Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial

David Laharie, Arnaud Bourreille, Julien Branche, Matthieu Allez, Yoram Bouhnik, Jerome Filippi, Frank Zerbib, Guillaume Savoye, Maria Nachury, Jacques Moreau, Jean-Charles Delchier, Jacques Cosnes, Elena Ricart, Olivier Dewit, Antonio Lopez-Sanroman, Jean-Louis Dupas, Franck Carbonnel, Gilles Bommelaer, Benoit Coffin, Xavier Roblin, Gert Van Assche, Maria Esteve, Martti Färkkilä, Javier P Gisbert, Philippe Marteau, Stephane Nahon, Martine de Vos, Denis Franchimont, Jean-Yves Mary, Jean-Frederic Colombel, Marc Lémann*†, for the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives*

Summary

Background Ciclosporin and infliximab are potential rescue treatments to avoid colectomy in patients with acute severe ulcerative colitis refractory to intravenous corticosteroids. We compared the efficacy and safety of these drugs for this indication.

Methods In this parallel, open-label, randomised controlled trial, patients were aged at least 18 years, had an acute severe flare of ulcerative colitis defined by a Lichtiger score greater than 10 points, and had been given an unsuccessful course of high-dose intravenous steroids. None of the patients had previously received ciclosporin or infliximab. Between June 1, 2007, and Aug 31, 2010, patients at 27 European centres were randomly assigned (via computer-derived permutation tables; 1:1) to receive either intravenous ciclosporin (2 mg/kg per day for 1 week, followed by oral drug until day 98) or infliximab (5 mg/kg on days 0, 14, and 42). In both groups, azathioprine was started at day 7 in patients with a clinical response. Neither patients nor investigators were masked to study treatment. The primary efficacy outcome was treatment failure defined by absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98, a severe adverse event leading to treatment interruption, colectomy, or death. Analysis was by intention to treat. This trial is registered with EudraCT (2006-005299-42) and ClinicalTrials.gov (NCT00542152).

Findings 115 patients were randomly assigned; 58 patients were allocated to receive ciclosporin and 57 to receive infliximab. Treatment failure occurred in 35 (60%) patients given ciclosporin and 31 (54%) given infliximab (absolute risk difference 6%; 95% CI –7 to 19; p=0·52). Nine (16%) patients in the ciclosporin group and 14 (25%) in the infliximab group had severe adverse events.

Interpretation Ciclosporin was not more effective than infliximab in patients with acute severe ulcerative colitis refractory to intravenous steroids. In clinical practice, treatment choice should be guided by physician and centre experience.

Funding Association François Aupetit, Société Nationale Française de Gastroentérologie, and the International Organization for the study of Inflammatory Bowel Disease.

Lancet 2012; 380: 1909–15

Published Online October 10, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61084-8

See Comment page 1887

*These authors contributed equally

†Deceased

CHU de Bordeaux, Hôpital Haut-Lévêque, Service d'Hépato-Gastroentérologie, Bordeaux, France (Prof D Laharie MD); **Université Bordeaux, Laboratoire de Bactériologie, Bordeaux, France** (Prof D Laharie); **CHU de Nantes, Hôtel-Dieu, Hépato-Gastroentérologie, Institut des Maladies de l'Appareil Digestif, Nantes, France** (A Bourreille MD); **CHRU de Lille, Hôpital Claude Huriez, Service des Maladies de l'Appareil Digestif—Endoscopie Digestive, Lille, France** (J Branche MD, Prof J-F Colombel MD); **Hôpital Saint-Louis, Service d'Hépato-Gastroentérologie, APHP—Université Paris VII, Paris, France** (Prof M Allez MD, Prof M Lémann MD); **Hôpital Beaujon, Gastroentérologie, Maladies Inflammatoires Chroniques de l'Intestin et Assistance Nutritive, APHP—Université Paris VII, Clichy, France** (Prof Y Bouhnik MD); **CHU de Nice, Hôpital de l'Archet 2, Service de Gastroentérologie et Nutrition Clinique, Nice, France** (J Filippi MD); **CHU de Bordeaux, Hôpital Saint André, Service d'Hépato-Gastroentérologie, Université Bordeaux Segalen, Bordeaux, France** (Prof F Zerbib MD); **CHU de Rouen, Hôpital Charles Nicolle, Service de Gastroentérologie, Appareil Digestif Environnement et Nutrition**

Introduction

Ulcerative colitis is a chronic inflammatory disorder of the colon characterised by mucosal ulceration, rectal bleeding, diarrhoea, and abdominal pain.[1] In 15–25% of cases, patients present with severe colitis that necessitates admission to hospital.[2,3] Intravenous corticosteroids are the conventional medical treatment in this circumstance. However, roughly 40% of patients are resistant to treatment.[4,5] Previously, colectomy was the only available option for these patients. The development of ciclosporin, a calcineurin inhibitor that selectively inhibits T-cell immunity, and infliximab, a monoclonal antibody that targets tumour necrosis factor α, has provided effective alternatives to surgery.[6–8] However, no randomised controlled trials have been done to compare the efficacy and safety of ciclosporin with those of infliximab, and thus practice guidelines do not state which treatment is preferable.[9,10] Assuming that ciclosporin was superior to infliximab, we compared the efficacy and safety of these drugs in patients with acute severe ulcerative colitis refractory to intravenous corticosteroids.

