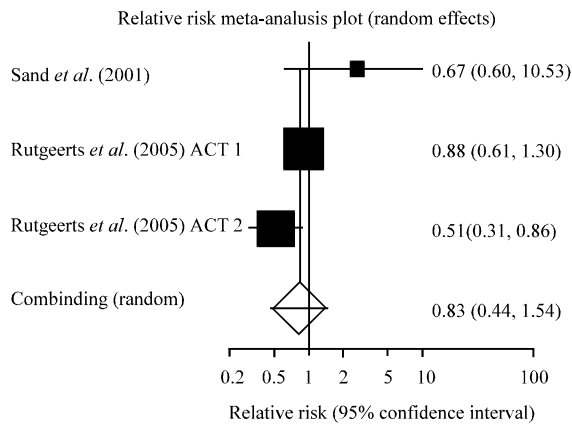


Fig. 3a: Individual and pooled relative risk for the outcome of “serious adverse events” in the studies considering Infliximab vs. placebo therapy

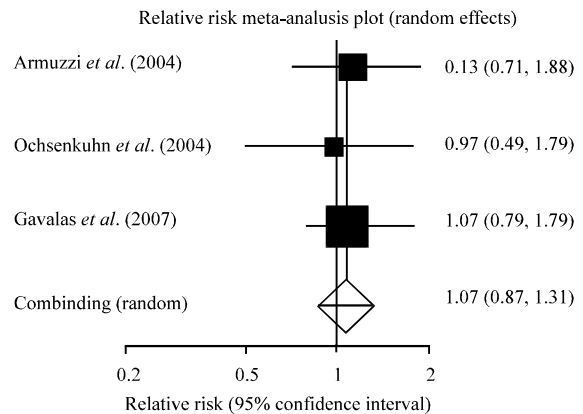


Fig. 4a: Individual and pooled relative risk for the outcome of “remission” in the studies considering Infliximab vs. corticosteroids therapy

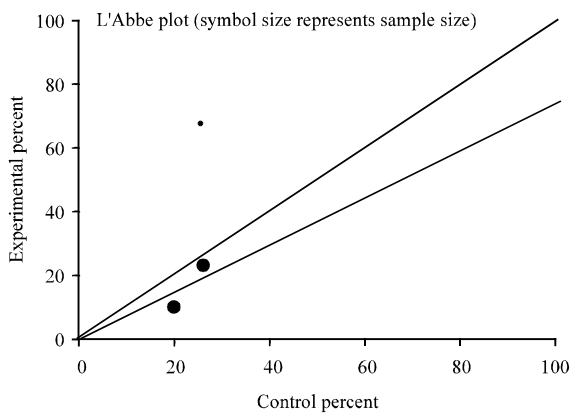


Fig. 3b: Heterogeneity indicators for the outcome of “serious adverse events” in the studies considering Infliximab vs. placebo therapy

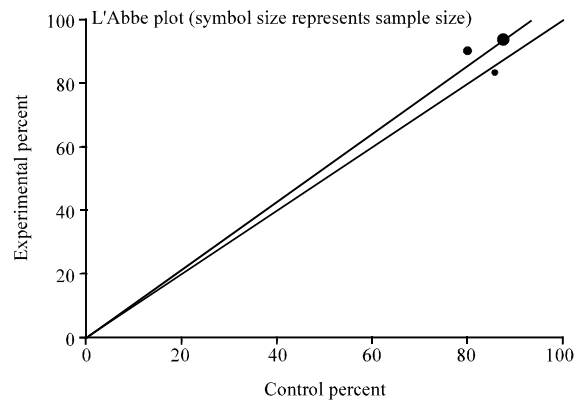


Fig. 4b: Heterogeneity indicators for the outcome of “remission” in the studies considering Infliximab vs. corticosteroids therapy

studies are not heterogeneous ($p = 0.8914$, Fig. 4b) and could be combined but because of few included studies the random effects for individual and summary of RR was applied. Regression of normalized effect versus precision for all included studies for remission among infliximab vs., corticosteroids therapy could not be calculated because of too few strata.

