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Original research

Outcomes and prediction of corticosteroid therapy after successive courses of ulcerative colitis treatments

Eva Barreiro-Alonso (1,#,*), Cristina Saro-Gismera (1) and Manuel Sánchez (2,#)

Affiliations:

(1)Sección de Aparato Digestivo, Hospital Universitario de Cabueñes, Gijón, Spain.

(2)Farmacología, Departamento de Medicina, Universidad de Oviedo; Instituto Universitario de Oncología del Principado de Asturias (IUOPA), Spain.

#Contributed equally to this work

*Corresponding author:

Eva Barreiro-Alonso

Hospital Universitario de Cabueñes

c/ Los Prados, 395

33394 Gijón, Asturias, Spain

Telephone number: 34-985 18 50 00

Fax number: 34- 985185033

e-mail: evabarreiroalonso@yahoo.es

ABSTRACT

Introduction: Ulcerative colitis (UC) may require systemic corticosteroid (CS) treatment often without a reliable predictable response, except the Ho-index, used to predict severe cases. The present study aims to determine CS-efficacy and CS-free remission for different courses and longer follow-ups, and a predictive value of CS-outcomes, by the Ho-index and the analysis of clinical variables.

Methods: An observational retrospective study performed with 136 patients was based on clinical and analytical characteristics, before successive CS-therapies.

Results: The age of UC onset showed three peaks. After the first course 55.6% were CS-responders, and 39% had CS-free remission by the 3-5 years follow-up. Successive CS courses presented less efficacy and CS-free remissions, associated with increased CS use-dependence. The Ho-index, might only predict the first course of CS and low score patients with severe UC. Logistic regression analysis gave a predictive response mainly due to the age at diagnosis, the interval from diagnosis to CS-therapy and C-reactive protein (CRP) or hemoglobin values.

Conclusions: One-third of cases were CS-free remission UC. Successive courses showed decreased efficacy and increased CS-dependence, limiting CS-treatment. An older age at diagnosis, longer interval from diagnosis to CS-therapy, lower CRP and higher hemoglobin predicted better prognosis. The accuracy of prediction should be validated and include additional markers.

Key Words: corticosteroid, corticosteroid-free remission, efficacy, predictors, ulcerative colitis.

1. Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD), localized in the colonic mucosa and that extends from the rectum to proximal segments of the colon [1, 2]. The main peak age of occurrence is between 30 - 40 years [2, 3], with a second peak being proposed in adults of 60 - 70 years of age [4].

UC is characterized by a relapsing-remitting course, with different types of flares (mild, moderate or severe) and patterns of clinical evolution [2, 3, 5]. The disease is associated with high morbidity and mortality, although the current medical and surgical management has improved the prognosis. However, severe UC is still a potentially life-threatening illness [1].

5-Aminosalicylates (5-ASA) are the mainstay of treatment from UC flare-ups. Corticosteroids (CS) are indicated in mild to moderate flares not responding to 5-ASA and severe active UC [1, 6]. In their lifetime, 25% of patients may require hospitalization to undergo intravenous CS-treatment [7, 8]. The failure of an optimal clinical response to CS, shown as CS-refractory or CS-dependent, in moderate and severe UC may lead to colectomy or to a more aggressive medical treatment [7, 9, 10]. The management of the first course of CS-therapy is mostly associated with immediate remission, after 30 days, but 16-18% of UC patients are non-responders [11, 12]. At one-year, 17-22% were CS-dependent, 21-29% required surgery, and 49-55% of patients maintained a prolonged CS-free response [11-13]. Although these percentages may vary, depending on the follow-up period. Thus, when prolonged, 35% may stay with sustained CS-free remission, with 38-42% being CS-dependent and 11-17% CS-refractory, with median follow-ups of 3.4 [14] and 7 years [15], respectively.

Great efforts have been made to determine early predictors of CS use [16] and

failure [17], especially for severe UC, to identify candidates for rescue therapies [18]. The early response to initial CS-therapy was the first valuable predictor proposed for the clinical outcome one year later [19]. This, in addition to clinical parameters, such as mean stool frequency (MSF), body temperature and C-reactive protein (CRP) [18], were later considered as predictors [17, 20]. Some indexes have been proposed, the Travis-index [17] and the Ho-index [21], based on the clinical response after 72 hours of the initiation of intravenous CS and the concurrency of diverse clinical variables. In acute severe activity UC the Ho-index allows the early identification of patients that would not respond to intravenous CS-therapy, requiring second-line medical treatment or a colectomy. This index scores MSF, the presence of colonic dilatation and hypoalbuminemia, allowing the triage of patients into low, intermediate and high risk, with CS failure rates of 11%, 45% and 85%, respectively [21]. A recent model has been proposed to predict CS utilization in newly diagnosed patients with UC [16].

There exist differences in CS-outcome, partly with regard to the follow-up period studied. The efficacy of CS-therapy in successive UC courses has not been widely studied. Nor are specific biological markers available to predict the clinical response to CS therapy, regardless of its severity. Taking this into account, the aims of this study were to analyse longer follow-up periods and successive courses of CS-therapy to establish the efficacy of the treatment. In addition, the lack of a validated index in these patients and, to our knowledge, the absence of studies reporting the predictive value of the Ho index (described for severe flares) [21] in mild or moderate UC patients led us to the aim of determining its potential predictive value. As well as to evaluating the predictable capability of clinical variables in CS-response.