Methods

Study design and patients

Our 98 day randomised, parallel, open-label trial compared ciclosporin with infliximab in patients admitted to hospital with severe colitis. We did our trial at 27 centres in France, Spain, Belgium, and Finland from June 1, 2007, to Aug 31, 2010. The study was designed by investigators from the Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID).

Equipe Avenir 4311, Université de Rouen, Rouen, France (Prof G Savoye MD); **CHU de Besançon, Hôpital Jean Minjoz, Service de Gastroentérologie, Besançon, France** (M Nachury MD); **CHU de Toulouse, Hôpital Rangueil, Service de Gastroentérologie et Nutrition, Toulouse, France** (J Moreau MD); **Hôpital Henri Mondor, Service d'Hépato-Gastroentérologie, APHP—Université Paris Sud 11, Créteil, France** (Prof J-C Delchier MD); **Hôpital St-Antoine, Service de Gastroentérologie, Paris, France** (Prof J Cosnes MD); **Gastroenterology Department, Hospital Clinic, Barcelona, Spain** (E Ricart MD); **Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid, Spain** (E Ricart); **Université Catholique de Louvain Saint Luc, Service de Gastroentérologie, Brussels, Belgium** (Prof O Dewit MD); **Hospital Ramon y Cajal, Unidad de EII, Servicio de Gastroenterología, Madrid, Spain** (A Lopez-Sanroman MD); **CHU Amiens, Hôpital Nord, Service d'Hépato-Gastroentérologie, Amiens, France** (Prof J-L Dupas MD); **Hôpital Bicêtre, Service d'Hépato-Gastroentérologie, APHP—Université Paris Sud 11, Le Kremlin Bicêtre, France** (Prof F Carbonnel MD); **CHU Clermont-Ferrand, Service Hépatologie-Gastroentérologie, Clermont-Ferrand, France** (Prof G Bommelaer MD); **Hôpital Louis Mourier, Service d'Hépato-Gastroentérologie, Pôle Maladie Appareil Digestif, APHP—Université Paris VII, Colombes, France** (Prof B Coffin MD); **CHU de Saint-Etienne, Hôpital Nord, Service de Gastroentérologie et Hépatologie, Saint-Etienne, France** (X Roblin MD); **Division of Gastroenterology, University Hospital of Leuven, Leuven, Belgium** (Prof G Van Assche MD); **Hospital Universitari Mútua de Terrassa, Department of Gastroenterology, University of Barcelona, Terrassa, Spain** (M Esteve MD); **Department of Medicine, Helsinki University, Helsinki, Finland** (Prof M Färkkilä MD); **Clinic of Gastroenterology, Helsinki University Central Hospital, Helsinki, Finland**

Patients were consecutively recruited. Eligible patients were at least 18 years of age and had an acute severe flare of ulcerative colitis defined by a Lichtiger score of greater than 10 points. The Lichtiger score is a clinical index of eight factors and ranges from 0 to 21 points; acute severe ulcerative colitis is defined as a score of more than 10.[6] All patients had been given an unsuccessful course of high-dose intravenous steroid therapy defined as a minimum of 0·8 mg/kg per day of methylprednisolone or equivalent for at least 5 days. None of the patients had previously received ciclosporin or infliximab. Patients were not given treatment with azathioprine or mercaptopurine at baseline, unless the drugs had been started less than 4 weeks before inclusion at a dose of 2·0–2·5 mg/kg per day of azathioprine or equivalent, in which case the same dose was maintained. Contraception use was mandatory throughout the study and at least 3 months after for all patients of childbearing potential.

We excluded patients with proctitis only; an indication for immediate colectomy as judged by the physician; a history of colorectal dysplasia; Crohn's disease; a positive stool test for enteric pathogens or *Clostridium difficile* B toxin; a positive chest radiograph for tuberculosis or tuberculin skin test; active hepatitis B or C virus infections; HIV infection; uncontrolled bacterial or active viral infection; a history of myocardial infarction, heart failure, or malignant disease in the past 5 years (except for basal-cell skin cancer); renal failure; or uncontrolled high blood pressure. The institutional review board at each centre approved the protocol, and all patients provided written informed consent.

Randomisation and masking

Study drugs were started on day 0 (inclusion visit). Patients were randomly assigned (1:1) to receive ciclosporin by continuous intravenous infusion at an initial dose of 2 mg/kg per day or a one-off 5 mg/kg dose of infliximab by intravenous infusion during 2 h. Randomisation was done centrally with computer-derived permutation tables of size two or four and stratified by centre. Patients were assigned identification codes, which were sent to the investigator after receipt and validation of the inclusion form by the statistical centre (this centre was independent from the funding source). Treatment allocation was included in a sealed opaque envelope with the patient's identification code. Patients and investigators were not masked to treatment.

