Corticosteroid treatment in active Crohn's disease

J. Belaiche, E. Louis

Service de gastroentérologie, CHU Sart Tilman, 4000 Liège.

Abstract

Despite recent improvements in the management of Crohn's disease, steroids are still the most efficacious treatment in flare ups of the disease. However they have significant side effects and are only effective in the short term. There is no consensus regarding initial dose or duration of corticotherapy. With 1 mg/Kg a day of oral prednisolone given for 3 to 7 weeks, 92% of the patients achieve clinical remission. Topical acting oral corticosteroids such as budesonide seem to represent an important therapeutic advance due to their better tolerance. The promising results of budesonide in mild and moderate flare ups need to be confirmed and its indication in severe disease beside high dose prednisolone has to be clarified. (Acta gastroenterol. belg., **1998**, 61, **153-157**).

Key words : Crohn's disease, active disease, prednisolone, budesonide.

Despite recent advances in the treatment of Crohn's disease (CD), corticosteroids remain the most efficacious drugs for inducing remission in active disease (1). Unfortunately their benefits are frequently offset by serious side effects. Moreover they are not effective in long term treatment. Recently, changes in the basic-hydrocortisone molecule structure have lead to so called topical acting oral steroids. These new corticosteroid analogues have high topical antiinflammatory activity but low systemic activity because of extensive hepatic metabolism. The aim of this work is to define the place of these new corticosteroids in the treatment of active CD.

I. Conventional corticosteroids

Prednisolone and methylprednisolone are the most commonly used steroids in CD.

1. *Results of controlled trials*

Two cooperative studies, one American (National Cooperative Crohn's Disease Study (NCCDS)) and one European (European Cooperative Crohn's disease Study (ECCDS)), have shown that oral steroids are more effective than placebo in the treatment of active CD (2,3). In the American study daily doses of prednisolone were adjusted to clinical activity : 0.75 mg/Kg in patients with a Crohn's Disease Activity Index (CDAI) $\geq$ 300 ; 0.5 mg/Kg in those with a CDAI between 150 and 300 and 0.25 mg/Kg in patients with CDAI $<$ 150. The treatment lasted for four months. In the European study, 6-methylprednisolone was given at an initial dose of 48 mg/day for one week followed by an automatic decrease to 12 mg/day over 6 weeks. If CDAI was not lowered below 150, the treatment was repeated. If that target was not reached after three drug cycles, it was considered as a therapeutic failure. The mean rate of clinical remission in patients treated with steroids were similar in the two studies : 60% after 17 weeks and 80% after 18 weeks. In the European trial the efficacy of methylprednisolone was the same in the various anatomical locations of the disease, while in the American one prednisolone was significantly more effective in ileal and ileo-colonic disease. However the number of patients with colonic involvement was quite low in that study. A more recent trial failed to show any influence of disease location on the response to corticosteroid treatment (4). No other predictive clinical or biological factors were identified in this prospective study.

2. *Dose and duration*

There has not been any clinical trial to evaluate the most appropiate dose of prednisolone. As we have seen, two therapeutic approaches have been used in controlled studies : ongoing adaptation to the activity index, or an automatic decrease regimen. In another large trial carried out by the Groupe d'Etudes Thérapeutiques sur les Affections Inflammatoires Digestives (GETAID) including active CD (CDAI $\geq$ 200), the dose of oral prednisolone was higher (1 mg/Kg/day for 3 to 7 weeks) (5). In patients achieving clinical remission, prednisolone was tapered by steps of 10 mg per 10 days to the dosage of 0.5 mg/kg/day and then by steps of 5 mg per 10 days to complete discontinuation. Earlier remission was achieved with this regimen : 63%, 80% and 92% at 4, 5 and 7 weeks, respectively, as compared to only 32% and 60% at 4 and 7 weeks respectively in the American cooperative study. These higher rates of remissi on are probably due to the higher doses used. Relapses during and after weaning were frequent as only 25% of the patients remained in clinical remission 18 months later. The optimal duration of treatment with prednisolone is unknown. Brignola *et al.* (6) have compared two steroid treatments of different duration. In both groups the starting dose of prednisolone was 40 mg/day i.m. for 3 weeks. The first group was then given 30 mg/day

Reprints : Prof. J. Belaiche, Service de Gastroentérologie, CHU Sart Tilman, 4000 Liège, Belgium.

i.m. for 3 weeks, then 20 mg/day i.m. for 3 weeks, then 12 mg a day by mouth for 3 weeks and finally 8 mg/day by mouth for 3 weeks. In the second group, the duration of the treatment was shorter since the decrease followed the same increments, but only the span of one week. The remission and relapse rates after 6 months were the same in the both groups. Thus prolonged steroid treatment does not seem to be useful in flare ups of CD.

