Steroids and 5-aminosalicylic acids in moderate ulcerative colitis: addressing the dilemma

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Abstract: Steroids have been a mainstay of ulcerative colitis (UC) therapy for many years, based on a thoroughly established efficacy profile for the induction of remission. However, in light of the considerable side effects and negative perceptions they carry, it is important to ensure such treatments are used as effectively as possible. For severe UC, the need for steroids is rarely questioned, and rightly so; it is for moderate UC that the role of steroids should be considered. Both patients and clinicians place a high importance on rapid, effective resolution of symptoms, yet at the same time wish to avoid unnecessary side effects. Through consideration of the available evidence, it becomes clear that both steroids and high-dose 5-aminosalicylic acid (5-ASA) are supported by robust trials demonstrating their efficacy. Indeed, both therapies have been shown to give rise to resolution of symptoms after 2 weeks in many patients. However, a paucity of head-to-head comparisons makes conclusive interpretation challenging. This paper therefore presents a practical approach, which builds on the available evidence and is developed from informed discussions with patients. This approach involves initiating therapy with high-dose 5-ASA, followed by a review of symptom improvements after 2–3 weeks. Steroids can then be introduced, when needed, with minimal delay. In this way, symptoms can be resolved rapidly, yet many patients may avoid unpleasant side effects.

Keywords: 5-aminosalicylic acid, inflammatory bowel disease, mesalazine, steroid avoidance, steroids, ulcerative colitis

Introduction

Steroids have been a mainstay of ulcerative colitis (UC) therapy for many years. Ever since the pivotal study with cortisone by Truelove and Witts in the mid 1950s [Truelove and Witts, 1955], and even as newer therapies have emerged, steroids have remained an important therapeutic option, in no small part thanks to their well established efficacy in inducing remission.

At the same time, the side effects of steroid therapy can be considerable. Approximately 50% of patients receiving steroids experience side effects [Mowat *et al.* 2011]. The key side effects arise due to supraphysiological doses (e.g. acne, oedema, sleep and mood disturbances), prolonged use (e.g. osteoporosis, osteonecrosis, susceptibility to infection) or withdrawal (e.g. adrenal insufficiency, myalgia, malaise) (Table 1) [Mowat *et al.* 2011]. Moreover, the side effects of steroids may be exacerbated by their often long-lasting nature, the need for gradual withdrawal, and the fact that patients may become dependent on steroids to control their disease.

As a consequence, it is important to consider the place of steroids within the armamentarium for modern UC therapy. On the one hand, making use of the effective induction of remission they offer, while on the other, avoiding unpleasant side effects wherever possible. This article reviews the clinical evidence surrounding the use of steroids in UC, and discusses a possible therapeutic approach to limit the impact of these side effects.

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Table 1. Adverse effects of steroids [Mowat *et al.* 2011].

Effects due to supraphysiological dose
- Cosmetic: acne, moon face, oedema
- Sleep and mood disturbance
- Dyspepsia
- Glucose intolerance
- Increased risk of infection
Effects due to prolonged use
- Posterior subcapsular cataracts
- Osteoporosis
- Osteonecrosis of the femoral head
- Myopathy
- Susceptibility to infection
Effects due to withdrawal
- Acute adrenal insufficiency
- Corticosteroid withdrawal syndrome: myalgia,malaise and arthralgia
- Raised intracranial pressure

Steroids: a time and a place

For severe UC, there is little question that steroids are the correct therapy to use; with the serious and potentially life-threatening consequences of severe colitis, intensive in-patient treatment with intravenous steroids is vital [Mowat *et al.* 2011; Travis *et al.* 2008]. Equally, at the other end of the spectrum, 5-aminosalicylic acids (5-ASAs) are usually sufficient to effectively treat mild exacerbations of UC.

It is for moderately active UC that the role of steroids becomes a key clinical dilemma. With symptoms including four to six stools per day, rectal bleeding and often several extra-intestinal manifestations [Stange *et al.* 2008], the need for fast, effective induction of remission is strong. At the same time, the balance between efficacy and side effects form an influential part of therapeutic decisions [Travis *et al.* 2008]. The two key therapies to consider are steroids and high-dose 5-ASA: are patients with moderately active UC being overtreated with steroids or undertreated with 5-ASA?