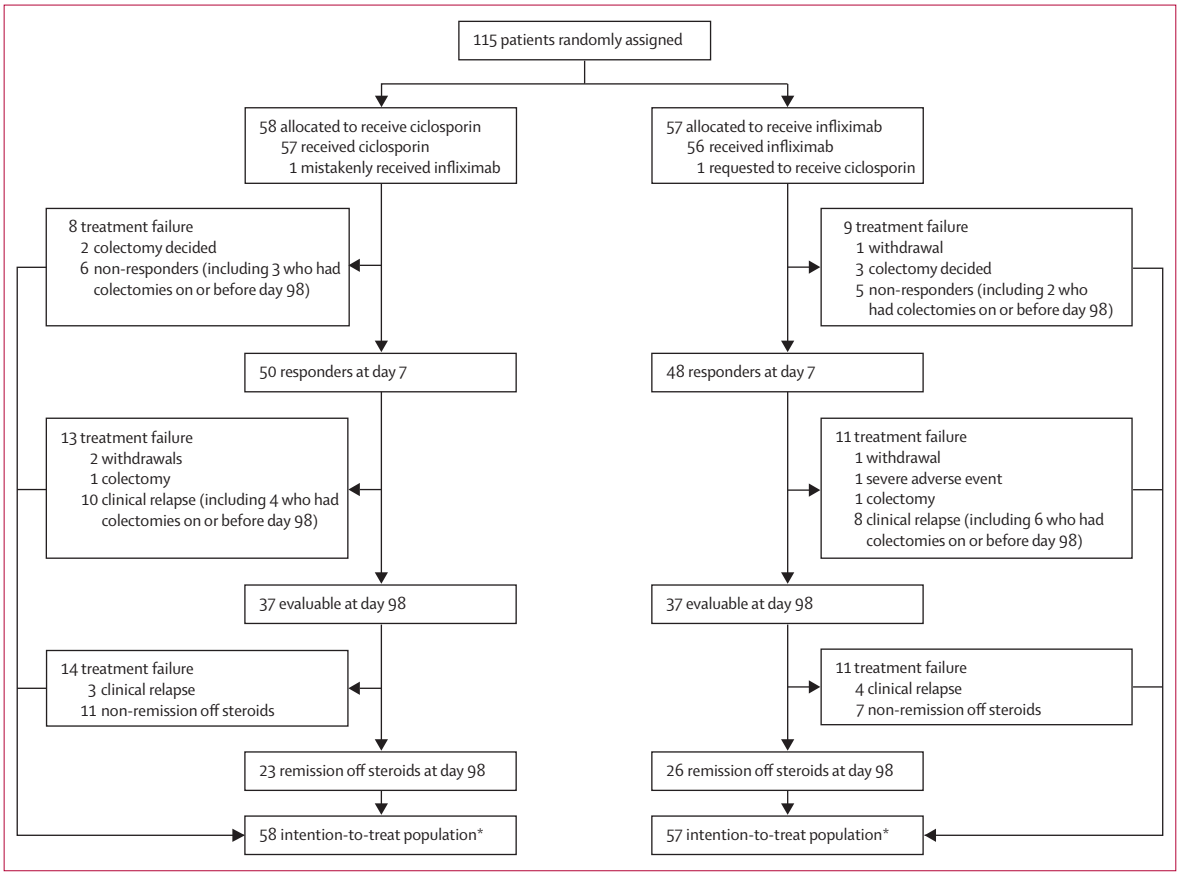

Figure 1: **Trial profile**
*All patients who were randomly assigned were included in the intention-to-treat population.

Procedures

In the ciclosporin group, trough concentrations were measured after 24 h of treatment and reassessed every 48 h during the first week. We subsequently adjusted doses to obtain a ciclosporin blood concentration of 150–250 ng/mL. Patients with a clinical response at day 7 (defined by a Lichtiger response at days 5, 6, and 7—ie, scores of fewer than 10 points with a decrease of at least 3 points compared with baseline scores) were switched to oral 4 mg/kg ciclosporin (Neoral; Novartis Pharma, Basel, Switzerland) in two divided doses until day 98, with weekly monitoring of trough concentrations for the first 4 weeks and then every 2 weeks for the next 8 weeks; we adjusted doses as necessary to maintain concentrations of 150–250 ng/mL. We gave prophylaxis against *Pneumocystis jirovecii* to all patients receiving ciclosporin.[11]

In the infliximab group, patients who had a clinical response at day 7 received two additional infusions of 5 mg/kg infliximab at days 14 and 42.

Intravenous corticosteroid therapy was maintained at a stable dose in all patients until day 7. Patients who responded at day 7 were switched to 30 mg oral methylprednisolone daily; we tapered the dose according to an established schedule (reduction by 10 mg in the first week to 20 mg per day, and then by 5 mg each week until discontinuation). Additionally, all patients with clinical responses at day 7 were given azathioprine, started at 2·0–2·5 mg/kg per day, or continued in patients previously treated. Antibiotics and nutritional support according to clinical need were allowed during the study in all patients, whereas oral or local aminosalicylates, tacrolimus and other biotherapies, loperamide, and non-steroidal anti-inflammatory drugs were not.

We calculated patients' Lichtiger scores daily from baseline to day 7 and then at days 14, 28, 42, 60, and 98. The Mayo disease activity index,[12] including the endoscopic subscore on flexible sigmoidoscopy, was calculated at baseline and at day 98. We recorded rescue treatments and colectomy status for patients withdrawn from the study before day 98. For all patients, we recorded adverse events and concomitant drug use to day 98.