3. *Criteria of efficacy of the steroid treatment*

The criteria of remission may be clinical, biological and/or endoscopic. The clinical condition of patient remains the major criterion of remission in all studies even if some subjective elements are included in the calculation of the CDAI. In the GETAID, the starting dose was maintained until clinical remission but not longer than 7 weeks (5). In the rare cases of steroid resistance (8%) other therapeutic options have to be discussed for each particular case : total parenteral nutrition, i.v. steroids, immunosuppressive drugs or surgery. As far as biological criteria are concerned the data are so far inconclusive. It is unknown whether the normalisation of biological tests of inflammatory parameters (ESR, CRP, acid alpha-1 glycoprotein) should be required before steroid tapering. The results regarding the predictive value of these inflammatory parameters on relapse are contradictory. In a recent study ESR was not predictive of the subsequent evolution of the disease (7). However in another study, the relapse rate correlated with serum levels of CRP, acid alpha-1 glycoprotein, alpha-2 globulin and theESR (8,9). New markers of inflammation or immune activation seem to be promising. In two recent studies we showed that a high serum concentration of s IL-2R and particulary IL-6 in patients in clinical remission were predictive of relapse (10,11).

Endoscopic criteria of remission have rarely been assessed. The GETAID trial showed that only 30% of patients with clinical remission on steroid therapy were also in endoscopic remission (5). A randomized study carried out by GETAID also showed that prolonged high dose steroid therapy in patients with persistent endoscopic lesions improved the endoscopic remission of 25% but did not influence the subsequent evolution of the disease (7). The proportion of patients successfully weaned from steroid treatment and the cumulative rate of clinical relapse after steroid discontinuation over a 18 month period were similar in both groups. Eighteen months after the end of steroid therapy, the patients in clinical and endoscopic remission at the end of the treatment had the same rate of relapse as those with remaining active endoscopic lesions. Thus, endoscopic remission does not seem to be associated with a more benign evolution of the disease and should not be a therapeutic goal. Therefor, repeat colonoscopy after induction of remission by steroid therapy is not contributative to subsequent management of these patients.

4. *Associated treatment*

The association of sulfasalazine and steroid does not seem to be beneficial. This combination may even decrease the response to prednisolone (12). An association of steroids with 5-aminosalicylic acid (5-ASA) has not been studied. However, it has recently been shown that treatment with mesalasine (4 g/day) starting at the onset of steroid tapering facilitated steroid withdrawal and, during the post weaning year, reduced relapse rate in some subgroups of patients (13). A controlled study of active CD treated for 4 months has shown that the combination of prednisolone with azathioprine at 2.5 mg/Kg was superior to treatment with prednisolone alone. Patients receiving azathioprine showed remission more frequently, more rapidly, and with lower doses of prednisolone (14).

An association of steroids and total parenteral nutrition does not improve the remission rate (15). However supplementary nutrition is worthwile in cases of significant malnutrition.

5. *Side effects*

Corticosteroid efficacy is hampered by side effects, sometimes severe, in case of prolonged use.

Several side effects are well known : moon facies, acne, bruises, irritability. These usually are transitory and regress at the end of the treatment. More severe side effects may also be observed : aseptic osteonecrosis (16), cataract, striae, growth delay in children, myopathies. It is of note that the frequency of side effects was not higher in the GETAID study despite high dose corticosteroids and none of these side effects was severe enough to justify a change in prednisone dosage (5). Osteopenia has been studied in several recent works. Its frequency varied between 20% and 59% depending on the method of evaluation (17,18). Trabecular and cortical bone loss have been evaluated at 3% to 6% per year in a prospective densitometry study (19). This osteopenia is multifactorial but corticoid therapy and inflammation are probably the most important factors (19). Osteopenia is characterised by a low level remodeling as confirmed by a recent histomorphometric study (20), and low level of osteocalcine (21). Prophylaxic calcium and vit D remains to be substantiated.

