Ciclosporin for Severe Refractory Colitis

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Ciclosporine au cours des colites aiguës graves

LA TUNISIE MEDICALE - 2010 ; Vol 88 (n°06) : 390 - 393

RÉSUMÉ

Prérequis : La ciclosporine par voie intraveineuse est un traitement efficace chez les patients présentant une colite aiguë grave résistante aux corticoïdes. Cependant, son utilisation est actuellement controversée du fait de la fréquence des effets indésirables d'une part et du doute sur les résultats à long terme d'autre part.

But : Le but de cette revue est de réunir les données concernant les indications, les modalités d'administration, les effets indésirables et la surveillance de la ciclosporine au cours des colites graves cortico-résistantes.

Méthodes: Revue de la littérature

Résultats : Sa toxicité est dominée par le risque d'infections opportunistes. Une neurotoxicité et une néphrotoxicité sont également possibles. Cette toxicité peut être réduite par l'utilisation de plus faibles doses, de la forme orale à type de micro-émulsion ou de monothérapie. La durée du traitement ne doit pas dépasser 3 à 6 mois. Actuellement, le rôle principal de la ciclosporine est un « bridge » au traitement d'entretien par azathioprine/6-mercaptopurine.

Conclusion : La ciclosporine est une alternative thérapeutique à la colectomie en urgence dans le colites ulcéreuses sévéres à court terme. Bien que ce bénéfice n'est pas obtenue chez tous les patients, plus de la moitié vont évité la colectotomie à long terme. Selection de patient, bien suivis avec une thérapie par voie orale à faible dose doit pouvoir diminuer les effets indésirables.

Mots-clés

colite aiguë grave – ciclosporine.

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SUMMARY

Background : Intravenous ciclosporin is a promising alternative, rapidly effective, for patients with severe steroid-refractory colitis previously facing only surgical options, however its use is controversial because of the frequency of adverse effects and the doubt about the long-term response.

Aim: This review will provide information on clinical pharmacology, clinical indications for use, methods of dose adjustment, monitoring of metabolites for efficacy and for potential side effects and the adverse event profile of ciclosporin in severe refractory colitis.

Methods: Literature review

Results: Toxicity is dominated by opportunistic infections. Renal and neurotoxicity are also recognized. Risks of toxicity can be reduced by using lower doses, by oral microemulsion or by monotherapy without corticosteroids. The drug should not be continued for more than 3 to 6 months. As a bridge to other maintenance therapy such as azathioprine or 6-mercaptopurine ciclosporin can be an effective treatment.

Conclusion : CSA is a viable alternative to emergency colectomy in severe UC in the short term. Although these benefits are not maintained in all patients, more than a half will also avoid colectomy in the longer term. Careful selection and monitoring of patients, use of lower doses, and oral therapy will help to reduce side effects.

Key-words

refractory colitis – ciclosporin

About 15% of patients with ulcerative colitis (UC) experience fulminant episodes requiring admission to hospital during the curse of their illness. Treatment with intravenous corticosteroids remains the mainstay of treatment for severe UC, but the colectomy rate for treatment failure is about 30 to 40%. The use of ciclosporin A (CSA) as a rescue therapy is the only significant advance in medical therapy since the introduction of intra-venous corticosteroids. In fact, CSA has provided an effective medical alternative to patients previously faced with the only surgical options. Nevertheless, the role of this drug remains controversial, with doubts about side effects and long-term efficacy and controversy has arisen whether the benefits use of CSA outweighs the risks.

This review will provide information on clinical pharmacology, clinical indications for use, methods of dose adjustment, monitoring of metabolites for efficacy and for potential side effects and the adverse event profile of ciclosporin in severe refractory colitis.

METHODS

To identify articles for this review, a PubMed search was conducted using the following key words individually and in various combinations: ciclosporin, severe refractory colitis, monitoring, adverse effects and toxicity. Search of reference lists from pertinent articles identified additional publications.

RESULTS

Mode of action:

CSA is a lipophilic cyclic peptide that binds with high affinity to its cytoplasmic receptor protein cyclophilin. This complex specifically and competitively binds to and inhibits calcineurin, a calcium and calmodulin dependant phosphatase. This prevents translocation of a family of transcription factors, nuclear factor activated T cells (NF-AT), which reduces activation of genes for interleukin (IL)-2, IL-3, IL-4, granulocyte macrophage colony-stimulating factor, tumor necrosis factor alpha and interferon gamma. T-cell transcription factors AP-1 and NF-kB are also inhibited. CSA acts predominantly on CD4 cells [1]. Consequently, CSA diminishes cytokine production and exerts an antiproliferative effect on lymphocytes [1,2,3].