The primary efficacy outcome was treatment failure at any time, defined as the presence during follow-up of any of the six following criteria: absence of clinical response at day 7; relapse between day 7 and 98 (defined as a Lichtiger score increase of at least 3 points from the previous value that lasts for at least 3 consecutive days and leads to treatment modification); absence of steroid-free remission at day 98 (defined as a Mayo disease activity index score ≤2 with an endoscopic subscore ≤1); a severe adverse event leading to treatment interruption; colectomy; and death.

Prespecified secondary outcomes were clinical response at day 7, daily Lichtiger score from day 0 to day 7, time to clinical response (defined as the third of the first 3 consecutive days with Lichtiger response), mucosal healing at day 98 (defined by a Mayo disease activity index endoscopic subscore of 0 or 1), quality-of-life changes from baseline to day 98 (measured with the inflammatory bowel disease questionnaire), colectomy-free survival, and safety (assessed by a data safety

	Ciclosporin (n=58)	Infliximab (n=57)
Female sex	28 (48%)	27 (47%)
Age (years)	39 (26–50)	36 (26–52)
Disease duration (years)	2·4 (0·4–7·1)	1·0 (0·2–4·4)
First attack of ulcerative colitis	10 (17%)	16 (28%)
Disease located in E3*	34 (59%)	31 (54%)
Patient naive to azathioprine	54 (93%)	53 (93%)
Duration of intravenous steroid treatment (days)	8 (6–9)	7·5 (6–9%)
Lichtiger score		
11	27 (47%)	12 (21%)
12–13	19 (33%)	24 (42%)
≥14	12 (21%)	21 (37%)
Mayo disease activity index		
≤10	30 (52%)	25 (44%)
11	17 (29%)	20 (35%)
12	11 (19%)	12 (21%)
Mayo endoscopic subscore of 3	55 (95%)	55 (96%)
IBDQ score	103 (89–118)†	96 (84–113%)‡
Haemoglobin (g/L)	105 (95–124)	115 (96–124)§
C-reactive protein (mg/L)	30 (16–67)¶	46 (28–73)§
Albumin (g/L)	28 (24–32) ¶	27 (23–33)‡

Date are number (%) or median (IQR). IBDQ=inflammatory bowel disease questionnaire. *Ulcerative colitis location according to the Montreal classification—ie, pancolitis defined by an ulcerative colitis extended above the splenix flexure.[39] †n=52. ‡n=50. §n=56. ¶n=55.

Table 1: **Demographic and clinical characteristics of patients**

	Ciclosporin (n=58)	Infliximab (n=57)	p
Absence of clinical response at day 7	8	9	0·80
Withdrawal	0	1	1·00
Surgery	2	3	1·00
Relapse	6	5	1·00
Failure after day 7 and before day 98*	13	11	0·82
Withdrawal	2	1	1·00
Severe adverse event	0	1	1·00
Surgery	1	1	0·81
Relapse	10	8	0·81
Failure at day 98†	14	11	0·62
Relapse	3	4	1·00
Lack of remission	10	7	0·68
Steroids not withdrawn	1	0	1·00
Total treatment failure	35	31	

*n=50 for ciclosporin and 48 for infliximab. †n=37 for both ciclosporin and infliximab.

Table 2: **Suboutcomes of treatment failure for ciclosporin and infliximab**

(Prof M Färkkilä); **Servicio de Aparato Digestivo, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP) y Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid, Spain** (J P Gisbert MD); **Hôpital Lariboisière, Département Médico-chirurgical de Pathologie Digestive, APHP—Université Paris VII, Paris, France** (Prof P Marteau MD); **CHI Le Raincy Montfermeil, Service d'Hépato-Gastroentérologie, Montfermeil, France** (S Nahon MD); **Ghent University Hospital, Ghent, Belgium** (Prof M de Vos MD); **Hôpital Erasme, Université Libre de Bruxelles, Gastroentérologie Hépato-Pancréatologie et Endoscopie Digestive, Brussels, Belgium** (Prof D Franchimont MD); **and INSERM U717, Biostatistics and Clinical Epidemiology, Université Paris Diderot, Paris, France** (J-Y Mary PhD)

Correspondence to:
Prof David Laharie, CHU de Bordeaux, Hôpital Haut-Leveque Hospital, Service d'Hépato-Gastroentérologie, Pessac, F-33600 France
david.laharie@chu-bordeaux.fr

monitoring board with two specialists in inflammatory bowel disease who were not involved in the study).

Statistical analysis

We did our analyses on an intention-to-treat basis. We used descriptive statistical techniques to assess patients' baseline characteristics. The proportion of patients in whom treatment did not work in the ciclosporin group was compared with that in the infliximab group with the χ^2 test and expressed as absolute difference with 95% CIs or as relative difference—ie, odds ratios (ORs) with 95% CIs. This approach was also used to compare rates of clinical response at day 7 and mucosal healing at day 98 between the groups. In these analyses, we deemed treatment in patients who were withdrawn before day 7 or day 98 to be unsuccessful.

