

CLINICAL TRIAL PROTOCOL

***“Azathioprine maintenance therapy in steroid-refractory
Ulcerative Colitis responsive to i.v. Cyclosporine A: Is a
‘therapeutic bridge’ with oral Cyclosporine A necessary?”***

Miquel A. Gassull, M.D.

(Final Version: 19th April 2002)

BACKGROUND

Intravenous corticosteroid therapy is the standard regime for patients with severe ulcerative colitis (UC). However, about 40% of these patients will fail to respond to i.v. corticosteroids. Until the 1990s, these patients underwent colectomy, but in the last decade growing evidence has shown that cyclosporine A (CsA) can be effective in these patients.

In 1990, Lichtiger et al. reported a pilot experience suggesting that i.v. CsA could be useful in steroid-refractory UC (1). Four years later, the same authors published the first and only randomised controlled trial on the use of i.v. CsA (4 mg/kg/day, adjusted for blood CsA levels, for 14 days) versus placebo in 20 steroid-refractory UC patients (2). Nine of the 11 CsA treated patients (82%) responded as compared to none of 9 (0%) receiving placebo (2). This initial controlled experience has been further confirmed by several uncontrolled series showing that, as a whole, i.v. CsA induces remission in about two thirds of steroid-refractory UC patients (3). Thus, i.v. CsA has been incorporated to the therapeutic armamentarium of severe UC (4).

Nevertheless, it became soon evident that the effect of i.v. CsA in refractory UC was short-lived even in those patients put on oral CsA maintenance therapy (5-7), and in addition oral CsA cannot be maintained for more than 6 months because of the risk of serious adverse events (8).

Because its better safety profile, azathioprine (AZA) – or its metabolite 6-mercaptopurine – appears as a good alternative for long-term maintenance therapy in i.v. CsA-responsive patients (9-11). However, controversy exists on how to shift from i.v. CsA to oral AZA in these patients. Most current therapeutic guidelines advocate for discontinuing i.v. CsA and start AZA plus oral CsA for 3 months (together with steroid tapering) and then discontinue oral CsA and maintain AZA on a long term basis (3,12). Other authors discontinue i.v. CsA and start AZA (as well as the steroid tapering) without using oral CsA as a “therapeutic bridge” (9). However, these two strategies have never been compared.

References

1. Lichtiger S, Present DH. Preliminary report: Cyclosporin in treatment of severe ulcerative colitis. *Lancet* 1990; 336:16-19
2. Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; 330:1841-1845
3. Sandborn WJ. Cyclosporine in ulcerative colitis: state of the art. *Acta Gastroenterol Belg* 2001; 64:201-204
4. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults. *Am J Gastroenterol* 1997; 92:204-211
5. Kornbluth A, Lichtiger S, Present DH, Hanauer SB. Long-term results of oral cyclosporin in patients with severe ulcerative colitis. *Gastroenterology* 1994; 106:A714 (abstract)
6. Carbonnel F, Boruchowicz A, Duclos B, Soule JC, Lerebours E, Lemann M et al. Intravenous cyclosporine in attacks of ulcerative colitis: short-term and long-term responses. *Dig Dis Sci* 1996; 41:2471-2476

7. Gurudu SR, Griffel LH, Gialanella RJ, Das KM. Cyclosporine therapy in inflammatory bowel disease: short-term and long-term results. *J Clin Gastroenterol* 1999; 29:151-154
8. Sandborn WJ. A critical review of cyclosporine therapy in inflammatory bowel disease. *Inflammat Bowel Dis* 1995; 1:48-63
9. Fernández Bañares F, Bertrán X, Esteve Comas M, Cabré E, Menacho M, Humbert P et al. Azathioprine is useful in maintaining long-term remission induced by intravenous cyclosporine in steroid-refractory severe ulcerative colitis. *Am J Gastroenterol* 1996; 91:2498-2499
10. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999; 94:1587-1592
11. Actis GC, Bresso F, Astegiano M, Demarchi B, Sapone N, Boscaglia C et al. Safety and efficacy of azathioprine in the maintenance of cyclosporin-induced remission of ulcerative colitis. *Aliment Pharmacol Ther* 2001; 15:1307-1311
12. Kornbluth A, Present DH, Lichtiger S, Hanauer S. Cyclosporin for severe ulcerative colitis: A user's guide. *Am J Gastroenterol* 1997; 92:1424-1428

AIMS

The aim of this trial is to compare the effectiveness and safety of two different strategies (with and without oral CsA as therapeutic bridge to AZA) for maintenance therapy in patients with steroid-refractory UC, responsive to i.v. CsA.