Clinical evidence of benefit:

Promising results from uncontrolled trials [4,5] were substantiated by a randomized, double-blind, placebo-controlled trial conducted by Lichtiger, whereby intravenous CSA showed an impressive 82% response rate in steroid refractory UC patients [6]. At 6 months, after conversion to oral CSA, 69% of patients were able to discontinue steroids and remain in remission. Intravenous CSA, with concurrent intravenous steroids has become an established therapy in severe steroid-resistant UC sparing 60-90% of patients from urgent colectomy [7]. Some responders to CSA will ultimately relapse, but 30-50% will not require surgery during long-term follow-up (table 1). The addition of azathioprine (AZA)/mercaptopurine (MP) improved long-term response rates. As a bridge to other maintenance therapy, CSA can be an effective treatment option, achieving rapid remission and even if the patients necessitate surgery, CSA offers the opportunity to avoid emergency colectomy and provides time for elective colectomy.

Table 1 : Results of intravenous ciclosporin in refractory ulcerative colitis.

Author	Year	Number of patients	Dose	Initial response	Long-term response
Cohen [13]	1999	42	4mg/kg	86%	62%
Stack [15]	1998	22	4mg/kg	91%	53%
Rayner [10]	2003	31	2mg/kg	77%	45%
Message [14]	2005	26	4mg/kg	77%	52%
Campbell [16]	2005	76	4mg/kg	74%	42%

Toxicity:

The use of CSA is associated with considerable morbidity. The risk of minor side effects ranges from 31 to 51%, including tremor, paraesthesia, malaise, headache, nausea/vomiting, abnormal liver function, gingival hyperplasia and hirsutism [1,3]. Major complications are reported with a frequency from 0 to 17%, including renal, infectious and neurotoxic effects [1].

Nephrotoxicity:

Mild, reversible renal impairment is common. There are only isolated reports of serious renal failure probably because of the short duration of therapy. Acute nephrotoxicity is due to a dose dependant vasoconstriction of afferent and efferent glomerular arterioles resulting in reduced renal blood flow and a fall in glomerular filtration rate. The effect can be reduced with calcium channel blockers, but may be increased by the concomitant prescription of other nephrotoxic drugs. A rare effect of CSA is a vascular lesion akin to that in haemolytic-uraemic syndrome. This is idiosyncratic and leads to irreversible renal failure. Chronic nephrotoxicity results from obliterative arteriolopathy, ischaemic collapse or scarring of glomeruli, vacuolization of tubules, focal tubular atrophy and interstitial fibrosis. A fourth renal problem is tubular dysfunction, resulting in hyperuricaemia, metabolic acidosis, hypophosphataemia and hypomagnesaemia [1].

Infections:

The profound immunosuppressive effects of CSA result in a significant risk of infection. The risk is dose dependant and compounded by co-treatment with corticosteroids, or other immunomodulators and the general condition of the patient [1,2]. Infections include opportunistic pathogens, particularly Pneumocystis Carinii but also Nocardia, Aspergillus fumigatus, Listeria monocytogenes, cytomegalovirus, herpes simplex and candida infections. Septicemia from conventional infections also occurs such as Staphylococcus aureus and Haemophilus influenzae [1]. Pneumocystis prophylaxis should be considered.

Neurotoxicity:
Minor neurotoxic effects of CSA include tremor, burning paraesthesiae, headaches, blurred vision and malaise. Serious effects include seizures, coma, spasticity, and ataxia. These effects are dose related, and reversible, but they can occur at low doses. The risk of neurotoxicity may be increased by many factors, including high-dose corticosteroids, hypertension, low serum cholesterol and hypomagnesaemia. Consequently, it is recommended that patients do not receive CSA if the cholesterol is below 3 mM and hypomagnesaemia should be corrected prior to treatment.

Dose and route of administration:
Successful trials with CSA for UC used doses of 2-4 mg/kg/day intravenous (IV) [1,2]. The dose that was widely used, in the past decade, is 4 mg/kg/day by continuous IV infusion [1], but the majority of side effects are dose dependent. One approach to decreasing the toxicity is to reduce the dose of CSA. Actis et al. showed that outcomes using low-dose intravenous CSA (2 mg/kg/day) are comparable with those with high-dose therapy with less toxicity [5]. So a dose of 2 mg/kg/day is used nowadays to improve risk/benefit ratios [7].

Oral treatment:
Bioavailability ranges from 10 to 89% and can be reduced by fat-rich meal. The microemulsion-based formulation of CSA was developed to overcome problems of poor and unpredictable absorption of the standard oral preparation. Oral microemulsion CSA is now widely used and may eventually replace IV administration [8,9]. An oral dose of 5 mg/kg/day would be equivalent to 2 mg/kg/day intravenously.

Monotherapy:
Other strategies to lessen the adverse effects of CSA include its use as monotherapy without corticosteroids avoiding its concurrent morbidity [10]. This strategy may be safer; however, combination therapy still seems likely to be more effective. Monotherapy with intravenous ciclosporin, to achieve a minimum therapeutic concentration, [11] is an option for patients intolerant of intravenous steroids (recommendation grade C) .

Ciclosporin enemas:
In spite of early promise, CSA enemas have been shown to be ineffective in a placebo controlled study in 40 patients with left-sided colitis [12].

