Corticosteroid use in patients with inflammatory bowel diseases: A real-life sub-analysis of the Italian DICE study

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Dear Sir,

Despite the availability of novel treatments such as immunomodulators and biologic therapies, corticosteroids (CS) still play an important role in inducing remission of chronic inflammatory bowel diseases (IBDs) including Crohn's disease (CD) and ulcerative colitis (UC) [1]. Indeed, while steroids are routinely used in IBD for the management of acute flares, some patients receive prolonged exposure to these drugs and the long-term administration of CS is associated with several side-effects and a lack of efficacy in maintaining remission [2,3]. Consequently, current guidelines for the treatment of IBD do not recommend the use of CS as maintenance treatment[4] and recommend to avoid prolonged use of CS and consider regular evaluation of CS use as an indicator of quality of care [5].

Despite the availability of guidelines on CS use, current literature evaluating prolonged steroid exposure in IBD is limited and no national IBD registry exists in Italy. To address this, the aim of the DICE (Determinants, Incidence, and consequences of Corticosteroid Excess in IBD) study was to describe the patterns of CS exposure in IBD patients, using a bespoke online monitoring tool.

DICE was a multi-country, cross-sectional retrospective survey and data were collected anonymously during outpatient visit via the Steroid Assessment Tool (SAT) [6] from July to November 2021. The present sub-analysis provides results from Italy. Ethics Committee approval was obtained for all 4 Italian sites. Inclusion criteria were adult outpatients diagnosed with IBD for >1 year according to ECCO criteria [4].

Outcomes included CS exposure and CS excess within the past 12 months. CS excess was defined as any of the following: ≥1 CS course in the last 12 months, CS course of ≥3 months or the inability to reduce CS below the equivalent of 10 mg/day

prednisolone or 3 mg/day budesonide within 3 months of starting CS without IBD recurrence or disease relapse within 3 months of CS cessation according to international guidelines [4,7]. Patients were excluded if diagnosed with suspected but not yet confirmed IBD, post-colectomy UC patients with no evidence for CD, patients <18 years old, use of investigational products and enrolled in clinical studies, solid organ transplantation, haemolytic anaemia, and the presence of current infection or any other inflammatory/autoimmune disease.

SAT is an online tool specific for monitoring steroid use in IBD patients according to ECCO guidelines[4] and contains 8 questions related to disease characteristics and treatment (Supplementary Material S1). The application can register the diagnosis of the patient, severity of the disease at the last evaluation, previous and current treatment and the use of CS in the past 12 months. If the patient received CS in the past year it can also be registered how many courses of steroids the patient has received, if bone-protection medication was prescribed, the longest duration of steroid use (in months), if it was possible to reduce the dose of steroids within 3 months of starting the treatment without recurrent disease, and if there was a relapse of the disease within 3 months of stopping steroids. The online survey was brief and data on age, sex, and disease duration were not included. Data on treatment and steroid use were presented as frequency and percentage and group comparisons of outcomes were performed using Fisher's exact test.

In this cross-sectional observational study in Italy, 360 patients were enrolled across 4 sites; 174 (48%) patients were diagnosed with UC and 176 (49%) with CD. Ten (2.8%) patients were diagnosed with undifferentiated IBD and excluded from the present analysis. Approximately half of patients presented with active disease

(92/176; 52% for CD and 82/174; 47% for UC) and 49/92 (53.3%) CD patients and 47/82 (57.3%) of UC patients presented with moderate-to-severe disease.

A summary of current and previous (non-steroidal) treatment is presented in Table 1. While the majority of patients were currently receiving 5-ASA for at least 3 months (N=218; 62.3%), a higher proportion of patients with UC (N=155; 89.1%) received 5-ASA treatment compared to CD (N=63; 35.8%; p<0.0001). Slight differences in the frequency of patients treated with biological therapies were observed, with a higher proportion of patients with CD treated with an anti-TNF agent or anti-IL-12/23 agent compared to patients with UC (Table 1). However, most patients (~80-90%) were never treated with any novel biological agents such as anti-integrin, anti-IL-12/23, or JAK inhibitors.

