THERAPY UPDATE

New steroids for IBD: progress report

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Corticosteroids remain the benchmark therapy for moderate to severe ulcerative colitis and Crohn's disease but are problematic due to unacceptable side effects and lack of maintenance benefits. Developments in corticosteroid chemistry have led to a series of anti-inflammatory glucocorticoids with enhanced topical (mucosal) potency and less systemic activity[1–4] such as prednisolone-metasulphobenzoate, beclomethasone diproprionate, tixocortol pivalate, fluticasone, and budesonide. To date, budesonide has been the primary alternative compound to hydrocortisone and prednisolone marketed in many parts of the globe and, most recently, has been introduced in an ileal release formulation in the USA.[3 5]

For many years, topical (rectal) steroids have had a primary role in the treatment of distal ulcerative colitis[6 7] and have been incorporated as an adjunctive treatment to parenteral steroids for treatment of severe colitis.[8 9] The relative potency of rectally applied steroids is increased compared with a similar systemic exposure, providing evidence that the mucosal and systemic effects of glucocorticoids can be divorced.[10] In comparative controlled trials, the "non-systemic" rapidly metabolised formulations (tixocortol, beclomethasone diproprionate, and budesonide) had equal therapeutic properties to systemically active glucocorticoids.[3 11] However, as firstline therapies for distal ulcerative colitis, the potent non-systemic glucocorticoids have been less effective than rectal formulations of mesalamine.[7]

The non-systemic glucocorticoids have yet to make an impact as oral therapies for ulcerative colitis as delivery of sufficient doses to the colon, and the distal colon in particular, is complicated by altered colonic motility in ulcerative colitis (delayed transit in the right colon and rapid transit in the left colon) allowing metabolism of the steroid molecule by normal colonic microflora.

Similar to conventional glucocorticoids, budesonide is well absorbed from the proximal and distal intestine, relying on rapid hepatic metabolism to reduce systemic impact, including inhibition of the hypothalamic-pituitary-adrenal axis. To achieve distal mucosal activity, budesonide has been formulated in oral controlled released formulations that minimise proximal absorption and allow high drug concentrations in the ileum and caecum. Theoretically, with such targeted delivery, the combination of increased topical potency and low systemic availability should provide benefits (improved efficacy with less systemic side effects) compared with conventional glucocorticoids.[4] However, due to the increased potency at the steroid receptor (100 times that of hydrocortisone), suppression of the hypothalamic-pituitary-adrenal axis can occur with treatment.[12] Budesonide in a controlled ileal release formulation, administered as 9 mg/day, has been shown to be efficacious for active ileal and ileocecal Crohn's disease.[12–15] In addition to the reduction in intestinal symptoms and signs assessed by the Crohn's disease activity index, budesonide successfully improved quality of life as assessed by the inflammatory bowel disease questionnaire[16] and extraintestinal arthritic manifestations associated with active Crohn's disease.[17] The controlled ileal release formulation of budesonide has also been used to "switch" patients from prednisone with a 4–10 week transition and follow up for an additional three months of sustained clinical benefits and reduced steroid associated toxicity[18] but, like other corticosteroids, at doses of 3–6 mg/day budesonide was ineffective for the maintenance of remission at one year[19–21] or for the prevention of postoperative recurrence.[22 23] Overall, compared with conventional steroids, the better side effect profile of budesonide is balanced by somewhat lower efficacy than conventional steroids in treating active disease.[13 14 24]

In summary, the concept of separating the mucosal effects of glucocorticoids from the systemic effects has been demonstrated in both ulcerative colitis and Crohn's disease. In ulcerative colitis, while rectal administration of budesonide and tixocortol are safe and effective, neither has been as effective as rectal mesalamine for distal disease and the complexities of pancolonic mucosal "coating" of steroids remains impractical. In Crohn's disease, controlled release formulations of budesonide have found a niche for the acute treatment of mild-moderate ileal and right colonic disease with intermediate efficacy superior to mesalamine, but are somewhat less effective than prednisone. There remains considerable potential for developments in steroid pharmacology and enteric delivery to improve both mucosal potency and rapid metabolism that would further improve the therapeutic potential for these agents to induce remission while minimising systemic impacts. The role for glucocorticoid therapy for maintaining remissions in either ulcerative colitis or Crohn's disease remains to be established.

Key points

- Non-systemic steroids for IBD have increased potency and first pass metabolism
- Rectal (enema) formulations are effective for active distal ulcerative colitis, but not as efficacious as rectal mesalamine
- Controlled (delayed) release budesonide is effective for active ileal and right colonic Crohn's disease with a low side effect profile
- Similar to other corticosteroids, no maintenance benefits have been identified for non-systemic steroids used on a long term (one year) basis

Conflict of interest: S B Hanauer has worked as a consultant for Astra-Zeneca, Centocor, Proctor and Gamble, Salix, and Solvay. He has also carried out clinical research and given lectures on behalf of Astra-Zeneca, Centocor, and Proctor and Gamble.

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