II. Topical acting oral corticosteroids

In comparison with classical corticosteroids, topical acting oral corticosteroids have a strong affinity for their receptor and a more rapid metabolism. This is due to a high first-pass hepatic metabolism, which theoretically results in decreased side effects. Among these new steroids only fluticasone and budesonide have been used for the treatment of CD.

1. *Budesonide*

Ileal release capsules (Entocort CIR) consist of microgranules of ethylcellulose, which are stable in an

acidic environnment and containing budesonide. They are wrapped in Eudragit L 100-55 that is disolved at a pH higher than 5.5. This formulation of budesonide has been developed to deliver the active drug to the ileal and ileocecal area. In normal subjects, 52 to 79% of the budesonide is absorbed in the ileocecal region, the rest being absorbed in the proximal intestine. Bioavailability is around 10%.

1.1. Results of controlled studies

Five large therapeutic trials were undertaken after promising open trials (22-27).

1.1.1. Dose-finding study and comparison between budesonide and placebo

A Canadian trial compared 3 different doses of budesonide to placebo (22). Two hundred and fifty eight patients with mild-to-moderately-active ileal or ileocolonic disease (CDAI $>$ 200) were randomly assigned to receive placebo or one of three doses of budesonide : 3, 9, or 15 mg daily. After eight weeks of treatment, remission occured in 51% of the patients in the group receiving 9 mg of budesonide, 43% of those receiving 15 mg, and 33% of those receiving 3 mg, as compared with 20% of those receiving placebo. It is noteworthy that 15 mg/d was not statistically superior to 9 mg/d. The efficacy of budesonide was comparable in ileal and right ileocolic disease. A very recent study has confirmed that in the majority of patients with moderately active Crohn's ileocolitis (CDAI $<$ 300) 9 mg (3 $\times$ 3 mg) budesonide per day is sufficient to induce remission at 6 weeks (23). Patients with more active disease (CDAI $>$ 300) responded better to a higher dose (remission rates 25% and 75% with 9 mg/day and 18 mg/day, respectively). In another study once daily pulse therapy seems the most efficient form of therapy (24).

1.1.2. Comparison between budesonide and prednisolone

A European trial was published simultaneously with the Canadian one and compared budesonide and prednisolone in 176 patients having active ileocaecal CD (CDAI $>$ 200) (25). The daily dose of budesonide was 9 mg for 8 weeks and then 6 mg for the last two weeks. The dose of prednisolone was 40 mg/day for two weeks. The dose was than gradually reduced to 5 mg/day during the last week. At 10 weeks, 53% of the patients treated with budesonide were in remission, as compared with 66% of those treated with prednisolone, the difference being not statistically significant ($p = 0.12$). This could lead to the conclusion that budesonide is comparable to prednisolone in the treatment of active CD. The results are less encouraging than they might seem at first glance (26). The rates of complete and partial remission were higher in the prednisolone group at every follow-up interval. The peak remission rate with prednisolone therapy was maximal at four weeks (67% vs 40% of remission with prednisolone and budesonide, respectively, $p < 0.001$). Later, the superiority of prednisolone decreased, but this is probably explained by the therapeutic scheme used. Moreover, the initial dose prednisolone (40 mg/day) was lower than the one used in the GETAID trial where the remission rate after 7 weeks reached 92% with a dose of 1 mg/Kg/day. Another recent study claimed also that oral budesonide is as effective as oral prednisolone in active CD (24). The study compared 2 different dosing schedules of administration of budesonide, 9 mg once daily and 4.5 mg twice daily, to 40 mg/day of prednisolone. The dose of budesonide was reduced to 6 mg/day after 8 weeks, then to 3 mg/day after 10 weeks of treatment. The dose of prednisolone was reduced to 30 mg/day after 2 weeks of treatment, then by 5 mg each week for the 3 following weeks. The remission rate after 2 weeks was 48% with 9 mg once daily of budesonide and 37% with prednisolone. After 8 weeks the remission rates were similar with budesonide 9 mg once daily and prednisolone (60%) but was lower in the group of patients getting the budesonide in twice daily dose of 4.5 mg (42%), however the difference was not significant. The same remarks as those regarding the European trial may be applied here.