CRITERIA FOR ELIGIBILITY

Inclusion criteria

1. Suffering from a moderate or severe acute attack of UC – as defined as a modified Truelove-Witts score >10 (ANNEX 1) – not responding to 3 days of i.v. steroid therapy (60 mg/day methylprednisolone)
2. Response to 7 days i.v. CsA (4 mg/Kg/day), as assessed by an “inactive” modified Truelove-Witts index (ANNEX 1)
3. Absence of colonic cytomegalovirus (CMV) infection as assessed by immunohistochemistry, prior to CsA therapy
4. Informed consent

Exclusion criteria

1. Disease involving less than 50 cm of distal colon
2. Arterial hypertension
3. Increased serum creatinine

4. Blood granulocyte count lower than 1,500 cells/mm³
5. Toxic megacolon
6. Active infection
7. Severe associated disease
8. UC attack occurring in patients already treated with AZA for more than 3 months.
9. Pregnancy or lactation

DESIGN OF THE STUDY

This is a multicentric, randomised, open-label, controlled trial with parallel groups. Eligible patients will be randomised in separate strata according to the extension of the disease (left-sided colitis *versus* extensive/pancolitis) into two therapeutic groups:

1. BRIDGE group: receiving AZA together with oral CsA during the initial phase of maintenance therapy (see below)
2. NON-BRIDGE group: receiving AZA *without* oral CsA during the initial phase of maintenance therapy (see below).

Patients of both groups will be followed for 12 months or until colectomy if required.

STUDY TREATMENTS

“Bridge” Group

After randomisation (Day 0) i.v. CsA will be discontinued and the patients put on the following treatment:

1. Oral AZA (2.0-2.5 mg/Kg/day) for the entire period of study (maximum 12 months or until colectomy). In patients with gastric upset due attributable to AZA, this will be replaced by 6-mercaptopurine (1.5 mg/Kg/day).
2. CsA Neoral[®] (6 mg/Kg/day), and then adjusted monthly to maintain serum CsA levels between 150-300 ng/mL, during 4 months.
3. Methylprednisolone will be shifted to the oral route at a daily dose of 40 mg, and reduced by 8 mg every week until reaching a daily dose of 24 mg; then the dose will be reduced by 4 mg per week until steroid discontinuation (the complete process will take 8 weeks)

4. Co-trimoxazole (one double-strength tablet – 800 mg of sulfamethoxazole plus 160 mg of trimethoprim – twice weekly) during the 4-month period the patient is on CsA Neoral[®], for the prophylaxis of opportunistic *Pneumocystis carinii* infection.

“Non-Bridge” Group

After randomisation (Day 1) i.v. CsA will be discontinued and the patients put on the following treatment:

1. Oral AZA (2.0-2.5 mg/Kg/day) for the entire period of study (maximum 12 months or until colectomy). In patients with gastric upset due attributable to AZA, this will be replaced by 6-mercaptopurine (1.5 mg/Kg/day).
2. Methylprednisolone will be shifted to the oral route at a daily dose of 40 mg, and reduced by 8 mg every week until reaching a daily dose of 24 mg; then the dose will be reduced by 4 mg per week until steroid discontinuation (the complete process will take 8 weeks)
3. Co-trimoxazole (one double-strength tablet – 800 mg of sulfamethoxazole plus 160 mg of trimethoprim – twice weekly) during the same 4-month period as patients in BRIDGE group

Assessment of compliance to study medications

The adherence of patients to the study medications will be assessed by counting of returned supply at each follow-up visit.

OTHER MEDICATIONS

At the beginning of the trial, no other medications, except for systemic steroids and i.v. CsA will be allowed.