Patient and physician perspectives

Moderately active UC may be defined using a number of key criteria. In clinical trials, it is typically defined based on specific measurement scales [for example, a Physician's Global Assessment (PGA) score of 2 in the Assessing the Safety & Clinical Efficacy of a New Dose of 5-ASA (ASCEND) studies]. In clinical practice, more practical methods are available. For example, treatment guidelines from the European Crohn's and Colitis Organisation (ECCO) recommend an adaptation of the Truelove and Witts criteria, defining moderate activity as four or more stools per day with no tachycardia, fever or elevated inflammatory markers [Travis *et al.* 2008]. In day-to-day practice, it is also important to take a holistic approach and consider other aspects such as urgency or the disruption a flare may cause to a patient's ability to function (for example, during key life events such as exams, relocation or getting married). In terms of treatment choices, evidence-based recommendations from ECCO advocate 5-ASAs as a first step for mild to moderate UC [Travis *et al.* 2008]. At the same time, ECCO recognizes that it is common practice in many European centres to introduce oral steroids at an early stage due to the speed of response they offer [Travis *et al.* 2008].

As one may expect, the ECCO consensus confirms that treatment choices for active UC are influenced by the balance between drug potency and side effect profile [Travis *et al.* 2008]. Likewise, recently updated guidelines from the British Society of Gastroenterology include the tradeoff between efficacy and side effects as part of the decision to treat with steroids [Mowat *et al.* 2011].

Moving beyond published guidelines, we can gain an interesting further insight by considering patients' perspectives. Anecdotal reports abound: from clinical experience, meetings with patient groups and even online, it is clear that steroids and their side effects are highly unpopular with many patients. Examples from real-life practice can provide a helpful illustration of some of the key concerns that patients identify (Box 1). Adding weight to these experiences, a large survey of patients' experiences with UC conducted by Loftus found that patients considered high levels of efficacy and minimal side effects to be the most desirable attributes of a treatment for UC [Loftus, 2006].

Examining the evidence for steroids and 5-ASA

To understand and optimize the use of both steroids and 5-ASA for moderate UC, we must look at the published evidence. The pivotal studies supporting the use of steroids predate those for modern 5-ASA preparations by more than 40 years; nevertheless, they provide an important insight into their efficacy and speed of action.

Box 1. Side effects of steroids: a spectrum of examples from practice.

Many of the side effects of steroids are well known, yet even with careful management can remain problematic and worrisome for patients.

- A patient with severe, steroid-responsive ulcerative colitis (UC) and diabetes reported considerable concerns regarding glycaemic control and long-term complications. Despite ongoing attempts to ameliorate these effects, the patient decided to undergo colectomy to avoid the need for further steroids.

Similarly, clinicians are usually well aware of many of the mental effects of steroids, but their impact should not be underestimated. Interestingly, patients highlight effects beyond those we immediately associate with steroids, such as a loss of concentration.

- A female patient reported that she felt unable to cross the road safely, due to lost confidence in her ability to concentrate sufficiently.
- An 18-year-old patient treated with prednisolone for active Crohn's disease experienced manic episodes, culminating with streaking up a busy road.
- A 26-year-old patient with quiescent UC attempted suicide after treatment with prednisolone for asthma.

The latter example represents an extreme illustration of the extent that the mental effects of steroids may reach in some cases. While the majority of cases encountered regularly in practice will not be this serious (sleep disturbance or moodiness due to either low-level mania or depression, for example), it is helpful to recall the full spectrum that such side effects can cover.

Steroids

Truelove and Witts published their seminal study demonstrating the efficacy of cortisone as early as 1955 [Truelove and Witts, 1955], and a recent systematic review by Ford and colleagues brings this research up to date in confirming the efficacy of steroids compared with placebo in active UC [Ford *et al.* 2011]. Looking to the head-to-head studies, two key papers published in the 1960s compared steroid therapy with 5-ASA therapy, in the form of sulfasalazine. Firstly, Lennard-Jones and colleagues found that prednisolone was associated with a significantly faster induction of remission than sulfasalazine (3.9 *versus* 8.5 weeks, $p \leq 0.02$), although the overall success rate of the two treatments was similar [Lennard-Jones *et al.* 1960]. Two years later, Truelove and colleagues demonstrated that combined therapy with oral prednisolone and topical hydrocortisone was associated with a substantially higher rate of remission after 2 weeks than sulfasalazine (76% *versus* 52% respectively) [Truelove *et al.* 1962].