1.1.3. Comparison between budesonides and 5-ASA

An important American trial carried out on 310 mildly to moderately active CD patients (CDAI between 151 and 400) had shown that treatment with mesalasine 4 g/day induced remission in 43% of the patients after 16 weeks of treatment (27). It was thus interesting to compare 5 ASA and budesonide in such a situation. Preliminary results of an international multicentric study seem to confirm the superiority of budesonide over mesalasine in inducing remission in active CD (28). 182 patients with active ileal or ileocolonic disease (200 $\geq$ CDAI $<$ 400) were randomized into 2 groups treated for 16 weeks either with mesalamine 4 g/day ($n = 89$) or with budesonide 9 mg/day ($n = 93$). The remission rate was significantly higher with budesonide than with mesalasine. The difference was already present after 8 weeks (69.2% vs 24.7%) and remained until 16 weeks (61.5% vs 36.1%).

1.2. Side effects

Budesonide is better tolerated than conventional corticoids (29). The frequency of side effects was not higher with budesonide than with placebo, except from moon facies observed in 7% and 2% of cases respectively (22). In contrast, the side effects with prednisolone were more frequent (53% vs 33%) (25). Budesonide caused a dose-related reduction in basal and corticotropin-stimulated plasma cortisol concentrations but less than prednisolone (25). Budesonide was not associated with clinically important corticosteroid-related symptoms or

other toxic effects. The diminished adrenal suppression was no longer significant 2 weeks after stopping the treatment. Effects of budesonide on bone mineral density is currently being evaluated.

2. Other topical acting oral corticosteroids

Fluticasone propionate is the only other new oral corticosteroid analogue already tested in active CD (30). This trial proved that oral fluticasone propionate had poor clinical efficacy. Further trials with this molecule have not been attempted in CD. Other corticosteroids with colonic delivery derived from prednisolone metasulfobenzoate, dexamethasone and methylprednisolone are currently under evaluation.

III. Therapeutic approach to patients with active Crohn's disease

Conventional corticosteroids are the most potent agents in the management of active CD (31). Dramatic results are often achieved quickly. There is no consensus regarding their use as first line therapy in every flare up of CD. The treatment of ambulatory patients with mild to moderate active disease (CDAI between 150 and 300) is usually based on mesalasine 4 g/day as initial therapy (27). There is a minimum time of 8 weeks, at which point the therapeutic efficacy is evaluated, thus the period seems reasonable before judging the final results of this therapy. If the superiority of budesonide over 5 ASA is confirmed, oral budesonide may become the first therapeutic option. It has to be kept in mind that the currently available pharmaceutical form of budesonide has been specifically designed for ileal or right ileocolonic disease. Moreover the effect of budesonide on extra intestinal manifestations has not been completely evaluated, preliminary results are contradictory (32,33). Prednisolone would then be reserved for therapeutic failures with other drugs. However, broad-spectrum antibiotics can be considered as initial therapy. The association of ciprofloxacine and metronidazole has been recently compared to methylprednisolone in flare up of CD (34). After 3 months, the remission rate was 45% with antibiotics compared to 63% with steroids. There was thus a trend toward a higher efficacy of corticosteroid therapy not reaching statistical significance however, probably due to the small size of the popultion studied. Moreover 50% of patients treated with antibiotics did not complete therapy (most due to side effects) versus 26% of patients with steroids. Antibiotics may considered in the presence of major suppurative complications such as an intra-abdominal or perineal abcess. In patients with a palpable inflammatory mass, corticosteroids should always be administred with antibiotics (35). In severe flare ups (CDAI > 300) patients generally require corticosteroids and often hospitalization. Conventional corticosteroid treatment remains the first choice, preferentially high dose as shown in the GETAID study. Finally in steroid dependent CD it would be interesting to know whether budesonide permits a weaning from conventional corticosteroids (32,33).