Preliminary results were communicated as an abstract form at the 24th United European Gastroenterology (UEG) Week 2016 [22].

2. Patients and methods

2.1. Study design

A retrospective observational study was performed in Caucasian adult patients of both sexes, diagnosed from 1980 to 2014. For this period, the historical database of the IBD Unit comprised 797 UC patients diagnosed by means of clinical, endoscopic and/or histopathological criteria. To carry out the present study we chose the patients who met the Lenard-Jones criteria (clinical, endoscopic and histopathological) for UC [23] and had an active follow-up in the IBD Unit of *Hospital de Cabueñes* (Gijón, Spain) until 2017. These criteria were met by 136 patients, with the remainder only being used to compare the mean age and the distribution of the age peaks at diagnosis.

2.2. Experimental procedures

Patient data such as: epidemiological and sociodemographic (gender, date of birth, age at diagnosis, urban or rural environment and consumption of tobacco), clinical (family history of IBD, MSF, inflammatory affection and activity, according to the endoscopy to the diagnosis of the different colorectal segments), radiological, histological and analytical (hemoglobin, leucocytes, platelet count, albumin, iron, ferritin, erythrocyte sedimentation rate (ESR), fibrinogen and CRP) were obtained from the medical records. Clinical and analytical data were annotated before each successive treatment for systemic CS, also considering the days of interval from the diagnosis of the disease for each CS-treatment. The patients lacking of a particular variable from the medical record for the determination of the Ho-index (MSF, colonic dilatation and

hypoalbuminemia) were not taken into account when this index was analysed.

The first course of UC treated with CS was referred to as corticosteroid 0 (CS0) and the successive CS-treatments with ascending numbers. The protocol and systemic doses of CS prescribed, orally or intravenous, was based on the severity of the disease, according to the European Consensus Guidelines [10, 24].

2.3. Case definitions

The diagnosis of UC was confirmed by the criteria of Lennard-Jones, which include clinical, radiological, endoscopic and histological criteria [23]. The extension was determined using the Montreal classification, and the severity by this and Truelove and Witts [7, 10]. There were mild to moderate active UC patients not responding to other medications or severe UC treated with systemic CS. The Ho-index was based on the following variables: MSF (0: ≤ 4 stools/24 h; 1: > 4 and ≤ 6 stools/24 h; 2: > 6 and ≤ 9 stools and 4: > 9 stools/24 h), the presence of colonic dilatation (0: absence and 4: presence) and hypoalbuminemia (0: > 30 g/L and 1: ≤30 g/L). Based on the total score, the patient triage were low-risk (0-1), intermediate-risk (2-3) and high-risk (≥4), with CS failure rates of 11%, 45% and 85%, respectively [21].

2.4. Outcomes of CS-therapy in UC

The effect of CS-treatment, UC patients or flares (episodes or courses of illness) were classified as CS-responders and CS-non-responders. The former included: patients that did not require more CS and those who showed CS-free flare remission. CS-non-responders included: CS-dependency (patients who are either unable to reduce CS

below the equivalent of prednisolone 10 mg/day within 3 months of starting CS, without recurrent active disease, or who have a relapse within 3 months of stopping CS) [9] and CS-refractory (patients who have clinical activity despite treatment during 4 weeks with full doses (0.75 mg/kg/day of prednisolone or 1 mg/kg/day of prednisone, or equivalent) over a period of 4 weeks for mild or moderate flares, and 5-7 days for severe ones [10].

2.5. Ethical Considerations

The study was approved by the *Comité de Ética de la Investigación del Principado de Asturias*, Spain, reference 58/17.

2.6. Statistical analysis

The age of the patients was expressed as the median and the interquartile range (IQR). The years of follow-up of the patients and the intervals between successive CS treatments in months as the mean (Standard Error of the mean: SE). When required, Student's t-test for unpaired data, a two-way between-groups analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA), with the post hoc test, were performed. This was followed by discriminant analysis to differentiate the outcomes of CS-therapy.

Binary (CS-response or CS-non-response) and multinomial logistic regression (for the four outcomes considered) was used to establish the interaction of variables studied on the CS response. Odds ratio (OR) with 95% confident interval (CI) was calculated to determine the differences in the occurrence of the qualitative variables.

The Pearson's correlation coefficient (r) was used to determine the linear relationship between variables.

The number of patients was at least four in each case, otherwise data were not averaged. For all analysis, values of $p \leq 0.05$ were considered as significant. The statistical calculations were performed by means of IBM SPSS Statistics version 22.0 (IBM Corp.).

3. Results

3.1. Characteristics of the UC patients studied

One hundred and thirty-six (136) patients were studied, 74 men (median 47, IQR: 33-61 years old) and 62 women (median 44.5, IQR: 29-61 years old), whose ages at diagnosis fitted to three Gaussian distribution peaks: at 31, 47 and 69 years of age (Figure 1). The median age of the UC patients from the historical database of the IBD Unit was 43 years (IQR: 30-57), also showing three peaks at similar ages: 29, 47 and 69 years old. The mean follow-up was of 15.73 (SE: 0.73) years.

Of the sample studied, 28 patients had never needed CS, at diagnosis or during their follow-up. The clinical characteristics of CS-responders, CS-non-responders and those never treated, regarding overall outcome of the patients during the study period are presented in Table 1.