Median Lichtiger scores from day 0 to day 7 were compared between the treatment groups with the Mann-Whitney test. Treatment was judged unsuccessful in patients withdrawn before assessment day; such patients were included in the analysis with the maximum score of 21. We used the Mann-Whitney test[13] to compare time to clinical response in the ciclosporin group with that in the infliximab group; patients withdrawn before assessment day were deemed to have had no clinical response. We compared median differences between groups in scores on the inflammatory bowel disease questionnaire between day 0 and 98 with the Mann-Whitney test. We calculated colectomy-free survival Kaplan-Meier[14] curves for each treatment group from randomisation to day 98 and compared them with the log-rank test;[15] differences were expressed as hazard ratios (HRs) with 95% CIs.[16] We did safety analyses for all treated patients, irrespective of treatment duration.

We used a logistic regression model[17] to assess predictors of treatment failure, with treatment as a factor in the model (appendix). We estimated from the final model ORs with 95% CIs for the treatment effect of ciclosporin relative to infliximab.

For the primary outcome, we estimated that randomisation of 100 patients would provide an 80% power to detect a 30% difference in failure rate between the ciclosporin and infliximab groups in a two-sided test with type I error of 5%. We worked with the initial assumption that the rate of failure would be 60% in the infliximab group and 30% in the ciclosporin group, corresponding to an OR of 3·5, and assumed a loss of 4% due to misdiagnosis.[18] A planned interim analysis based on data from the first 30 patients given infliximab led to a recalculation of sample size to 116; with an observed failure rate in the infliximab group of 45%, this sample would have 80% power to detect a difference corresponding to the initially defined OR in the same conditions.

We did post-hoc analyses that described the use of rescue therapy within the study period and the incidence of postcolectomy complications. To assess if one treatment might be preferred in specific situations, we also explored predictors of treatment effect. We used SPSS software for our analyses. The significance threshold was 0·05 for all analyses.

See Online for appendix

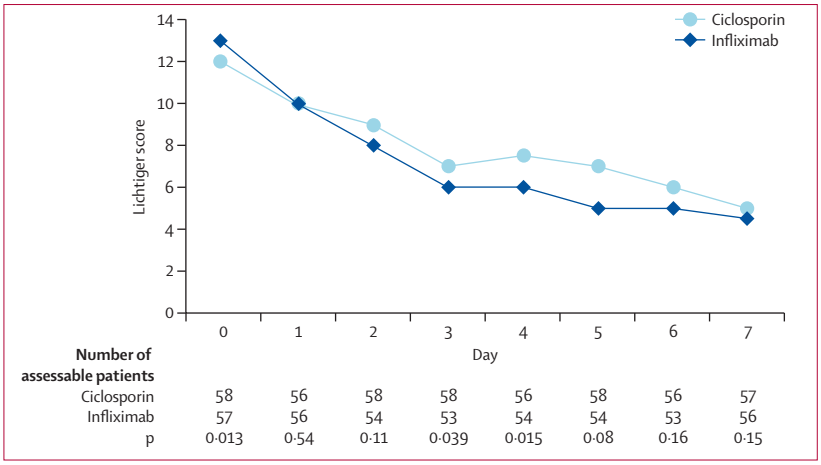

Figure 2: **Lichtiger scores from day 0 to day 7, by treatment**

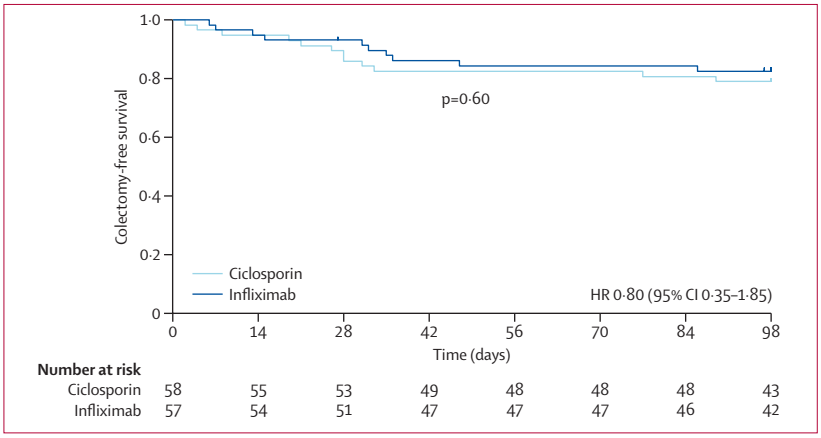

Figure 3: **Kaplan-Meier curves for colectomy-free survival**
In the infliximab group, nine patients in whom treatment was unsuccessful had rescue therapy before day 98: four were switched to ciclosporin (two colectomies), three received extra (ie, not on days 0, 14, or 42) infliximab infusions of 5 mg/kg (one colectomy), and two received scheduled infliximab infusions of 10 mg/kg (ie, a double dose on day 14 or 42; one colectomy). In the ciclosporin group, six patients in whom treatment was unsuccessful had rescue therapy before day 98: five received infliximab, including four infusions of 5 mg/kg (two colectomies) and one of 10 mg/kg (one colectomy) and we increased one patient's steroid dose (no colectomy). HR=hazard ratio.

Role of the funding source

No commercial entity had any role in the study. The funding sources had no role in study design or data collection, analysis, or interpretation. DL, J-YM, J-FC, and ML had full access to all the study data. All authors made the decision to submit the report for publication and vouch for the veracity and completeness of the data and their analyses.