Although difficult to interpret - both studies are old, and predate the robust UC scoring systems in common use today - these studies show that steroid therapy is indeed effective for the treatment of UC compared with sulfasalazine. Moreover, steroids appear to act faster than sulfasalazine.

Importantly, both of these studies used sulfasalazine for the 5-ASA arm rather than mesalazine. Indeed, head-to-head comparisons of steroids with mesalazine are lacking. The one such comparison published to date examines beclomethasone and found almost identical rates of remission at 4 weeks in the beclomethasone and mesalazine treatment arms (63.0% *versus* 62.5% respectively) [Campieri *et al.* 2003]. No studies have yet been conducted to compare oral prednisolone with mesalazine.

High-dose 5-ASA

Given the lack of head-to-head data comparing mesalazine and prednisolone, it is appropriate to consider the evidence supporting mesalazine in isolation. A number of recent studies have looked at high-dose mesalazine (≥4 g/day) for mild to moderate UC, and the results have been promising [Hanauer *et al.* 2005, 2007; Kamm *et al.* 2007; Lichtenstein *et al.* 2007; Marteau *et al.* 2005; Sandborn *et al.* 2009].

Evidence of a dose response with 5-ASAs has previously been reported. For example, in a study of mesalazine pellets (Salofalk; Dr Falk Pharma GmbH) in patients with mild to moderately active UC, the remission rate was increased from 47% to 67% after a dose escalation for nonresponders from 1.5 to 3.0 g/day [Marakhouski *et al.* 2005]. However, the precise nature of the dose response effect with 5-ASA has often been difficult to interpret, partly due to variations in methodology between trials. For example, the

ASCEND I study was conducted in patients with mild to moderately active UC, and found no significant difference between mesalazine 4.8 g/day and 2.4 g/day (Asacol; Warner Chilcott) in this population [Hanauer *et al.* 2007]. The MMX mesalazine (Mezavant XL; Shire Pharmaceuticals) studies were also conducted in patients with mild to moderately active UC, and evaluated mesalazine 2.4 g/day and 4.8 g/day compared with placebo [Lichtenstein *et al.* 2007]. The MMX mesalazine studies were not designed nor powered to demonstrate differences between the two doses, so the results are difficult to interpret; however, similar efficacy results were observed between the two dosages [Sandborn *et al.* 2007]. These findings may be partly due to the inclusion of patients with mild and moderate UC. Therefore, returning to the ASCEND trials, results from prespecified subanalyses looking at patients with moderately active UC only (PGA score of 2) offer further insights into the dose response effect of 5-ASAs. In patients with moderately active UC taken from ASCEND I and II, mesalazine 4.8 g/day was associated with a significantly higher rate of treatment success at week 6 compared with 2.4 g/day [Hanauer *et al.* 2005, 2007]. ASCEND III showed no significant benefit for mesalazine 4.8 g/day compared with 2.4 g/day in patients with moderate UC [Sandborn *et al.* 2009]. However, it is important to note that endoscopy scoring in ASCEND III was different to previous studies, making comparison difficult. Interestingly, taking endoscopy out of the equation and evaluating symptom response only, a significant benefit for the higher dose was observed in terms of clinical remission (43% *versus* 35% for 4.8 g/day *versus* 2.4 g/day at week 6; $p = 0.04$) [Sandborn *et al.* 2009].

Again, looking at moderately active UC specifically, an interesting insight into the speed of symptom resolution with mesalazine has been provided by examining patient diary data from the ASCEND studies. Orchard and colleagues analyzed diary data from a subgroup of patients with moderately active UC in ASCEND I and II (note that patient diaries were not included in the protocol for ASCEND III, so could not be included in this analysis). The authors found that high-dose oral mesalazine was associated with rapid resolution of symptoms. The median time to resolution of rectal bleeding, the most important symptom for many patients, was 9 days with mesalazine 4.8 g/day, and 73% of patients experienced improvements in both rectal bleeding and stool frequency at 2 weeks with this dose [Orchard *et al.* 2011].