Of the patients treated with CS (n = 108) 45 were CS-non-responders (33 CS-dependence and 12 CS-refractory) and 63 were CS-responders (36 required more CS and 27 showed good flare response). These were compared to patients who were never treated with CS (n = 28). According to the Montreal classification, 82.1% of patients not treated with CS were older, category A3 (*OR*: 0.24, CI: 0.08-0.68, p = 0.0049), had

proctitis (E1) as the main extension (*OR*: 3.46 (CI: 1,3 - 9.2, $p = 0.01$) and were mainly quiescent or with mild activity (S0 and S1) (*OR*: 4.11, CI: 1.45-11.62, $p = 0.0049$), by comparison with patients treated with CS.

After UC diagnosis within the first month 54% of patients required the first CS-therapy, that cumulatively increased to 65%, 70%, 74% and 77% within the first, second, third and fifth year.

UC patients were treated with CS 20.4% were treated intravenously (60 mg/24 h of methylprednisolone) and 79.6% orally (1 mg/kg/day of prednisone). The treatment required by the patients is described in Table 1.

The mean time from diagnosis to the first treatment with CS was of 46.14 (SE: 8.3) months. The intervals between successive CS-treatments were not statistically significant, being from first to second CS treatment 29.66 (SE: 5.39) months, from the second to third 25.74 (SE: 4.73) months, from the third to the fourth 18.02 (SE: 3.75) months, and from the fourth to the fifth 31.77 (SE: 12.88) months.

3.2. Response to CS-treatment

The response to the first course of treatment with CS showed that 34.26% (n=37) of the patients did not require more CS, 55.56% (n=60) of patients with good flare responses, CS-dependent 3.7% (n=4) and CS-resistance 6.48% (n=7) (Table 2). The cumulative probability of remaining CS-free decreased with every subsequent course that required CS-therapy. After the first one, CS-free clinical relapses were 71% within the first year, 60% within the second, 52% within the third, 44% within the fifth and 38% within the tenth. These decreased after subsequent courses treated, with 60%, 45%, 33%, 27% and 20% of the patients, cumulatively CS-free after the second course,

within the first, second, third, fifth and tenth years, respectively. And, after the third course these were 44%, 29%, 24% and 15%, within the first, second, third and fifth year, respectively (Figure 2A and Table 2)

The plot of successive CS-treatments *versus* the percentage of CS-responders showed a linear decrease for clinical efficacy. This fitted to an equation:

$$Y_{Percentage\ CS\text{-}responders} = -13.53 + 92.38 \times number\ of\ courses\ treated \quad (1)$$

with 98.9% predictively (Figure 2B). The separate analysis for the four CS-outcomes (not requiring more CS, good flare response, CS-dependence and CS-refractory) showed that the percentage of CS-dependence linearly increased with successive treatments. This fitted to an equation:

$$Y_{Percentage\ CS\text{-}dependence} = 11.1 + 7.9 \times number\ of\ course\ treated \quad (2)$$

with 93.2% predictively. These patients were mainly good flare responders in previous treatments (69.23% of the CS1, 64.71% of CS2, 66.67% of CS3 and 75% of CS4). The percentage of patients that did not require more CS-treatments dropped 20% after the first flare was treated. Good flare response and CS-refractory were similar for the first three courses, decreasing and increasing afterwards, respectively (Figure 2C). Considering all the UC flares treated, the patients that did not require more CS were 19.49%, good flare response were 53.31%, CS-dependent were 22.06% and CS-refractory were 5.15%. The total number of patients that at any course presented CS-resistance were 12 (11.11%) and CS-dependence (30.56%). Surgery occurred in 11 patients (10.2%).

3.3. Analysis of the quantitative variables regarding CS-outcome

The MANOVA used to investigate CS-non-responders or CS-responders, showed a significant difference between the independent variable on the combined dependent variables, F (11, 113) = 3.92, $p < 0.001$; Wilks' Lambda = 0.72; partial eta squared = 0.27. When the results for the dependent variables were considered separately, the only differences with statistical significance, using a Bonferroni adjusted alpha level of 0.025, were in the age at diagnosis (F (1, 123) = 8.54, $p = 0.004$, partial eta squared = 0.06), in the number of courses treated (F (1, 123) = 33.40, $p < 0.001$, partial eta squared = 0.21) and for the interval from diagnosis to CS-therapy (F (1, 123) = 5.09, $p = 0.026$, partial eta squared = 0.04). The discriminant analysis revealed one discriminant function, that explained 100% of the variance, canonical $R^2 = 0.27$. The discriminant function significantly differentiated the effect of CS-treatment groups, $\lambda = 0.73$, $\chi^2(10) = 37.81$, $p < 0.001$. The correlations between outcomes and the discriminant functions revealed that number of courses treated fitted well the function ($r = 0.85$), followed by the age at diagnosis ($r = -0.43$), interval from diagnosis to CS-therapy ($r = 0.34$), age at treatment ($r = -0.29$), platelets ($r = 0.24$), hemoglobin ($r = -0.22$), and with r below 0.1 were CRP, iron, albumin and leukocytes.