DISCUSSION

The present meta-analysis found that patients receiving infliximab were 1.93 times more likely to go to the remission as compared to those receiving placebo while the risk of adverse events in the patients receiving infliximab was just 1.07 times as compared to the placebo group. Among these adverse events, the risk of serious ones was 0.83 times in the infliximab group in comparison to placebo. Also it was shown that patients receiving infliximab were 1.07 times more likely to go to the remission compared to those receiving corticosteroids. Comparison of remission in infliximab group and that of placebo was statistically significant but other Relative Risks (RR) were not significant. Fortunately, all trials were homogenous and a random effect model was used for the meta-analysis of remission following use of infliximab when compared to corticosteroids and meta-analysis of adverse events and serious adverse events of infliximab in comparisons to placebo. In the random model, the magnitude of the effect can vary between studies. Therefore, the confounding parameters cannot be biasing for this meta-analysis.

The present results are supported by the conclusion of a previous meta-analysis of the efficacy of anti TNF- α in managing UC when administered in combination with corticosteroids by Rahimi *et al.* (2007a) although some differences exist between these two studies. In the previous meta-analysis, five trials, published between 1966 to September 2006, were included while in the present one, the search was extended up to September 2010 and eight trials were included. All the three new studies compared infliximab with corticosteroids (Armuzzi *et al.*, 2004; Ochsenkuhn *et al.*, 2004; Gavalas *et al.*, 2007). Analysis was done in two different groups. The trials comparing infliximab with placebo were analyzed separately and the trials comparing infliximab with corticosteroids were analyzed individually. The study done by Probert *et al.* (2003) was also divided into two trials according to two different doses of infliximab used (Probert *et al.*, 2003). Furthermore, we improved the present work by analyzing the adverse events and the serious adverse events of infliximab versus placebo. We included only randomized controlled trials; however

several uncontrolled trials have provided evidence for the use of infliximab in UC. Ferrante *et al.* (2007) evaluated the efficacy of infliximab in 100 patients with UC. Eighty-four patients received 5 mg kg⁻¹ infliximab and 37 patients received a 3-dose infliximab induction at weeks 0, 2 and 6. Early complete and partial clinical responses were observed in 41% and 24% of patients. Gornet *et al.* (2003) evaluated 30 patients, 19 with UC and 11 with indeterminate colitis in an open label multicenter study. Infliximab was given because of steroid resistance ($n = 18$), dependence ($n = 5$) or intolerance ($n = 7$); five patients had failed on cyclosporine; 19 patients had a severe flare-up. In 28 patients with active disease, the response rate was 75% at day 7, with 43% having a complete remission and 50% at month 1, with 32% having a complete remission. In indeterminate colitis, response rate was only 50% at day 7 and 30% at month 1. Bermejo *et al.* (2004) reported the effectiveness of infliximab for UC. Seven cases of UC, 6 with chronic active disease despite immunosuppressive therapy and one with acute steroid-refractory UC were treated with infliximab 5 mg kg⁻¹ of body weight. In 2, 4 and 8 weeks after infusion, 6 of 7 patient's inflammatory activity diminished significantly both from clinical and biochemical points of view. Five out of six patients with corticosteroid-dependent disease could be successfully weaned off these drugs. Although infliximab showed significant effect in remission of UC symptoms against placebo but effectiveness of infliximab versus corticosteroids was not different.

Regueiro *et al.* (2006) evaluated 12 inpatients with UC refractory to intravenous corticosteroids. They were treated with 5 mg kg⁻¹ infliximab in an open label experience. Nine of 12 patients (75%) failed to respond to infliximab and required a colectomy. Three patients (25%) responded to infliximab and were able to withdraw from corticosteroids. In this open-label analysis, infliximab was not effective for the majority of UC patients refractory to intravenous corticosteroids.

Results of present meta-analysis showed that infliximab could be considered safe in comparison to placebo. The results of pooling data for adverse events and serious adverse events were slightly more than placebo but not statistically significant. For evaluation of tolerability of infliximab comparing to corticosteroids data were not sufficient for meta-analysis. However the risk of opportunistic infection is considered high in patients who have failed steroids and cyclosporine and were using infliximab as supported by previous study (Caviglia *et al.*, 2007). Therefore, safety issues and development of adverse events in using of infliximab in UC patients should be considered with caution. Our final opinion is

that although infliximab is more effective than corticosteroids in inducing clinical remission, further trials are still needed to judge stronger in this respect.

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