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Differences in the Adverse Event Burden of Corticosteroid Use in Inflammatory Bowel Disease as Reported Between Adverse Event Reporting Systems and a Patient Questionnaire

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KEYWORDS: Epidemiology; quality of life; socio-economical and psychological endpoints

ABSTRACT

Background and Aims: Corticosteroids are widely used in managing inflammatory bowel disease (IBD). While adverse events (AEs) of cortico-steroids are well recognized, current understanding of corticosteroid-related AE burden in IBD remains incomplete.

Methods: AE reports for prednisone/prednisolone and budesonide were extracted from the Food and Drug Administration Adverse Event Reporting System (FAERS) and VigiBase databases. Total and

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frequently reported AEs were tabulated, and AEs of special interest were compared with reports for all drugs using proportional reporting ratio criteria. Database reports were compared with AEs reported in a patient survey capturing corticosteroid exposure and AE recall.

Results: In FAERS and VigiBase, 344 140 and 42 836 AEs were reported, respectively, in patients with IBD; among these, 10 157 (3.0%) and 11 391 (26.6%), respectively, were related to prednisone/prednisolone or budesonide. AEs associated with corticosteroid use in IBD increased over time. Adrenal insufficiency, Cushingoid complications, osteonecrosis, osteoporosis, diabetes, and pancreatitis were disproportionately reported for corticosteroids. Among 9229 patients who responded to the survey, 6434 (69.7%) reported corticosteroid exposure. AEs were more frequently recalled by patients exposed to prednisone (61.9%) vs budesonide (274%; $p = 0.0001$). The most commonly recalled AEs differed from those reported in the pharmacovigilance databases and included weight gain, sleep problems, mood disturbance, and skin changes. Younger patients and those with mental health disorders were more likely to recall suicidal thoughts/attempts.

Conclusions: Adverse events associated with IBD-related corticosteroid use were frequent. Patients reported AEs affecting quality of life, while clinicians disproportionately reported AEs based on objective diagnostic criteria.

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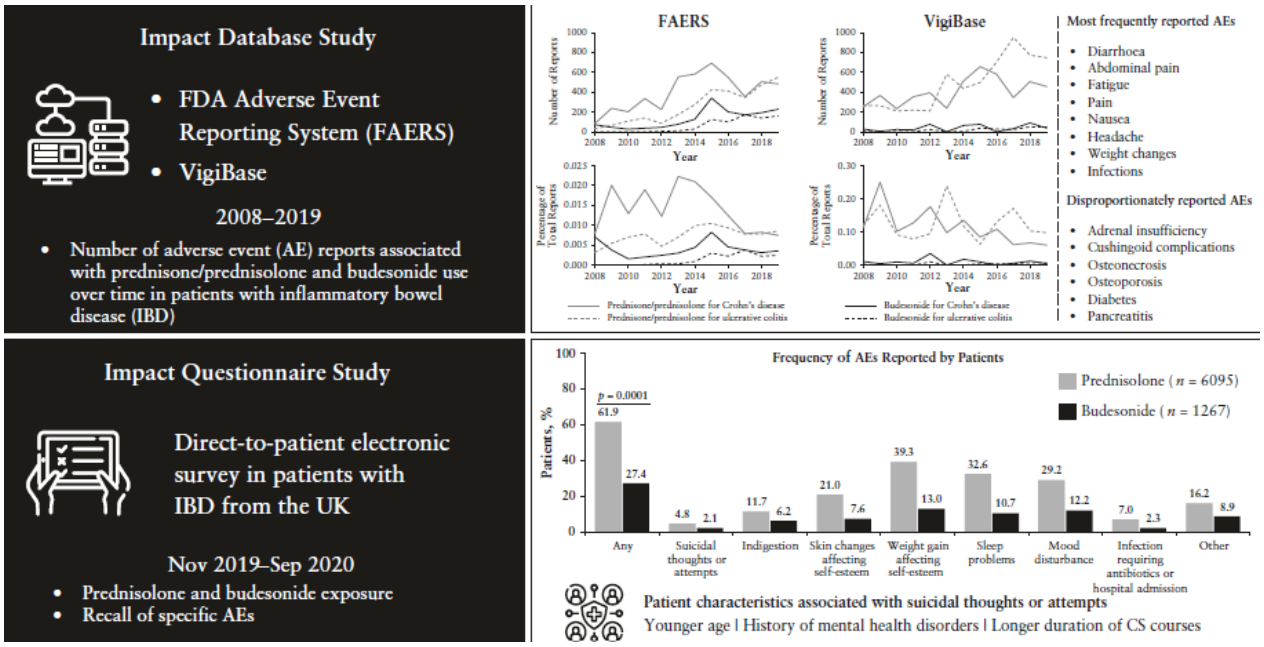
GRAPHICAL ABSTRACT