The MANOVA used to establish the effect of CS-therapy (no more CS required, good flare response, CS-dependence and CS-refractory) showed a significant difference between the independent variable and the combined dependent variables, F (33, 339) = 2.83, $p < 0.001$; Phillia's Trace = 0.65; partial eta squared = 0.21. When the results for the dependent variables were considered separately, the only differences to reach statistical significance, using a Bonferroni adjusted alpha level of 0.0125, were in the age at diagnosis (F (3, 121) = 6.99, $p < 0.001$, partial eta squared = 0.15) and at

treatment (F (3, 121) = 5.14, p = 0.002, partial eta squared = 0.11), the number of course treated (F (3, 121) = 14.95, $p < 0.001$, partial eta squared = 0.27) and for CRP (F (3, 121) = 3.61, p = 0.015, partial eta squared = 0.08). The discriminant analysis showed three discriminant functions, explaining 60.3% (R^2 = 0.35), 27.6% R^2 = 0.19) and 12.1% (R^2 = 0.10) of the variance. In combination these discriminant functions significantly differentiated the response of the treated groups, 1 through 3 with $\lambda = 0.48$, $\chi^2(30) = 86.67$, $p < 0.001$, 2 through 3 with $\lambda = 0.73$, $\chi^2(18) = 37.08$, $p = 0.005$, but removing the first two functions indicated that the third function did not significantly differentiate the treated groups, $\lambda = 0.90$, $\chi^2(8) = 11.78$, $p = 0.161$. The discriminant function indicated that the first function discriminated the patients that did not require more CS-therapy from the others, and the second function differentiated the CS-refractory group from the remaining groups. The correlations between outcomes and the discriminant functions showed that several variables fitted well with the function.

3.4. Outcome of CS-treatment with respect to the extension and activity of UC

For the first course treated, the positive response to CS (did not require more CS and good flare response) was not significantly related to the extension of the disease, although there was a decrease in the percentage of patients that did not require more CS-treatment from E1 to E3. The patients with S0 to S2 activity at diagnosis showed a significantly lower percentage of CS-refractory (3 out of 99, 3.03%) by comparison with the S3 (4 out of 9, 44.44%), *OR*: 0.039 (IC: 0.007-0.224, $p < 0.001$) (Table 3).

Considering all flares treated, no differences existed between CS-outcome and the extension of the disease. Severe cases (S3) were associated the most with CS-refractoriness (21.74%), being below 5% for S0 to S2, and the lowest for patients that

did not required more CS-therapy (4.35%), being roughly 20% for S0 to S2 (*OR* of S3: 7.41 (IC: 2.24-24.44, $p < 0.001$), CS-refractory versus no required CS).

3.5. Ho-index in UC patients

The number of courses of UC with severe activity (S3), used to calculate the percentage of CS-non-responders was low: total courses were 17 (5 scored 0-1, 2 scored 2-3 and 10 scored ≥4) of 165 flares of UC treated with CS (Figure 3A). The percentage of CS-non-responders, for the three categories of the Ho-index without taking into account the degree of activity, was calculated for each successive treatment (if available for at least four patients for each category). The percentage of CS-non-responders increased for each flare treated. No significant difference existed among the different categories of Ho-indexes (Figure 3B).

3.6. Predictors of response to CS-therapy

The binary logistic regression analysis used to evaluate the predictable capability of clinical variables in CS-response gave a predictive model of response (in 75.7% of cases) only for the first course treated (CS0), and contained three independent variables: the age (years) of the patients at diagnosis, the days of interval from the diagnosis to the initiation of CS-therapy and the CRP (mg/L). The equation was:

$$Y_{CS\text{-}Responders\ (no/yes)} = -1.5717 + (age \times 0.045) + (days\ interval\ from\ diagnosis\ to\ CS \times 0.0007) + (CRP \times -0.0105) \quad (3)$$

the cut off value for CS-responders was 0.5 (Table 4). When this equation was applied

in the first course treated (CS0), the cases with a result ≥0.5 predicted that 94.7% of the patients treated would be CS-responders.

A binary logistic regression analysis was performed to find an equation to predict the response for any flare treatment. This gave a predictive model of response (in 72.9% of cases) containing three independent variables, with the following equation (Table 4):

$$Y_{CS\text{-}Responders\ (no/yes)} = -2.7068 + (age\ at\ diagnosis \times 0.0347) + (days\ of\ interval\ from\ diagnosis\ to\ CS \times -0.000135) + (hemoglobin \times 0.1836) \quad (4)$$

In the sample studied a value above 0.5 predicted that 87% of the patients treated would be CS-responders, but 40% of CS-non-responders were also included.

Multinomial logistic regression was performed to predict the four groups of CS response at any flare treated. This gave a predictive model of response, not significant, which included, with different degrees of significance variables for the different outcomes. Thus, using as reference category CS-refractoriness by comparison to the patients that did not require more CS-therapy the main predictable variables were the age at diagnosis ($p = 0.007$, OR: 1.10 (95% CI: 1.03 - 1.18) and the number of episodes treated ($p = 0.003$, OR: (0.24 (95% CI: 0.10 - 0.61). Regarding good flare response these were CRP ($p = 0.008$, OR: 0.98 (95% CI: 0.97 - 1.00)), albumin ($p = 0.032$, OR: 2.70 (95%CI: 1.09 - 6.68) and iron ($p = 0.002$, OR: 0.97 (95% CI: 0.95 - 0.99)) and for CS-dependence were CRP ($p = 0.045$, OR: 0.98 (95% CI: 0.97 - 1.00), albumin ($p = 0.022$, OR: 3.64 (95% CI: 1.20 - 10.98) and iron ($p = 0.030$, OR: 0.98 (95% CI: 0.96 - 1.00).

