



TOPIC HIGHLIGHT

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Severe ulcerative colitis: At what point should we define resistance to steroids?

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and prolonged response to steroids may take longer. Either way, physicians taking care of these patients need to recognize that severe ulcerative colitis may be life-threatening, and they need to be careful with excessively prolonged medical treatment and delayed surgery.

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Abstract

Corticosteroids are still the first-line treatment for active ulcerative colitis more than 50 years after the publication of trials assessing their beneficial effect, with about a 50% remission rate in cases of severe disease. The mortality related to severe attacks of ulcerative colitis has decreased dramatically, to less than 1%, in experienced centers, due to the appropriate use of intensive therapeutic measures (intravenous steroids, fluids and electrolytes, artificial nutritional support, antibiotics, *etc*), along with timely decision-making about second-line medical therapy and early identification of patients requiring colectomy. One of the most difficult decisions in the management of severe ulcerative colitis is knowing for how long corticosteroids should be administered before deciding that a patient is a non-responder. Studies assessing the outcome of acute attacks after steroid initiation have demonstrated that, in steroid-sensitive patients, the response generally occurs early on, in the first days of treatment. Different indexes to predict treatment failure, when applied on the third day of treatment, have demonstrated a high positive predictive value for colectomy. In contrast to this resolute approach, which is the most widely accepted, other authors have suggested that in some patients a complete

RESISTANCE TO CORTICOSTEROIDS RELATED TO DOSE OR ROUTE OF ADMINISTRATION

The wide use of glucocorticosteroids in the management of active ulcerative colitis (UC) in the second half of the twentieth century had a major role in dramatically reducing the high mortality rate of this condition, from 75%^[1] to less than 1%^[2]. In 1955 Truelove and Witts published a summary of controlled trials using cortisone in 109 UC patients, most of them with moderate disease^[3]. In 1978, Truelove *et al*^[4] reported, in an uncontrolled study, a 60% remission rate in 87 patients with severe UC by using 60 mg intravenous prednisolone. More than 50 years after the publication of the initial trial, Corticosteroids are still the first-line treatment for moderate to severely active UC. Similar percentages of response and remission rates were reproduced in a number of subsequent studies^[2]. However, little evidence-based data are available indicating the optimal dose and route of administration in severe disease. Only one study performed in outpatients with moderate disease compared doses of 20, 40 and 60 mg of oral prednisone, and demonstrated a similar effect for 40 and 60 mg, and significantly higher than that for

20 mg/d^[5]. No trials assessing a dose-response rate have been performed in severe UC, and the majority of studies have used fixed doses, not adjusted to body weight, ranging from 40-80 mg of methylprednisolone and 100-400 mg of hydrocortisone. A recently published systematic review of cohort studies and controlled clinical trials assessing the response to Corticosteroids in severe UC addressed the issue of dose-related efficacy of steroids^[2]. The dose administered was reported in 24 studies, and no relationship was found between the dose administered-standardized as methylprednisolone equivalent while using a mean adult weight of 70 kg and colectomy rate. However, the mean daily dose was 68 ± 13 mg (range 40-100 mg); only 3 studies have used doses lower than 50 mg/d. Therefore, doses equivalent to 1 mg of prednisone per kg body weight seem to be the most effective, with higher doses apparently not adding more benefit. However, supraphysiological doses (equivalent to 1000 mg methylprednisolone), as used in other immunomediated inflammatory disorders, were evaluated in only one pilot study that used 100 mg dexamethasone pulse therapy for 3 d with good short term outcome^[6].

Previous to establish the criteria of steroid resistance, it is accepted that corticosteroids should be administered intravenously when a lack of response to oral treatment is observed. This recommendation is based on classical pharmacokinetic studies, performed with limited numbers of patients, which demonstrated delayed prednisolone absorption after an oral dose in patients with acute colitis as compared to healthy controls, and better plasma levels after intravenous administration^[7,8]. In addition, intravenous administration in the hospital setting ensures good treatment compliance.

Hospital admission for intensive intravenous treatment is consequently mandatory for those patients with moderate disease who have failed to respond to oral prednisone or those having clinical criteria of severe disease as defined by the classical clinical index^[3,9]. In addition to the life-saving benefit of corticosteroid administration, the decreased morbidity and mortality in severe UC was thought to be due to the appropriate use of intensive supportive measures (fluid and electrolyte replacement, artificial nutritional support, antibiotics, *etc*) and early identification of patients requiring colectomy^[10,11]. In fact, unacceptably high mortality rates have recently been reported in non-specialized centers, probably due to delayed decisions in perioperative management^[12,13]. Physicians treating UC patients should be able to recognize the severity of the condition and related complications and to be aware of the limits of all the therapeutic armamentarium, thereby avoiding unnecessary exposure to ineffective treatment. In this sense, the availability of several therapeutic alternatives such as cyclosporine, infliximab and granulocyteapheresis stimulated the search for predictive factors of treatment failure at an early stage. Thus, one of the most difficult questions in the management of severe UC is not deciding when corticosteroids should be administered,

but rather for how long they should be administered, and with what limits for their efficacy.