Results

Of the 115 randomly assigned patients, 58 were assigned to the ciclosporin group and 57 to the infliximab group (figure 1). Four of these patients had major inclusion

deviations (ie, did not meet eligibility criteria)—one patient in the infliximab group received 0·50 mg/kg per day of intravenous methylprednisolone for 2 days only before initiation of infliximab, whereas in the ciclosporin group, before initiation one patient received 0·42 mg/kg per day of intravenous methylprednisolone for 5 days, one had not been give intravenous corticosteroids, and one had a baseline Lichtiger score of 9. Furthermore, two patients did not receive the intended treatment (one patient in the infliximab group requested to receive ciclosporin instead and one in the ciclosporin group received infliximab because of an error in their identification code). Baseline disease characteristics were similar in the two groups except for Lichtiger score, which was higher in the infliximab than in the ciclosporin group (table 1).

At day 98, we noted treatment failure in 35 of the 58 (60%) patients given ciclosporin compared with 31 of 57 (54%) given infliximab (absolute risk difference 6%, 95% CI –7 to 19; OR 1·3, 95% CI 0·6 to 2·7; p=0·52). Table 2 shows suboutcomes included in the primary outcome (which were not predefined as endpoints). We did not record any difference between the two groups for these suboutcomes.

50 of 58 (86%) patients given ciclosporin had a clinical response at day 7 compared with 48 of 57 (84%) given infliximab (absolute risk difference 2%, 95% CI –11 to 15; OR 1·2, 95% CI 0·4 to 3·3; p=0·76). The Lichtiger score between day 0 and day 7 decreased faster in patients who received infliximab than in those given ciclosporin; this difference between groups was significant on days 3 and 4 (figure 2). The median time to clinical response was 5 days (IQR 4–7) in the ciclosporin group and 4 days (3–6) in the infliximab group (p=0·12).

26 of 55 (47%) patients given ciclosporin and 25 of 55 (45%) given infliximab achieved mucosal healing (absolute risk difference 2%, 95% CI –17 to 20; OR 1·1, 95% CI 0·5 to 2·3; p=0·85); three patients in the ciclosporin group and two in the infliximab group were not assessed endoscopically at day 98.

Responses to the inflammatory bowel disease questionnaire were available in only 36 patients evaluable at day 98. In patients given ciclosporin, the median score on the inflammatory bowel disease questionnaire increased by 78 points (IQR 66–104; n=19) between baseline and day 98 compared with a median increase of 100 points (75–112; 17) in the infliximab group, but this finding was not significant (p=0·19).

22 patients had colectomies during the study, 10 (17%) in the ciclosporin and 12 (21%) in the infliximab group; time to colectomy did not differ between the groups (p=0·60; figure 3).

In multivariate analysis, age greater than 40 years (OR 2·7, 95% CI 1·2–6·1; p=0·018) and haemoglobin concentrations of 95–125 g/L (2·5, 0·9–6·7) and greater than 125 g/L (8·5, 2·3–31·7) (p=0·003) were independent predictors of treatment failure. After adjustment for these variables, the OR for treatment failure with ciclosporin relative to infliximab was 1·4 (95% CI 0·6–3·2; p=0·36), compared with 1·3 (0·6–2·7; 0·52) without adjustment. We present an exploratory analysis of treatment effect according to different variables in the appendix.

	Ciclosporin (n=58)	Infliximab (n=57)
Death	0*	0
Cardiovascular event	1*	1†
Severe infections	5	4
Cytomegalovirus colitis	2	1
Septicaemia	2‡	0
Urinary tract infection	0	1
Anal abscess	0	1
Fever of unknown origin	1	1
Renal event	0	0
Hepatic event	0	4§
Pulmonary event	1¶	0
Worsening of ulcerative colitis	3	7
Degenerative arthrosis	0	1
Total events	10	17
Total patients (%)	9 (16%)	14 (25%)

*A 66-year-old man developed myocardial ischaemia during the study and died during follow-up (day 137) from a myocardial infarction. †Venous thromboembolism. ‡Central-venous-catheter-related septicaemia with non-*aureus Staphylococcus*. §Increased aminotransferases leading to treatment withdrawal (at least two cases related to azathioprine). ¶Suspected pneumonia (unconfirmed).

Table 3: **Severe adverse events during the study period according to treatment received**

Overall, nine (16%) patients given ciclosporin and 14 (25%) given infliximab had severe adverse events (table 3). Worsening of ulcerative colitis was the most frequent serious adverse event. The appendix shows recorded postoperative complications.

Discussion

Contrary to our initial hypothesis, ciclosporin was not more effective than infliximab in patients with acute severe ulcerative colitis refractory to intravenous steroids (panel). Responses at day 7 and colectomy rates at day 98 were similar in both groups, and both drugs were well tolerated.