4. Discussion

The clinical response to CS-therapy, of patients with mainly mild to moderate severity UC, showed that a large percentage of patients responded to the first course of CS. The efficacy decreased linearly and predictably with successive flares treated. This pattern corresponded with an increased CS-dependency, induced in two-thirds of patients who in a previous treatment had a good flare response. The clinical remission was in the range of previous reports. The Ho-index had a low predictable value, but some clinical and analytical parameters commonly requested in these patients might partially provide predictive equations.

The age of diagnosis, for the UC patients treated with CS, presented a wide range, with a median of 40 years in both sexes, similar to the cases of UC registered in the database of the IBD Unit. What was interesting was the distribution in three peaks in both groups, in the 30´s, 50´s and 70´s, instead of the bimodal reported in most studies (a first peak at 30-40 years and a second peak at 60-70 years) [4, 25].

The patients of the study that did not require CS-therapy, did not refer to a family history of IBD and presented lower extension (E1 of Montreal classification) and severity of the disease (S0-S1) than CS-treated patients. Of this final group, CS-non-responders were significantly younger at diagnosis, roughly 10 years, than CS-responders and patients never treated with CS. This suggests that the age at diagnosis could be one the variables determining the response to CS, also being described as predictor of CS use [16]. Although, its influence in the clinical course of UC is controversial [26].

The results showed that within a month of UC diagnosis half of patients required the first course of CS, cumulatively within one year 65% required treatment and within

two years this reached 70%. These are in the range of previous reports [14, 15], although slightly higher, which might be explained by the inclusion of mild UC patients.

The first UC course that required CS-therapy showed a high percentage of positive clinical responses, at 90%, of which 34% did not require more CS and 56% had good clinical flare remission (although CS could be required for a subsequent course), during the complete follow-up period. The time-course of relapsed CS-free patients of our study indicated that this was 20% superior than that reported within the first year (around half of patients)[11-13] and quite similar (66% *vs* 65%) to that described in a two year follow-up [11, 12]. When we estimated CS-free remission prolonging the follow-up period, this decreased to 35%, as previously reported in a median follow-up of 3.4 years [14], and reached the steady-state around the fifth year. Therefore, the time of follow-up determined the percentage of CS-outcome, being overestimated when the follow-up periods were below 3-5 years. The extension (a predictor of CS use)[16] and activity of the disease and concurrent pharmacological treatment may also play a role in the outcome to CS. Our sample included mainly mild to moderate patients and less with severe activity, as referred to in other reports [11, 15], in favour of better clinical prognosis, which might explain the differences in the time-course. The outcome seemed not to be influenced by 5-ASA, since all patients were treated prior to the CS-therapy. The sample size did not allow a segregation of the patients in order to determine the influence of different pharmacological therapies in CS response, especially after the introduction of biological treatments. Although, the results might not vary considerably since 20% of the patients were receiving biological treatment.

How successive UC flares requiring CS-therapy may respond has been less studied. Our result showed that each subsequent treatment was associated with a linear

predictable decrease of CS efficacy. The analysis of the time-course of the CS-free remission of the second and third courses showed that the drop in efficacy after the treatment was faster and the final CS-free remission decreased, with respect to the first course, being of one-fifth and one-tenth, respectively.

Considering all treated flares together, one-fifth of patients at some point did not require more CS-treatment, half had good response to CS, one-fifth were CS-dependent and 5% were CS-refractory. Thus, roughly two-thirds of flares had a positive clinical response to CS. It was interesting that the percentage of CS-dependence was the only outcome positively adjusted to a linear equation, independent of the clinical activity or the Ho-index presented by the patients. These went from 4% for the first flare to 50% for the fifth one. The initial percentage obtained was lower than that described by Faubion *et al.*[11] and Ho *et al*.[12], who reported around 20% in the first year, which may rise when the median period is increased, as in our study and that reported by Khan *et al*.[14], finding 38% after an average of a 3.4 year follow-up. The remaining three groups of outcomes, with the exception of the drop in the percentage of patients that did not require more CS, did not present major differences in the occurrence up to the fourth successive treatment.

The pattern of the increment of CS-dependence suggests an inducible effect due to repeated treatments, unrelated to the time of evolution of the disease as could be, since successive treatments correspond to greater evolution time of the disease. Therefore, the CS use-dependence and the faster time-course of loss in efficacy, by successive treatments, limits its use to a lower number of courses, to avoid the important adverse effects of CS-dependence.

The occurrence observed for CS-resistance was constant over the course of treatments, being present in 11% of UC patients as reported by Khan *et al*.[14],

although lower than previous reports (16-18%) [11, 12]. In our study, S3 UC patients presented, after the first course of CS-therapy, more chance of being CS-resistant than if they were S0 or S1. In the 15-year follow-up period, the percentage of UC patients treated with CS that required surgery was inferior than reported [11, 12], which could be explained by the lower active severity of UC of the patients in this study. However, the extension and severity of the disease was not associated with the need of surgery, as has been previously reported [12, 27].