During the trial, the use of other medications for the treatment of UC will be allowed under the following conditions:

1. Aminosalicylates (oral or topic) and topic steroids (including budesonide): These will be allowed for treating mild attacks of the disease, as defined by a Truelove-Witts index from 7 to 10 points (ANNEX 1), without discontinuing the study treatment. These drugs should be discontinued as soon as the disease became inactive (6 points)
2. Systemic steroids (including oral budesonide): These will be allowed for treating moderate or severe UC attacks (Truelove-Witts index >10, ANNEX 1), without discontinuing the study treatment. However, the need for systemic steroid therapy will be considered as a treatment failure (see below). Steroids will be tapered when remission was obtained until discontinuation.

Any other medication non-related to UC could be prescribed at discretion of the investigator, provided that the reason, dose of therapy is recorded in the case report form.

STUDY PROCEDURES AND ASSESSMENTS

The study will be structured in monthly visits from baseline (just before randomisation and starting treatment) to month 12. In addition, an extra LAB assessment will be scheduled at week 2 in order to assess initial tolerance to AZA. Procedures to be performed in each visit are as follows:

Baseline visit

1. Physical examination
2. Routine blood analysis, including complete blood cell counts, ESR, serum glucose, creatinine, sodium, potassium, cholesterol, albumin, bilirubin, AST, ALT, alkaline phosphatase, GGT, and prothrombin time.
3. C-reactive protein
4. Modified Truelove-Witts index (ANNEX 1)
5. Serum CsA levels
6. Quality of life as assessed by the IBDQ tool. (Irvine EJ, et al. Gastroenterology 1994; 106:287-296)

Extra LAB assessment (week 2)

1. Complete blood cell counts

Visits 1 to 4 (months 1 to 4)

1. As baseline visit, except for serum CsA levels, which will be measured only in patients from BRIDGE group
2. Quality of life as assessed by the IBDQ tool (only on visit 4)

Visits 5 to 12 (months 5 to 12)

1. As baseline, except for serum CsA levels
2. Colonoscopy and colonic biopsies (only in visits 6 and 12)
3. Quality of life as assessed by the IBDQ tool, (only on visits 8 and 12)

ASSESSMENT OF THE RESPONSE: PRIMARY AND SECONDARY END-POINTS

Definitions

Active disease: Symptomatic UC with a Truelove-Witts score greater than 6 points (ANNEX 1)

Significant (moderate-severe) relapse: Symptomatic UC with a Truelove-Witts score greater than 10 points (ANNEX 1) and/or the need for systemic steroid therapy (including oral budesonide).

Colectomy: The need for total colonic resection whatever was the reason (refractory attack, cancer or dysplasia,...)

Treatment failure: any of the following

1. Significant relapse
2. Colectomy
3. A serious adverse event requiring discontinuation of any of the study treatments.

Primary end-point

The PRIMARY END-POINT of the study will be the DEVELOPMENT OF SIGNIFICANT RELAPSE during the 12 follow-up months. However, the development of relapse will be not a reason for withdrawal from the trial.

Secondary end-points

Both therapeutic strategies will be also compared in terms of:

1. Significant relapse at 6 months
2. Need for colectomy within the 12-months of the study
3. Treatment failure
4. Adverse events
5. Quality of life

ADVERSE EVENTS

An adverse event (AE) is defined as any unfavourable and unintended symptom, sign (including an abnormal laboratory finding), or disease temporally associated with the use of an investigational treatment, whether or not related to this investigational treatment.

The severity of an AE will be graded as follows:

1. Serious: if the AE fulfils any of the following criteria:
 - a. Causes death or is life-threatening

- b. Is permanently disabling
 - c. Is a congenital abnormality
 - d. Is a cancer
 - e. The patient has to be hospitalised
 - f. Requires the discontinuation of the study treatment
2. Moderate: When any of the following occurs:
 - a. Requires specific treatment
 - b. Requires the transient withdrawal or reduction of the dose of the study treatment
 3. Mild: When none of the preceding circumstances does occur.

Relationship to study treatment

Relationship to study treatment will be assigned according to the following definitions:

1. Probable: An AE with a reasonable time sequence to administration of the study treatment unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
2. Possible: An AE with a reasonable time sequence to administration of the study treatment but which could be explained by concurrent disease or other drugs or chemicals. Information on treatment withdrawal may be lacking or unclear.
3. Unlikely: An AE with temporal relationship to the administration of study treatment which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations

Notification

Any AE occurring during the study period must be recorded in appropriate pages of the case report form. These will include the date when the AE occurred, its description, grading (mild-moderate-serious), consequences and specific therapy, as well as its assigned relationship to the study treatment.