In conclusion, conventional corticosteroids remain the treatment of choice for active CD. However, they do not have any effect on the long term evolution of the disease. Topical acting oral corticosteroids such as budesonide seem to represent a therapeutic advance because of better tolerance. However, the promising results of budesonide in mild to moderate flare ups of CD have to be confirmed and the place of such a treatment in comparison with high dose prednisolone and in corticodependent Crohn's disease remains to be clarified.

Acknowledgments

E. Louis is supported by the National Fund for Scientific Research (FNRS).

References

1. MEYERS S., SACHAR D.B. Medical therapy of Crohn's disease. *In* : J.B. KIRSNER, R.G. SHORTED (eds), Inflammatory bowel disease (fourth edition). Williams & Wilkins, Baltimore, Philadelphia, 1995, p. 695-714.
2. SUMMERS R.W., SWITZ D.M., SESSIONS Jr. J.T. *et al.* National Cooperative Crohn's Disease Study : results of drug treatment. *Gastroenterology*, 1979, **77** : 847-869.
3. MALCHOW H., EWE K., BRANDES J.W. *et al.* European Cooperative Crohn's Disease Study : results of drug treatment. *Gastroenterology*, 1984, **86** : 249-266.
4. MUNKHOLM P., LANGHOLZ E., DAVIDSEN M., BINDER V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut*, 1994, **35** : 360-362.
5. MODIGLIANI R., MARY J.Y., SIMON J.F. *et al.* Clinical, biological and endoscopic picture of attacks of Crohn's disease : evolution on prednisone. *Gastroenterology*, 1990, **98** : 811-818.
6. BRIGNOLA C., DE SIMONE G., LANNONE I. *et al.* Influence of steroid treatment duration in patients with active Crohn's disease. Agents actions. Special conference issue. 1992. C90-C92.
7. LANDI B., N'GUYEN ANH T., CORTOT A. *et al.* Endoscopic monitoring of Crohn's disease treatment : a prospective randomized clinical trial. *Gastroenterology*, 1992, **102** : 1647-1653.
8. BRIGNOLA C., CAMPIERI M., BAZOCCHI G. *et al.* A laboratory index for predicting relapse in asymptomatic patients with Crohn's disease. *Gastroenterology*, 1986, **91** : 1490-1494.
9. BRIGNOLA C., IANNONE P., BELLOLI C. *et al.* Prediction of relapse in patients with Crohn's disease in remission : a simplified index using laboratory tests, enhanced by clinical characteristics. *Eur. J. Gastroenterol. Hepato.*, 1994, **6** : 955-961.
10. LOUIS E., BELAICHE J., VAN KEMSEKE C. *et al.* Soluble interleukin-2 receptor in Crohn's disease. Assessment of disease activity and prediction of relapse. *Dig. Disease Sciences*, 1995, **40** : 1750-1756.
11. LOUIS E., BELAICHE J., VAN KEMSEKE C. *et al.* Crohn's disease relapse by interleukin-6 serum level. *Eur. J. Gastro. Hepato.* (in press).
12. SINGLETON J.W., SUMMERS R.W., KERN F. *et al.* A trial of sulfasalazine as an adjunctive therapy in Crohn's disease. *Gastroenterology*, 1979, **77** : 8887-8897.
13. MODIGLIANI R., COLOMBEL J.F., DUPAS J.L. *et al.* Mesalamine in Crohn's disease with steroid-induced remission : effect on steroid withdrawal and remission maintenance. *Gastroenterology*, 1996, **110** : 688-693.
14. EWE K., PRESS A.G., SINGE C.C. *et al.* Azathioprine combined with prednisolone or monotherapy with prednisolone in active Crohn's disease. *Gastroenteroloy*, 1993, **105** : 367-372.
15. LEREBOURS E., GALMICHE J.P., FOUIN-FORTUNET H. *et al.* Etude de l'utilité d'une corticothérapie au cours des poussées aigues de