Adverse events associated with IBD-related corticosteroid (CS) use were frequent and differed substantially between pharmacovigilance databases and a patient questionnaire



1. Introduction

Due to their potent anti-inflammatory properties, corticosteroids have been widely used in treating inflammatory bowel disease (IBD), which encompasses both Crohn's disease (CD) and ulcerative colitis (UC).[1] Corticosteroids can work effectively and rapidly in alleviating patients' symptoms during disease flares, improving patient comfort and providing short- term disease control.[1,2] However, corticosteroids do not provide long-term benefits and are associated with toxicities and increased mortality, complications that are particularly concerning given the chronic nature of IBD.[3,4] Due to the limitations and risks associated with corticosteroid use, current guidelines recommend using a corticosteroid-sparing strategy, with the ultimate goal of maintaining corticosteroid-free remission and improving patient quality of life.[5-9]

Despite these recommendations, corticosteroids are routinely overused in the management of

IBD.[10,11] In a study that assessed corticosteroid use in a large cohort of outpatients with IBD, approximately 15% of patients received corticosteroids above guideline recommendations.[11] Patients who receive corticosteroids in excess are more likely to be hospitalized for IBD and infections and are more likely to receive prescriptions for antibiotics than patients who are not exposed to corticosteroids.[12]

While the safety profile of corticosteroids is well characterized, studies reporting AEs related to corticosteroid exposure are typically based on studies in diseases other than IBD (eg, rheumatology and asthma) where low doses of corticosteroids are used for typically long durations, compared with the higher dose and shorter exposures commonly observed in IBD treatment.[13] Therefore, there exists a knowledge gap in the safety of corticosteroid use in patients with IBD.[1] Furthermore, it is important to recognize that patients and healthcare providers (HCPs) may view corticosteroids differently.[14] AEs such as osteoporosis, hyperglycemia and in-creased susceptibility to infections are concerns well known to HCPs and may, therefore, be more frequently reported. Conversely, patients may perceive other AEs to be of greater concern, which may not be systematically captured and thus remain underappreciated.[14]

The Determinants, Incidence, and Consequences of Corticosteroid Excess (DICE) study is a group of 4 studies designed to assess the impact and epidemiology of corticosteroid use in patients with IBD. This report focuses on 2 of these 4 studies: the impact database and impact questionnaire studies. The impact database study aimed to provide a global picture of reported AEs associated with corticosteroid use in patients with IBD through a retrospective examination of data from 2 large spontaneous reporting systems (SRS), which contain reports from HCPs, patients, and manufacturers.[15] The impact questionnaire study was a single-country analysis of electronic questionnaire results that aimed to define the patient-reported burden of corticosteroid use in IBD through recall of corticosteroid exposure and associated AEs. Patient recall of AEs has proven to be informative in other disease states, such as oncology,[16,17] and can help characterize the patient perspective.

In this report, we characterize the safety profile of corticosteroid use in patients with IBD and assess differences in the AE burden of corticosteroids between AEs reported in the databases (with a focus on CD and UC) and those reported in the patient questionnaire.