The efficacy of ciclosporin in our trial was similar to that noted in previous clinical trials.[6,7] The efficacy of infliximab in refractory ulcerative colitis is somewhat controversial. Three placebo-controlled studies have been done. A trial[24] that included 43 ambulatory patients with moderately severe steroid-resistant ulcerative colitis showed no benefit. A second small study[25] in patients with severe steroid-refractory ulcerative colitis was stopped prematurely and yielded inconclusive results. In the largest trial,[8] 45 hospital inpatients were randomly assigned. Seven patients in the infliximab group and

Panel: Research in context

Systematic review

We searched PubMed for original research articles published before April 30, 2012, in any language, with the terms "cyclosporine", "infliximab", "ulcerative colitis", "severe ulcerative colitis", and "ulcerative colitis attack", to identify papers about the treatment of acute severe ulcerative colitis refractory to intravenous steroids. The efficacy of ciclosporin in severe colitis was first shown in a randomised placebo-controlled trial[6] in which nine of 11 patients given the drug had a response within a mean of 7 days compared with zero of nine patients who received placebo (p<0·001). Efficacy was confirmed in several retrospective cohorts,[20–23] and a randomised controlled study[7] showed no difference in efficacy between intravenous doses of 2 mg/kg per day and 4 mg/kg per day. The efficacy of infliximab has been shown in only one of the three placebo-controlled studies that have been done,[8,24,25] and in retrospective cohorts.[26–31] We identified no studies comparing the efficacy of ciclosporin with that of infliximab, and thus no comparative data are available.

Interpretation

Ciclosporin was not more effective than infliximab in achievement of short-term remission and evasion of urgent colectomy in hospital inpatients with acute severe ulcerative colitis refractory to intravenous steroids. When used in association with azathioprine, both drugs had high efficacy and good safety profiles in this difficult population. Our short-term results do not favour one drug over the other, and thus in clinical practice treatment choice should be guided by physician and centre experience.

14 in the placebo group had colectomies (p=0·02) within 3 months of randomisation. Infliximab had a less pronounced effect in patients with more severe ulcerative colitis than in those with less severe ulcerative colitis.[8] We speculate that the high rate of treatment success with infliximab in our study might be due to a beneficial interaction between infliximab and azathioprine in patients naive to both drugs, which was shown in a 2011 study[32] of patients with less severe disease.

Safety is a major concern in patients with acute severe ulcerative colitis who are critically ill, malnourished, and taking several immunosuppressants. Both ciclosporin and infliximab have been associated with serious opportunistic infections and death.[26,33] We recorded few serious infections and no death during the study period. Adherence to international guidelines for management, including systematic prophylaxis against *Pneumocystis jirovecii* in patients given ciclosporin, and the low dose of ciclosporin that was given, are potential explanations for this finding.[11] Further postmarketing surveillance would be helpful to establish whether infliximab or ciclosporin is safer in patients with acute severe ulcerative colitis.

Our trial's strengths include the high number of patients enrolled (one of the largest trials so far in steroid-refractory acute severe ulcerative colitis); that the study was done at 27 centres in four European countries, making our conclusions widely applicable; and the chosen composite and objective primary outcome that avoid differences between centres about indications for surgery.[34]

Our study had several limitations. First, treatment assignment was open label. Masking of ciclosporin treatment is very difficult because of the high incidence of abnormal results of blood biochemical tests, the common minor side-effect of paraesthesia, and the necessary dose adjustments. Furthermore, the use of composite criteria as a primary outcome, including objective measures such as the Lichtiger and Mayo scores, rather than colectomy alone, probably restricted the effect of unmasking on therapeutic decisions. Second, our study was powered to detect a large difference in effect between the two drugs. When a 30% superiority of ciclosporin over infliximab was assumed, then the trial had four chances of five to detect the difference, but had the superiority been only 10%, the study had only one chance of eight to detect the difference. Finally, our findings about the efficacy of ciclosporin versus infliximab need to be interpreted with caution because of the sample size (shown by the width of the 95% CIs for the failure rate difference).

Contributors

DL and J-FC were study investigators, conceived and designed the study, interpreted data, and drafted and critically revised the report. AB, JB, MA, YB, JF, FZ, GS, MN, JM, J-CD, JC, ER, OD, AL-S, J-LD, FC, GB, BC, XR, ME, MF, JPG, PM, SN, MDV, and DF were study investigators. GVA had a role in study conception and was an investigator. J-YM had a role in study conception and design, data interpretation, statistical analysis, and drafting and critical revision of the report. ML was a study investigator and had a role in conception and design, data interpretation, and drafting of the report. DL, AB, JB, MA, YB, JF, FZ, GS, MN, JM, J-CD, JC, OD, J-LD, FC, GB, BC, XR, PM, SN, MDV, DF, J-YM, J-FC, and ML are members of the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives.