With regard to combined oral and topical therapy with 5-ASA, two studies have shown particularly interesting results. The Pentasa in ulcerative Colitis with addition of Enema (PINCE) study of patients with extensive mild or moderate UC found that patients treated with oral mesalazine 4 g/day (Pentasa; Ferring Pharmaceuticals) and a 1 g/day mesalazine enema experienced a shorter time to resolution of rectal bleeding than those treated with oral therapy alone ($p = 0.0025$) [Marteau *et al.* 2005]. A smaller study of patients with frequently relapsing disease found that dose escalation of oral mesalazine combined with the addition of topical 5-ASA significantly reduced the number of disease recurrences and courses of steroids ($p < 0.0001$) [Frieri *et al.* 2005].

These studies therefore confirm that high-dose mesalazine has demonstrated efficacy for moderately active UC and offers rapid resolution of symptoms.

Recommended approach

We have seen, then, that steroids indeed offer a rapid, effective treatment for active UC. However, while the historic perception is that the speed of action of steroids is faster than that of 5-ASAs, recent studies of high-dose mesalazine throw this into question. Unfortunately, with a paucity of head-to-head data, conclusive interpretation is challenging, and there may well remain room for debate.

Nevertheless, the evidence is sufficient to advocate a practical approach to managing moderate UC. Given the considerable side effects and negative perceptions carried by steroids, and considering the robust evidence supporting high-dose 5-ASA, it would seem prudent to use 5-ASA as first-line therapy. Oral 5-ASA of at least 4 g/day has a high success rate in clinical trials, and topical therapy may also be a beneficial addition when acceptable to the patient. The doctor and patient should then agree to review symptoms after 2–3 weeks. Many patients will have begun to show symptom improvements with 5-ASA by this point, but if no improvement is observed, therapy escalation with steroids can be considered. In this way, patients may successfully avoid steroids (Box 2), while those who fail to respond can still receive timely treatment with steroids.

Box 2. Steroid avoidance: an example from practice.

Although steroids still retain an important role in the treatment of ulcerative colitis (UC), the described approach may allow many patients with moderately active UC to avoid steroids and their side effects, without suffering continuing debilitating symptoms.

- A security guard presented with newly diagnosed moderately active UC, and a history of severe depression. Aware of the potential for steroids to adversely affect depression, treatment was initiated with high-dose 5-aminosalicylic acid followed by ongoing symptom review. In this case, the patient's symptoms resolved, without the need for steroids.

The importance of adherence and informed concordance

An additional element to consider as part of the treatment process is that of adherence. Ensuring adherence is important to treatment success for all UC therapy, yet it is a complex subject influenced by a broad range of factors [Kane and Robinson, 2010]. One such factor which gains much attention, particularly in 5-ASA therapy, is that of a daily regimen; convenience is important for patients, although the true difference between once daily and twice daily is a matter for debate [Kane and Robinson, 2010]. In the case of steroids, concern regarding side effects could be a significant factor. In both cases, careful discussion of the available treatment options allows a joint decision to be made, matching therapy decisions to patients' specific preferences and concerns.

It is also important to discuss treatment aims and timelines. An informed discussion to agree realistic goals with patients can help to give an idea of the likely timescale of symptom remission. For the approach described above, careful agreement of the 2–3-week review period may help patients to maintain confidence and remain in control of their treatment.

Conclusion

Steroids represent a well established, effective treatment for active UC, supported by strong clinical data and several decades of successful use. Nevertheless, the side effects they carry, combined with evidence supporting high-dose 5-ASAs, offers an incentive to consider the optimal place for steroids, particularly in the treatment of moderate disease.

Unfortunately, the paucity of head-to-head comparisons between steroids and 5-ASA makes developing a conclusive approach challenging. However, the current literature, as reviewed above, does provide enough evidence to support a pragmatic approach. The suggested approach places 5-ASA as the first-line therapy, while steroids offer an option for therapy escalation after 2–3 weeks if required. In this way, through informed agreements with patients, unnecessary courses of steroids may be avoided yet the rapid efficacy they offer remains available for those patients who need it.

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