2. Materials and Methods

2.1. IMPACT DATABASE STUDY

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We examined AE reports in well-recognized SRS databases, specifically focusing on 2 databases, the US Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) and the World Health Organization's (WHO) global database of individual case safety reports (VigiBase).[18] These 2 databases were selected as they were available in English, provided detailed AE reports, and allowed researchers full access to data.

The FAERS database is an SRS data source that contains AE reports, medication error reports, and product quality complaints resulting in AEs that were submitted to the US FDA.[15] VigiBase, which is developed and maintained by the Uppsala Monitoring Centre, includes reported potential AEs of medicinal products and contains over 19 million unique case reports of suspected AEs of medicines submitted by member countries of the WHO Program for International Drug Monitoring.[19] The drugs recorded on the AE reports were coded according to WHODrug and the Medical Dictionary for Regulatory Activities (MedDRA; version based on the version at the time of the reported event). Reports in VigiBase come from a variety of sources, and the probability that the suspected AE is drug related is not the same in all cases. Information in this report does not represent the opinion of the Uppsala Monitoring Centre or the WHO. Both the FAERS and VigiBase SRS databases conform to standards for the collection of information on AEs. We used data from the FAERS and VigiBase databases to examine AE reports associated with corticosteroid use in patients with IBD (CD or UC).

2.1.1. **Sample selection**

Reports of AEs associated with prednisone, prednisolone or budesonide use from 2008-2019[20] were extracted. As prednisone is a prodrug for prednisolone, AEs associated with prednisone and prednisolone were pooled for analysis. AE reports for all other drugs were also extracted for comparison.

2.1.2. Analysis

Total counts of AE reports associated with prednisone/prednisolone or budesonide use to treat CD or UC were tabulated as total counts by year and also expressed as a percentage of all drug reports. The 15 most frequently reported AE terms for each drug in patients with CD and UC were summarized. Adverse event terms reflecting the primary indication for prescribing corticosteroids (ie, CD or UC) were excluded from the analysis of most frequently reported AEs at the discretion of medical experts.

After an initial review of the SRS databases, the incidence of adverse events of special interest (AESI) was quantified for prednisone/prednisolone or budesonide therapy and all other drugs. These AESIs

included osteonecrosis, hyponatremia, hematopoietic cytopenias, diabetes, adrenal insufficiency, pancreatitis, Cushingoid symptoms, glaucoma, cataract, osteoporosis, and psychiatric morbidity.[21] The association of AESIs with corticosteroid therapy was assessed using the proportional reporting ratio (PRR) criteria. The PRR is a statistical measure that is used to identify disproportionate number of AE reports associated with corticosteroids compared with all other drugs in the databases. The PRR is a data mining algorithm that is widely used in SRS databases to detect signals of disproportionate reporting.[22,23] Disproportionate reporting signals were indicated by PRR ≥ 2, the lower bound of the PRR confidence ≥ 1, associated $x^2 \geq 4$, and the number of events in each treatment group ≥ 3.[24,25] The PRR and its accompanying criteria for detecting disproportionality are not specific to any therapeutic area or AE being analyzed. There is no further consideration to data sparsity beyond the criteria described when applying this data mining algorithm.

2.2.Impact questionnaire study

2.2.1. DATA SOURCE

The impact questionnaire study was a single-country, retrospective analysis of an electronic survey of patients with IBD enrolled in the UK IBD BioResource, which is a national platform designed to advance research in CD and UC.[26] The IBD BioResource comprises patients with a confirmed diagnosis of IBD who are enrolled at >100 active National Health Service hospitals across the UK.

2.2.2. DATA COLLECTION

All patients registered in the UK IBD BioResource were invited to complete an electronic survey. To reduce participation bias, the survey was a component of an annual questionnaire sent as part of routine participant follow-up. Questions related to corticosteroid use and experience formed a small component of the overall questionnaire, and no mention of corticosteroids was made in the survey invitation or associated materials. Study data were collected between November 2019 and September 2020 and were managed using Research Electronic Data Capture (REDCap) tools hosted at the IBD BioResource.[27,28]