Monitoring:
Baseline medical history including patient's medication list, physical examination and laboratory studies are needed prior to initiation of therapy (table 2 and 3).

Table 2 : Pre-treatment

Pre-treatment parameters
Counsel patients regarding risk/benefits
Check blood pressure
Cholesterol (if < 3mM, increased risk of neurotoxicity)
Magnesium (correct if < 0.6mM)
Renal function (in particular serum creatinine and potassium)
Complete blood count
Liver function test
Pregnancy test

Table 3 : Contra-indications

Absolute and relative contra-indications
Pregnancy
Hypertension
Renal impairment
Poor general condition
Epilepsy
Long-standing pan-colitis or colonic dysplasia
Cancer

Bedside monitoring should be performed every 15 min for the first hour of the infusion for signs of allergy or anaphylaxis such as wheezing, urticaria, hypotension [1,3]. Blood pressure should be monitored every 4h while awake. Daily clinical monitoring of disease activity and for side effects is imperative. After initiating therapy as a continuous IV infusion, CSA levels should be obtained every day or 2 days [1,3]. Serum creatinine, potassium, magnesium and liver function test should be checked every 2 days, unless abnormal, in which case they should be checked daily. Serum cholesterol should be measured daily if ≤ 3.1 -3.6 mM. CSA dose should be reduced if drug levels are > 500 ng/mL for 2 consecutive days or if serum creatinine rises > 30% over baseline, serum liver enzymes double, diastolic blood pressure exceeds 90 mmHg, or systolic blood pressure exceeds 150 mmHg despite antihypertensive treatment. If any of these occurs, the dose should be decreased of 25% at least [1,3]. Pneumocystis prophylaxis should be undergone with either trimethoprim/sulfamethoxazole 160/800 1 tab per os three times weekly or pentamidine aerosol (table 4). A clinical response should be noticed within 4 – 5 days. If clearly responding, CSA infusion should be continued for a minimum of 7 days before conversion to oral CSA. If there is not a significant improvement in clinical status after 10 days of IV therapy, patients should be referred for surgery [1,3].

Table 4 : Treatment schedule

Treatment schedule
Dose: 2mg/kg/day by continuous infusion. Consider oral microemulsion of 5 mg/kg/day in b.d
Consider Pneumocystis prophylaxis
Discontinue if no response in 7 days
In responders:
Aim for trough level of 100 – 200 ng/ml
Add purine analogues
Measure potassium, creatinine, Magnesium, liver function test and blood pressure regularly
Tail off gradually after 3 to 6 months.

Patients can be safely discharged home after 1 – 2 days of observation on oral CSA. The total daily oral dose is twice the daily IV dose, divided and given every 12 h. While on oral CSA, patients should be seen weekly for the first month, biweekly for the second month, and then every 3 – 4 weeks. CSA levels, serum chemistries, magnesium and full blood count

should be performed at he same intervals as the clinic visits or weekly for any dose changes. Prednisone should be slowly tapered with a goal to be entirely weaned off by 6 months. AZA/MP should be started about 2 – 3 months after hospital discharge with plans to maintain remission on this medication after stopping CSA. CSA should be discontinued at 6 months, by reducing the dose by 50% for 2 weeks followed by complete CSA withdrawal. Others treat with CSA for a shorter period of time, stopping by 3 months, in which case maintenance therapy will need to be initiated sooner than 2 – 3 months after discharge [2].

Ciclosporin or surgery:

The timing of colectomy for severe colitis remains one of the most difficult decisions that a gastroenterologist has to make. CSA is indicated for patients with severe UC that are refractory to steroid therapy, as a second line therapy (recommendation grade B) [11]. This is generally defined as persistently active colitis despite 7 – 10 days of high dose intravenous steroids [3]. The primary use is to induce remission and serve as a bridge for AZA/MP therapy in UC patients with severe colitis [3, 13]. Patients with refractory colitis face a stark choice between prompt surgery and CSA therapy. CSA presents no easy option and should not delay appropriate surgery. Patients being considered for CSA must be counseled about toxicity, the need for ongoing immunosuppression, and close follow-up, often over many months [1,2]. In spite of the risks, and inconvenience, most patients do opt for CSA, and the quality of life in responders has been reported to be better than in those who have undergone colectomy [14].

If CSA is considered, it must be considered at an early stage [11]. One approach is to use the 3-day predictive index of the stool frequency and C-reactive protein and abdominal radiography (recommendation grade B). If there is clinical deterioration colectomy is recommended. If there is no improvement within a further 4 – 7 days, colectomy should usually be recommended (recommendation grade D).

CONCLUSION

CSA is a viable alternative to emergency colectomy in severe UC in the short term. Although these benefits are not maintained in all patients [15, 16], more than a half will also avoid colectomy in the longer term. Careful selection and monitoring of patients, use of lower doses, and oral therapy will help to reduce side effects [1].

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