maladie de Crohn traitées par alimentation parentérale. *Gastroenterol. Clin. Biol.*, 1982, **6** : 1450-1455.
16. VAKIL N., SPARBERG M. Steroid-related osteonecrosis in inflarnmatory bowel disease. *Gastroenterology*, 1989, **96** : 62-67.
17. COMPSTON J.E., JUDD D., CRAWLEY E.O. *et al.* Osteoporosis in patients with inflammatory bowel disease. *Gut*, 1987, **28** : 410-415.
18. PIGOT F., ROUX C., CHAUSSADE S. *et al.* Low bone mineral density in patients with inflammatory bowel disease. *Dig. Dis. Sci.*, 1992, **37** : 1396-1403.
19. ROUX C., ABITBOL V., CHAUSSADE S. *et al.* Bone loss in patients with inflammatory bowel disease : a prospective study. *Osteoporosis Int.*, 1995, **5** : 156-160.
20. CROUCHER P.I., VEDI S., MOTLEY R.J. *et al.* Reduced bone formation in patients with osteoporosis associated with inflammatory bowel disease. *Osteoporosis Int.*, 1993, **3** : 236-241.
21. ABITBOL V., ROUX C., CHAUSSADE S. *et al.* Metabolic bone assesment in patients with inflammatory bowel disease. *Gastroenterology*, 1995, **108** : 417-422.
22. GREENBERG G.R., FEAGAN B.G., MARTIN F. *et al.* Oral budesonide for active Crohn's disease. *N Engl J Med*, 1994, **331** : 836-841.
23. GROSS V., CAESAR I., ANDUS T. *et al.* Dose-finding study with oral budesonide in patients with active Crohn's ileocolitis. *Gastroenterology*, 1997, **112** (4 suppl.) : A 986 (abstr.).
24. CAMPIERI M., FERGUSON A., DOE W. *et al.* Oral budesonide is as effective as oral prednisolone in active Crohn's disease. *Gut*, 1997, **41** : 209-214.
25. RUTGEERTS P., LOFBERG R., MALCHOW H. *et al.* A comparison of budesonide with prednisolone for active Crohn's disease. *N. Engl. J. Med.*, 1994, **331** : 842-845.
26. SACHAR D.B. Budesonide for inflammatory bowel disease. Is it a magic bullet ? *N. Engl. J. Med.*, 1994, **331** : 873-874.
27. SINGLETON J.W., HANAUER S.B., GITNICK G.L. *et al.* Mesalamine capsules for the treatment of active Crohn's disease : result of a 16-week trial. *Gastroenterology*, 1993, **104** : 1293-1301.
28. THOMSEN O.O., CORTOT A., JEWELL D. *et al.* Budesonide CIR is more effective than mesalazine in active Crohn's disease. A 16 week, international randomized double-blind multicentrique trial. *Gastroenterology*, 1997, **112** (4 suppl.) : A 1104 (abstr.).
29. LOFBER R. New steroids for inflammatory bowel disease. *Inflamm. Bowel. Dis.*, 1995, **1** : 135-141.
30. WRJGHT J.P., JARNUM S., SCHAFFALITZKY DE MUCKADEL O. *et al.* Oral fluticasone propionate compared with prednisolone in treatment of active Crohn's disease : a randomized double-blind multicentre study. *Eur. J. Gastro. Hepato.*, 1993, **5** : 499-503.
31. D'HAENS G.R., RUTGEERS P. How should corticosteroids be used in inflammatory bowel disease ? *Clinical Immunotherapeutics*, 1996, **5** : 334-340.
32. ANDUS T., GROSS V., CAESAR T. *et al.* Replacement of conventional steroids by budesonide in active or inactive Crohn's disease. Interim analysis of an open, prospective, multicenter trial. *Gastroenterology*, 1995, **108** : A 771 (abstr.).
33. NOVACEK G., KLEINBERGER M., VOGELSANG H. *et al.* Budesonide in glucocorticoid dependent chronic active Crohn's disease, a pilot study. *Z. gastroenterol.*, 1995, **33** : 251-254.
34. PRANTERA C., ZANNONI F., SCRIBANO M.I. *et al.* An antibiotic regimen for the treatment of Crohn's disease : a randomized, controlled clinical trial of metronidazole plus ciprofloxacine. *Am. J. Gastroenterol.*, 1996, **91** : 328-332.
35. FELINER J.B., ADLER D.J., KORELITZ B.I. The safety of corticosteroid therapy in Crohn's disease with an abdominal mass. *Am. J. Gastroenterol.*, 1991, **86** : 1450-1455.