AT WHAT POINT SHOULD WE DEFINE RESISTANCE TO STEROIDS: 3, 7 OR 21 DAYS AFTER INITIATION?

The colectomy rate in severe UC (30%-35%), as well as percentages of remission and response, have remained unchanged since the introduction of corticosteroids in UC treatment, and similar results have been reported in both clinical trials^[2] and in the clinical setting^[14]. The classic limit of 7-10 d for establishing the criteria of steroid resistance was based on the results of historical series showing that the median time of remission was 7.5 d and that prolonged administration beyond 10 d did not increase the percentage of remission^[15].

However, some authors have argued in favor of a more conservative approach since a group of "slow responders" have been identified^[16,17]. These patients showed a partial response within 10 d of admission, defined as a decrease in stool frequency, with little or no blood. In the largest retrospective series of a single experienced hospital (149 episodes in 115 patients), 19% fulfilling this criteria entered into remission within the first 21 d of treatment^[16]. More importantly, the long-term follow-up of these "slow-responders" showed that none of them required colectomy within a median follow-up period of 49 mo. These data are in contrast with the high colectomy rate of corticosteroid refractory patients one year after ciclosporin-induced remission when azathioprine is not administered to maintain it^[18].

In contrast with this point of view, a more resolute approach is based on the results of several studies which have identified factors predictive of treatment failure soon after corticosteroid initiation^[19-22]. The study of Travis *et al*^[19] was a pioneer in this area, demonstrating a prospective day-by-day evolution, during the first days after admission, of several inflammatory parameters (C reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelets, *etc*) and clinical symptoms (bowel movements, blood in stools, pulse rate, *etc*) in 51 consecutive episodes of severe UC. This study identified a turning point in the disease outcome on the third day of treatment, establishing a critical limit for deciding whether patients are responders or non-responders. Two simple parameters (stool frequency of > 8 per day or 3-8 bowel movements per day and CRP > 45 mg/dL on the third day of therapy) have a positive predictive value (PPV) of 85% for colectomy. Similar results (decreased CRP and Montreal classification^[23] of UC activity as independent predictive factors for response on the 3rd day of treatment) have been obtained in a recent validated prospective study published as an abstract form^[20]. Two additional studies retrospectively analyzed clinical and biochemical data at 1, 3 and 7 d^[21], or within the first 3 d^[22] of medical therapy, to obtain

predictive models of the likelihood of colectomy. In one of these, a value higher than 8 obtained by the formula $\text{stool frequency}/d + 0.14 \times \text{CRP (mg/dL)}$ calculated on the 3rd day after initiation of treatment had a PPV for colectomy of 72%^[21]. This study confirmed that a regression formula including the same simple parameters used in the Travis *et al* study allows prediction of treatment failure and colectomy in a high percentage of severe UC patients. These results were prospectively validated in the only randomized, placebo-controlled study assessing infliximab as rescue therapy in severe UC, showing that patients fulfilling an index criteria of fulminant colitis (value ≥ 8) in the placebo arm had a PPV for colectomy of 69%^[24]. In the other retrospective study, a risk score was proposed to identify patients who are at low, intermediate or high likelihood of not responding to intensive medical treatment, aiding in the early selection of patients for second-line medical therapy or colectomy^[22]. Multiple logistic regression analysis identified mean stool frequency (graded from 0 to 4 points) and colonic dilatation (4 points) within the first three days and hypoalbuminemia (1 point) on day 1 of treatment, as significantly predictive of the need for surgery within the hospitalization period. The risk score allowed the stratification of patients into those with low (11%; score 0-1), intermediate (45%; score 2-3) and high risk (85%; score ≥ 4) of not responding to medical therapy. With a cut-off of ≥ 4 points, the sensitivity and specificity in predicting non-response to medical therapy were 85% and 75% respectively.

The results of these studies are in agreement with previous observations showing that complete remission, which takes longer than response, is achieved, in the majority of steroid-sensitive cases, within 7 to 8 d of beginning corticosteroid treatment^[15].

In conclusion, to evaluate steroid resistance, steroids must be intravenously administered, in the hospital setting, at a dose equivalent to 1 mg/kg per body weight of prednisone. The lack of response at day three of steroid treatment, as defined by well-established clinical parameters, suggests a high probability of colectomy and should be used in general as a limit point to define steroid resistance. Whether 3, 7 or 21 d are used as a limit marker for steroid resistance, judicious decisions by physicians, skilled in Inflammatory Bowel Disease management, should prevail. The risks and benefits of any decision have to be carefully weighed, taking into account that the priority in the management of severe UC is to save the patient and, if possible, the colon.

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