In addition, any serious AE must be notified to the co-ordinator of the study within 48 hours, either by phone, fax or e-mail.

WITHDRAWAL FROM THE STUDY

A patients could be withdrawn from the study because any of the following reasons:

1. Development of a serious AE
2. Low compliance to the study treatment, defined as discontinuation of the medication for a single period of more than 30 days, or more than 60 days (in different periods of time)
3. Pregnancy
4. The patient's own will
5. Protocol violation

STATISTICAL ISSUES

Sample size

The sample size has been estimated in order to demonstrate the equivalence between both therapeutic strategies in terms of 12-month relapse rate. This means that the probability of relapse with oral CsA as “therapeutic bridge” (π_1) would be equal to that without using oral CsA ($\pi_2=\pi_1$).

Assuming a 12-month probability of relapse of 50% with the “therapeutic bridge” ($\pi_1=0.50$), and considering a 15% difference as equivalent ($\varepsilon=\pi_2-\pi_1=0.15$), with a one-sided α error of 0.05, a β error of 0.20, and foreseeing a 10% drop-out the sample size would be 304 patients (152 per group).

Statistical analysis

Baseline comparisons

Comparisons of qualitative baseline characteristics between groups will be performed by means of the chi-square test. Baseline quantitative variables will be compared by means of the Student-t-test for unpaired data, or is equivalent non-parametric (Mann-Whitney U) test, as required.

Primary end-point analysis

The proportion of significant relapses in each therapeutic group will be compared by means of the chi-square test, with a significance levels of 0.05 (one-sided).

In addition the cumulative probabilities of significant relapse of both groups (as assessed by the Kaplan-Meier method) will be compared by means of the log-rank test.

All primary end-point analyses will be primarily performed on an intention-to-treat basis (i.e. including all randomised patients). Analysis per protocol (i.e.

after excluding patients prematurely withdrawn from the study) will also be performed.

Secondary end-points analysis

For all secondary end-points, a significance level of 0.05 (two-sided) will be used. As for the primary end-point, analyses will be performed using both the chi-square test and the log-rank test.

Looking for the effect of covariates

The effect of covariates, such as age, sex, disease extension, smoking status, baseline laboratory parameters, etc., together with the study treatment, on the significant relapse rate will be assessed by means of stepwise Cox proportional hazards model.

ANNEX 1

Modified Truelove and Witts activity index for Ulcerative Colitis

	1 point	2 points	3 points
No. stools/day	<4	4-5	>5
Macroscopic blood in faeces	-/+	++	+++
Axillary temperature (°C)	<37	37-37.5	>37.5
Pulse rate (bpm)	<80	80-90	>90
Haemoglobin (g/L)			
- Male	>14	10 -14	<10
- Female	>12	9 -12	<9
ESR (mm/h)	<15	15-30	>30

TOTAL =

Scored Index:

- 6 points = Inactive disease
- 7-10 points = Mild disease
- 11-14 points = Moderate disease
- 15-18 points = Severe disease

SUMMARY OF TRIAL PROCEDURES

	<i>Visits (months)</i>													
	B	LA	1	2	3	4	5	6	7	8	9	10	11	12
<i>Time (months)</i>	0	½	1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent	x													
Randomization	x													
Physical examination	x		x	x	x	x	x	x	x	x	x	x	x	x
Routine blood analyses	x	x ¹	x	x	x	x	x	x	x	x	x	x	x	x
CRP	x		x	x	x	x	x	x	x	x	x	x	x	x
Modified Truelove-Witts	x		x	x	x	x	x	x	x	x	x	x	x	x
Serum CsA levels	x		x ²	x ²	x ²	x ²								
AE recording		x	x	x	x	x	x	x	x	x	x	x	x	x
QoL (IBDQ)	x					x				x				x
Compliance assess.			x	x	x	x	x	x	x	x	x	x	x	x
Colonoscopy + biopsy								x						x

¹Only blood cell counts

²Only in the BRIDGE group