With regards to CS use, a similar proportion of CD and UC patients (N=51/176; 29% and N=54/174; 31%, respectively) were treated with oral CS in the previous 12 months. While a higher proportion of patients with CD received just 1 course of CS in the previous 12 months (N=40/51; 78% vs. 31/54; 57%, p=0.024), a higher number of UC patients received 2 or more courses of CS compared with CD patients (Figure 1A). Among IBD patients treated with CS, the longest duration of steroid use during a single course was 2 to 4 months, with no discernible differences among the two patient groups (Figure 1B)

Of patients treated with CS (N=105), only 32/51 (63%) of patients with CD and 30/54 (56%) of patients with UC were able to reduce CS below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within 3 months, without disease relapse (Figure 1C). Patients with CD also experienced a lower rate of relapse within 3 months after CS withdrawal, compared to UC patients (16% vs. 30%; p=0.0005). CS dependency or excess was experienced in 42/54 (78%) of

patients with UC compared to 24/51 (47%) of patients with CD, this difference attaining statistical significance (p=0.0013). Among patients receiving CS in the previous 12 months, bone protective medication was given to 36/51 (71%) and 40/54 (74.1%) of UC and CD patients, respectively.

Results from this cross-sectional survey highlight a notable CS use in IBD patients in Italy. Our findings reveal that 30% (105/350) of all IBD patients were treated with oral CS, with an excess rate of 18.9% (66/350); higher rates observed in UC (24.1%; 42/174) compared to CD patients (13.6%; 24/176; p=0.014).

Our results corroborate with findings from other studies performed in the UK[2,8] and Romania[9].

Two large multi-centre audits by Selinger and colleagues evaluated excess steroid use in the UK[2,8]. In the first audit, including 1,176 IBD patients, CS use was observed in 30% of patients and 14.9% had steroid dependency or excess, similar to values that we observed in Italy. A second audit including 2,385 patients with IBD by this same group revealed similar rates (28% for CS use and 14.8% for CS excess)[8].

A similar study from Romania by Goran et al., evaluated CS use in 44 IBD patients in 2019 and in 84 patients in 2020[9]. In 2019, CS use was 34% and decreased to 25% in 2020 and steroid excess was 20.4% in 2019 and was observed to decrease to 5.95% in 2020. Bone protection medication was prescribed in only 6.6% of patients treated with CS in 2019, but a significant increase to 95% in 2020 was observed[9], similar to values also observed in our Italian cohort (72.4%).

A similar reduction in steroid use (from 30% to 23.8%) and excess (from 13.8% to 11.5%) was also observed by Selinger and colleagues in their follow-up analysis where interventional sites made changes following initial audit findings[8].

Corroborating findings from these studies, we also noted that a higher proportion of UC patients compared to CD patients experienced CS excess.

Besides the level of CS exposure highlighted in this cohort, our findings also reveal a notable lack of biological therapy for the treatment of IBD. Although approximately half of patients had previously been treated with an anti-TNF agent (~20% currently receiving anti-TNF), between 80-90% of patients had never been treated with any novel biological agents such as anti-integrin, anti-IL-12/23, or JAK inhibitors despite over half of patients having moderate-to-severe disease.

In this sub-analysis of the multicounty DICE study, we observed a clinically significant level of steroid exposure in our IBD cohort in Italy (approximately one-third of patients, regardless of disease type) in the past 12 months. A higher proportion of patients with UC were treated with more courses of CS, relapsed after CS reduction, and were CS dependent compared to CD patients, as expected in a disease with a higher inflammatory burden. The longitudinal monitoring of steroid use will help raise awareness of this problem in this setting in addition to providing tools to improve in the therapeutic management of these patients.

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Author contribution

F.S.C., D.G.R., M.M. and A.V. participated in the collection of patient data. L.G. and P.M. contributed to data analysis. All authors participated in the preparation of the manuscript and reviewed the final version prior to submission.

Competing interests

Francesco Simone Conforti has nothing to disclose. Davide Giuseppe Ribaldone discloses lecture fees and participation at Advisory Board for Janssen-Cilag, Takeda, Galapagos, Biogen. Anna Viola has received lecture fees from Pfizer. Mauro Mastronardi has received lectures fees and advisory board for Galapagos, Takeda, Pfizer. Lorenzo Gemignani, Paride Maddalena are AbbVie employees and may own AbbVie stocks/options.

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Figure legend

Figure 1. Oral CS use in the previous 12 months in UC and CD patients. A) Frequency of patients taking different course of CS in the previous 12 months. B) Longest duration of a single course of CS in the previous 12 months. D) Ability of patients to reduce or stop CS.