Further analysis were performed to find factors related to CS-outcome based on clinical and analytical variables commonly requested in active UC patients. First, it was analysed whether they may discriminate between groups of patients, considering the outcome of CS effect as binary or for the four types. The MANOVA and discriminant analysis indicated that the number of flares treated, age at diagnosis and the interval from the diagnosis of the disease to CS-treatment could be seen as variates that differentiate CS-responders and CS-non-responders, explaining one-third of the variance. Thus, the variates may be used to differentiate between CS-outcomes.

The linear equations, mentioned above, cannot inform about the effect of CS on an individual patient, nor was the Ho-index useful (as it only predicted in terms of percentage those cases with lowest score (0-1 points) and for the first course treated with CS). Binary logistic regression estimated a predictor equation for CS-outcome, CS-non-responders or CS-responders, in 75.7% of patients. When the formula was applied to our sample, values equal or above 0.5 predicted 95% of CS-responders. An equation also estimated the response to any flare treated in 72.9% of cases. This pointed out that the older the age at diagnosis, greater the interval from diagnosis to CS-treatment for the first CS-therapy, and lower the value of CRP or, for any flare treated, higher levels of haemoglobin were favourable factors of CS-response. Some of these have already been

pointed out as predictors of CS requirement[16] and as prognosis factors [28].

The lack of precision of these formulas could be related to the heterogeneity of the patients when considered as CS-responders together with those not requiring more CS and good flare response, and as CS-non-responders, the CS-dependency and CS-refractoriness, whose underlying mechanisms that determine CS-outcome could differ. The MANOVA and discriminant analysis showed that the four outcomes of CS-therapy showed significant differences in the number of courses treated, their age at diagnosis, age at treatment and CRP (close to being statistically significant), explaining two-thirds of the variance. The discriminant functions discerned the type of response to CS-therapy, indicating that there are differential clinical entities susceptible to the realization of multinomial logistic regression. To perform this analysis, all flares that required CS-therapy were included, using as reference the courses showing CS-refractoriness, due to the absence of CS effect. Older age at diagnosis, elevated CRP, and decreased albumin were associated with the three remaining CS-outcomes. The number of courses treated was inversely associated with the number of patients that did not require more CS and with a good flare response, and in favour of CS-dependence.

It would be interesting to pursue this study further, in particular the response to CS in UC patients in a bigger sample to allow the comparison of different pathological conditions and treatments (medical and surgical) to the response.

5. Conclusions

The results support previous reports regarding CS-outcome of the first course that required CS-therapy and suggested that successive courses with CS were associated with a decreased efficacy and induced CS-dependence, limiting the CS courses to

prevent adverse effects. A favourable clinical response for the first UC course that had required CS were older at the age of diagnosis, had a longer interval from UC diagnosis to the first CS-therapy and lower CRP values. The age and interval of CS-therapy were related to a favourable clinical response, and successive CS-therapy was a factor for CS-dependence. Less determinant were other analytical variables. The utility of the predictive equations should be validated in new samples of patients, and include additional markers for a more accurate prediction useful in clinical decision making.

6. Key issues

- The age of UC onset fitted to three Gaussian distribution peaks: at 31, 47 and 69 years of age.
- Systemic corticosteroid (CS) may be necessary to treat ulcerative colitis (UC), without a reliable predictable response, except Ho-index in severe cases.
- The Ho-index, might only predict the first course of CS and low score patients with severe UC.
- The outcome of CS was similar to other reports, but the study provided additional information that successive CS treatments were associated with a decreased efficacy and induced CS-dependence.
- It suggests that the number of courses should be limited to prevent CS adverse effects.
- An older age at diagnosis, longer interval from diagnosis to CS-therapy, lower CRP and higher hemoglobin predicted better prognosis. The accuracy should be validated and include additional markers.

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Declaration of interest

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Author Contributions

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Reference annotations

* Of interest

** Of considerable interest

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Figure legends

Figure 1. Frequency of age distribution of the UC patients that required corticosteroid (CS) therapy (black bars; the solid lines represent the fitting) and of the complete database of the IBD Unit (grey bars; the dashed lines represent the fitting), during the same period, expressed as percentage of cases.

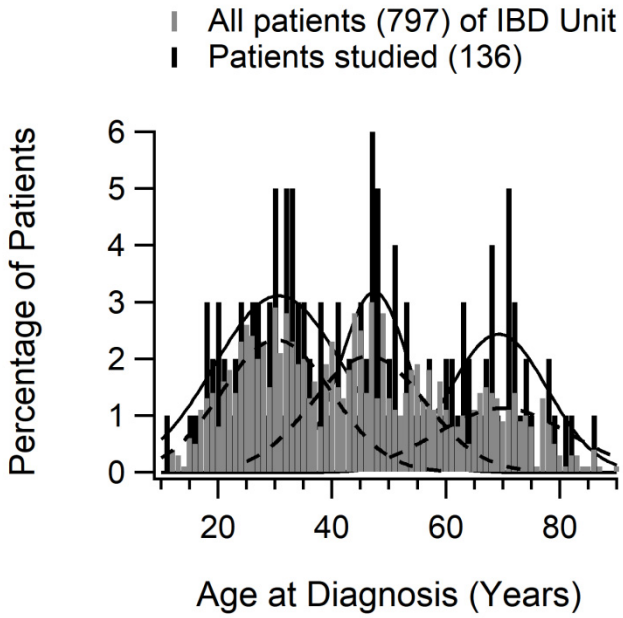

Figure 2. Time-course of the evolution of probability for corticosteroid (CS)-free remission, for the first three courses of CS treated (A). Linear decrease of the percentage of positive outcome to CS by successive treatments (B), and of the four considered outcomes (C).