Conflicts of interest

DL, AB, MA, GS, ER, OD, and ML have lectured for Merck Sharp & Dohme. YB has lectured for Merck Sharp & Dohme, Abbott, Ferring, Norgine, and Vifor Pharma. FZ has received travel grants from Merck Sharp & Dohme. JC has lectured for Abbott, Merck Sharp & Dohme, and Tilliot Pharma, and has received research funding from Abbott. AL-S and MF have lectured for Abbott and Merck Sharp & Dohme. GVA has received honoraria and research support from Merck Sharp & Dohme and honoraria from Novartis. ME has been on the advisory board and lectured for Merck Sharp & Dohme, Abbott, and Shire Pharmaceuticals. MDV has received consultancy fees from Abbott, Merck Sharp & Dohme, and Ferring, research and educational grants from Merck Sharp & Dohme and Abbott, and has lectured for Abbott, Ferring, and Merck Sharp & Dohme. J-FC has received consulting fees from or been on paid advisory boards for Abbott, ActoGeniX NV, Affilogic, AlbireoPharma, AstraZeneca, Bayer Schering Pharma, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix SL, Chemocentryx, Centocor, Cosmo Technologies, Danone France, Elan Pharmaceuticals, Genentech, Giuliani SPA, Given Imaging, GlaxoSmithKline, Merck, Millennium Pharmaceuticals, Neovacs SA, Ocerra Therapeutics, Otsuka American Pharmaceuticals, PDL Biopharma, Pfizer, RiboVacs Biotech, Schering Plough Corporation, Shire Pharmaceuticals, Synta Pharmaceutical Corporation, Takeda, Teva Pharmaceuticals, Therakos, UCB Pharma, and Wyeth Pharmaceuticals and received grant support from AstraZeneca, Ferring, Schering Plough Corporation, UCB Pharma, Lesaffre, Giuliani SPA, Danisco, Ocerra Therapeutics, Danone, Roquette, Mapi Naxis, and Dysphar. JB, JF, MN, JM, J-CD, J-LD, FC, GB, BC, XR, JPG, PM, SN, J-YM and DF declare that they have no conflicts of interest.

Acknowledgments

This study was funded by the Association François Aupetit, the Société Nationale Française de Gastroentérologie, and the International Organization for the Study of Inflammatory Bowel Disease. We thank Patricia Détré, Julie Demolin, Colette Geneix, and Cendrine Chaffaut for their clinical research and technical help and David Sachar and

Brian Feagan for providing expert suggestions. ML died suddenly on Aug 26, 2010. We remember our esteemed friend and colleague who initiated this study and recognise his contributions to advancing the understanding and treatment of inflammatory bowel disease.

References

1 Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011; **365:** 1713–25.

2 Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. *Gut* 1963; **4:** 299–315.

3 Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohns Colitis* 2010; **4:** 431–37.

4 Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *BMJ* 1955; **2:** 1041–48.

5 D'Haens G, Lemmens L, Geboes K, et al. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001; **120:** 1323–29.

6 Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330:** 1841–45.

7 Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003; **125:** 1025–31.

8 Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005; **128:** 1805–11.

9 Travis SP, Stange EF, Lemann M, et al. European evidence-based consensus on the management of ulcerative colitis: current management. *J Crohn Colitis* 2008; **2:** 24–62.

10 Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105:** 501–23.

11 Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn Colitis* 2009; **3:** 47–91.

12 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317:** 1625–29.

13 Siegel S. Non parametric statistics for the behavioral sciences. New York: McGraw-Hill Book Co, 1956.

14 Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

15 Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Rep* 1966; **50:** 163–70.

16 Cox DR. Regression models and life-tables (with discussions), series B. *J R Stat Soc* 1972; **34:** 184–92.

17 Cox DR, Snell EJ. Analysis of binary data. London, Chapman & Hall, 1989.

18 Dupont WD, Plummer WD. Power and sample size calculations. A review and computer program. *Control Clinical Trials* 1990; **11:** 116.

19 Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55:** 749–53.

20 Actis GC, Bresso F, Astegiano M, et al. Safety and efficacy of azathioprine in the maintenance of ciclosporin-induced remission of ulcerative colitis. *Aliment Pharmacol Ther* 2001; **15:** 1307–11.

21 Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999; **94:** 1587–92.

22 Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55:** 47–53.

23 Cacheux W, Seksik P, Lemann M, et al. Predictive factors of response to cyclosporine in steroid-refractory ulcerative colitis. *Am J Gastroenterol* 2008; **103:** 637–42.

24 Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003; **52:** 998–1002.

25 Sands BE, Tremaine WJ, Sandborn WJ, et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflamm Bowel Dis* 2001; **7:** 83–88.

26 Kohn A, Daperno M, Armuzzi A, et al. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther* 2007; **26:** 747–56.

27 Su C, Salzberg BA, Lewis JD, et al. Efficacy of anti-tumor necrosis factor therapy in patients with ulcerative colitis. *Am J Gastroenterol* 2002; **97:** 2577–84.

28 Gornet JM, Couve S, Hassani Z, et al. Infliximab for refractory ulcerative colitis or indeterminate colitis: an open-label multicentre study. *Aliment Pharmacol Ther* 2003; **18:** 175–81.

29 Eidelwein AP, Cuffari C, Abadom V, Oliva-Hemker M. Infliximab efficacy in pediatric ulcerative colitis. *Inflamm Bowel Dis* 2005; **11:** 213–18.

30 Jakobovits SL, Jewell DP, Travis SP. Infliximab for the treatment of ulcerative colitis: outcomes in Oxford from 2000 to 2006. *Aliment Pharmacol Ther* 2007; **25:** 1055–60.

31 Oussalah A, Evesque L, Laharie D, et al. A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. *Am J Gastroenterol* 2010; **105:** 2617–25.

32 Panaccione R, Ghosh S, Middleton S, et al. Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: the UC SUCCESS trial. *J Crohn Colitis* 2011; **5:** S8.

33 Arts J, D'Haens G, Zeegers M, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. *Inflamm Bowel Dis* 2004; **10:** 73–78.

34 Hoie O, Wolters FL, Riis L, et al. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007; **132:** 507–15.