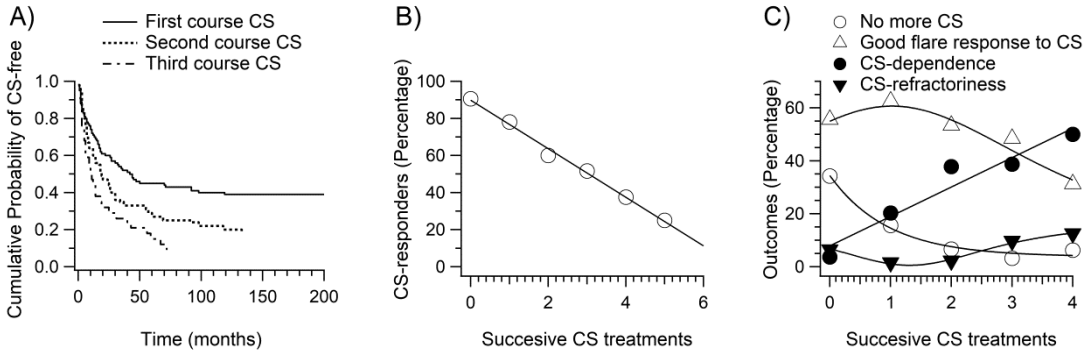

Figure 3. Percentage of corticosteroids (CS)-non-responders regarding the activity (mild, moderate and severe) of UC and the Ho-index of each category (A), and with respect to the number of flares treated and the Ho-index, disregarding the UC activity (B). In (A) filled circles represent the reported [21] percentages of UC patients with severe flares not responding to CS in accordance with different Ho-indexes (11% for a score of 0 - 1, 45% for a score of 2 - 3 and 85% for a score of ≥ 4), also being represented in (B) by different types of discontinue lines.

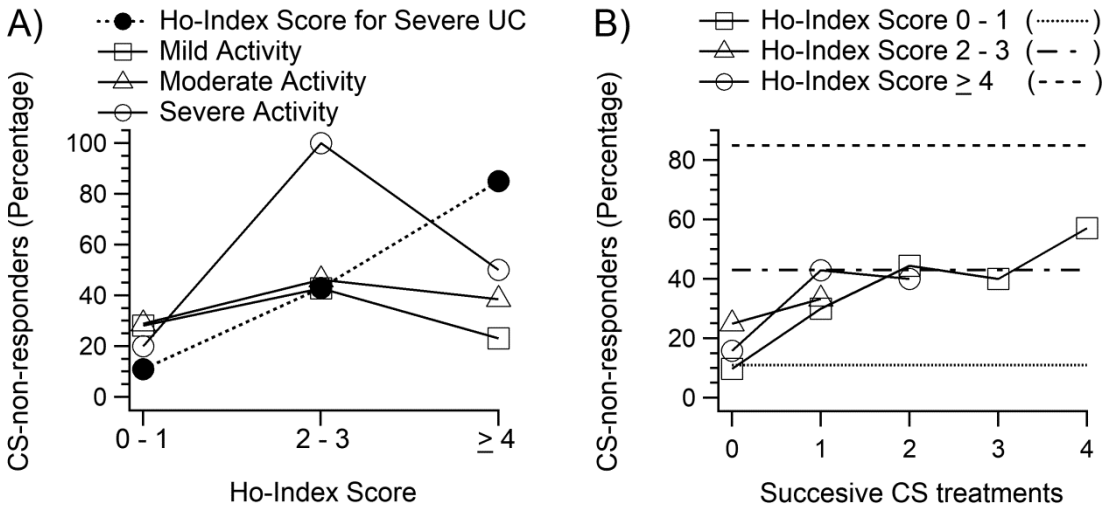

Table 1. Characteristic of the patients with UC, regarding corticosteroids (CS) treatment, expressed as number of cases (*n*), the percentage (%) or median ± Interquartile Range (IQR).

	CS Treated (All)	CS-non-responders	CS-responders	Never treated with CS
	n (%), median (IQR)	n (%), median (IQR)	n (%), median (IQR)	n (%), median (IQR)
Number of patients (N=136)	108	45	63	28
Median age at diagnosis (years) (IQR)	40 (29-62)	32 (24-47)***	48 (33-65)	48 (43-58)
Gender, male/ female, n (%)	61 (56.5%)/ 47 (43.5%)	27 (60%)/ 18 (40%)	34 (54%)/ 29 (46%)	13 (46.4%)/ 15 (53.6%)
Family history-IBD, n (%)	18 (16.7%)	5 (11.1%)	13 (20.6%)†	0 (0%)
Smoking, n (%)	58 (53.7%)	27 (60%)	32 (50.8%)	11 (39.3%)
Urban/ rural area, n (%)	85 (78.7%)/ 23 (21.3%)	35 (77.8%)/ 10 (22.2%)	50 (79.4%)/ 13 (20.6%)	23 (82.1%)/ 5 (17.9%)
Disease onset (Age, Montreal classification):				
A1	3 (2.8%)	1 (2.2%)	2 (3.2%)	0 (0%)
A2	51 (47.2%)	29 (64.4%)	22 (34.9%)	5 (17.9%)
A3	54 (50%)	15 (33.3%)	39 (61.9%)	23 (82.1%)
Disease extent (Montreal classification):				
Proctitis (E1)	13 (12.0%)	4 (8.9%)	9 (14.3%)	9 (32.1%)
Left-sided colitis (E2)	51 (47.2%)	18 (40%)	33 (52.4%)	14 (50%)
Extensive colitis (E3)	44 (40.7%)	23 (51.1%)	21 (33.3%)	5 (17.9%)
Active disease (Montreal classification):				
S0	3 (2.8%)	2 (4.4%)	1 (1.6%)	1 (3.6%)
S1	54 (50.5%)	15 (33.3%)	39 (61.9%)	22 (78.6%)
S2	41 (38.3%)	20 (44.4%)	22 (34.9%)	5 (17.9%)
S3	9 (8.4%)	8 (17.8%)	1 (1.6%)	0 (0%)
Disease progression (%)	27 (25%)	13 (28.9%)	14 (22.2%)	0 (0%)
Pharmacological Treatments:				
5-ASA	108 (100%)	45 (100%)	63 (100%)	28 (100%)
Azathioprine	43 (39.8%)	36 (80%)†††	7 (11.1%)	0 (0%)
Cyclosporin♦	1 (0.9%)	1 (2.2%)	0 (0%)	0 (0%)
Infliximab	15 (13.9%)	15 (33.3%)	0 (0%)	0 (0%)
Adalimumab	7 (6.5%)	6 (13.3%)	1 (1.6%)	0 (0%)
Leukocytapheresis	4 (3.7%)	4 (.9%)	0 (0%)	0 (0%)
Colectomy	11 (10.2%)	11 (24.4%)	0 (0%)	0 (0%)

CS: Corticosteroids; IBD: Inflammatory Bowel Disease; IQR: Interquartile range; UC: Ulcerative Colitis; 5-ASA: 5-aminosalicylates.
***p< 0.001 and †p = 0.0094 by means of Student´s t Test for unpaired data.
†††p<0.001 by means of Chi-squared
♦Levels of cyclosporine not available in our hospital

Table 2. Percentage of clinical response of the UC patients, regarding first episode treated with corticosteroids (CS) treatment, and of CS-free clinical relapse along follow up years, regarding the course treated with CS.

		CS-good-responders, no more CS	CS-good-responders	CS-dependence	CS-resistance
First course response		34%	56%	4%	6%
		CS-free clinical relapse (Follow up)			
Course	**First year**	**Second year**	**Third year**	**Fith year**	**Tenth year**
First	71%	60%	52%	44%	38%
Second	60%	45%	33%	27%	20%
Third	44%	29%	24%	15%	

CS: Corticosteroids; UC: Ulcerative Colitis.

Table 3. CS outcome of patients treated for the first course (CS0) with corticosteroids (CS), regarding extension and clinical activity, expressed as number of cases (*n*) and percentage (%).

	All	**No more CS**	**Good flare CS-response**	**CS-dependence**	**CS-refractoriness**
Extension					
E1	13	6 (46.15%)	6 (46.15%)	1 (7.69%)	0
E2	51	19 (37.25%)	28 (54.9%)	1 (1.96%)	3 (5.88%)
E3	44	12 (27.27%)	26 (59.09%)	2 (4.55%)	4 (9.09%)
Activity					
S0-S1	57	23 (40.35%)	30 (52.63%)	2 (3.51%)	2 (3.51%)
S2	42	13 (30.95%)	26 (61.9%)	2 (4.76%)	1 (2.38%)
S3	9	1 (11.11%)	4 (44.44%)	0	4 (44.44%)

CS: Corticosteroids.

Table 4. Binary logistic regression analysis to predict corticosteroid (CS) outcome (CS-response or CS-non-response), for the first course treated or any episode.

	B	SE	Wald	df	*p*	OR (95% CI)
Binary Logistic Regression to predict the first course treated						
Days from UC diagnosis to the beginning of CS	0.0007	0	5.976	1	0.015	1.001 (1 - 1.001)
Age at diagnosis (years)	0.0448	0.015	8.384	1	0.004	1.05 (1.02 - 1.08)
CRP (mg/L)	-0.0105	0.004	6.311	1	0.012	0.99 (0.98 - 1)
Constant	-1.5717	0.743	4.478	1	0.034	0.208
Binary Logistic Regression to predict any course treated						
Age at diagnosis (years)	0.0347	0.013	7.156	1	0.007	1.04 (1.01 - 1.06)
Days from UC diagnosis to CS-treatment	-0.000135	0.00006	3.989	1	0.045	0.99 (0.99 - 1)
Hemoglobin (g/dL)	0.1836	0.084	4.764	1	0.029	1.20 (1.02 - 1.42)
Constant	-27.068	1.278	4.484	1	0.034	0.067

CI: Confidence Interval; CRP: C Reactive Protein; CS: Corticosteroids; OR: Odds Ratio; SE: Standard Error; UC: Ulcerative Colitis.