2.2.3. DATA CAPTURED BY THE QUESTIONNAIRE

Data captured by the impact questionnaire included patient demographics and disease characteristics, patient re-call of corticosteroid exposure and patient recall of specific AEs (Supplementary Figure S1). The questionnaire included questions about patient recollection of specific AEs associated with oral prednisolone and oral budesonide. Specific AEs were selected by a small focus group of patients who

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had prior corticosteroid exposure and included those AEs that the group believed may negatively affect patients' lives. The final list was chosen by consensus among the group and comprised suicidal thoughts or attempts, indigestion, skin changes that affected self-esteem, weight gain that affected self-esteem, sleep problems, mood disturbance (eg, anxiety, depression) and infection requiring antibiotics and/or hospital admission. In the questionnaire, patients could also select 'other' and enter free text.

2.2.4. STATISTICAL ANALYSIS

Baseline demographics and disease characteristics, corticosteroid exposure and frequency of recalled AEs were summarized by descriptive statistics. Associations between occurrences of corticosteroid-related AEs with patient characteristics were assessed in contingency tables by calculating odds ratios (ORs) with 95% CIs. For this analysis, we initially conducted univariate logistic regressions for each available variable, which included age, gender, diagnosis, CD behavior, UC extent, smoking status, number of prednisolone and budesonide courses received, duration of prednisolone and budesonide courses, history of IBD surgery, presence of stoma, and presence of mental health disorders. We selected variables yielding p values < 0.01 in the univariate logistic regression analyses and included these in several stepwise logistic regression analyses. The final regression models were chosen based on the lowest Akaike information criterion (AIC). The final model for prednisolone included prednisolone course duration, gender, presence of mental health disorders, and age; the final model for budesonide included gender and age. Correlations between patient-recalled AEs were also assessed.

3. Results

3.1. IMPACT DATABASE STUDY

From 2008 to 2019, a total of 420 913 all-cause AEs for prednisone/prednisolone and 33 215 all-cause AEs for budesonide were reported in the FAERS database, and 1 103 988 and 15 636 AEs were reported for prednisone/prednisolone and budesonide, respectively, in VigiBase. In the same period, a total of 344 140 AEs were reported in the FAERS database among patients with IBD; of these, 2.3% (n = 7870) and 0.7% (n = 2287) were associated with prednisone/prednisolone and budesonide use, respectively. In VigiBase, 42 836 AEs were reported in patients with IBD; of these, 25.1% (n = 10 731) and 1.5% (n = 660) were associated with prednisone/prednisolone and budesonide use, respectively.

Demographics of patients with IBD and reports of AEs for prednisone/prednisolone or budesonide in the FAERS and VigiBase databases are presented in Supplementary Tables 1 and 2. In both databases, most patients were aged 18-64 years. In the FAERS database, most reports of AEs occurred in female patients, while in VigiBase, reports were balanced by sex.

In the FAERS database, AE reports related to prednisone/ prednisolone and budesonide use in CD and UC increased significantly over time from 2008 to 2019 ($p < 0.05$); when expressed as a percentage of all reports, significant upward trends were observed only in AE reports related to prednisone/prednisolone and budesonide use in UC ($p < 0.05$; Figure 1 and Supplementary Figure S2). In VigiBase, AE reports related to prednisone/prednisolone use in CD and UC and budesonide use in UC increased significantly over time from 2008 to 2019 ($p < 0.05$); when expressed as a percentage of all reports, a significant downward trend was observed in the number of AE reports related to prednisone/prednisolone use in CD ($p < 0.05$).

Figure 1 *Total number of reports over time for corticosteroid use in inflammatory bowel disease from the (A) FAERS database and (B) VigiBase, and as a percentage of reports based on total report count per year from the (C) FAERS database and (D) VigiBase. Percentages of reports were calculated by dividing the total number of reports for adverse events due to corticosteroids taken for inflammatory bowel disease by the total number of reports in each database. Time of data retrieval: FAERS, November 11, 2020; VigiBase, November 26, 2021. CD, Crohn's disease; FAERS, FDA Adverse Event Reporting System; UC, ulcerative colitis.*

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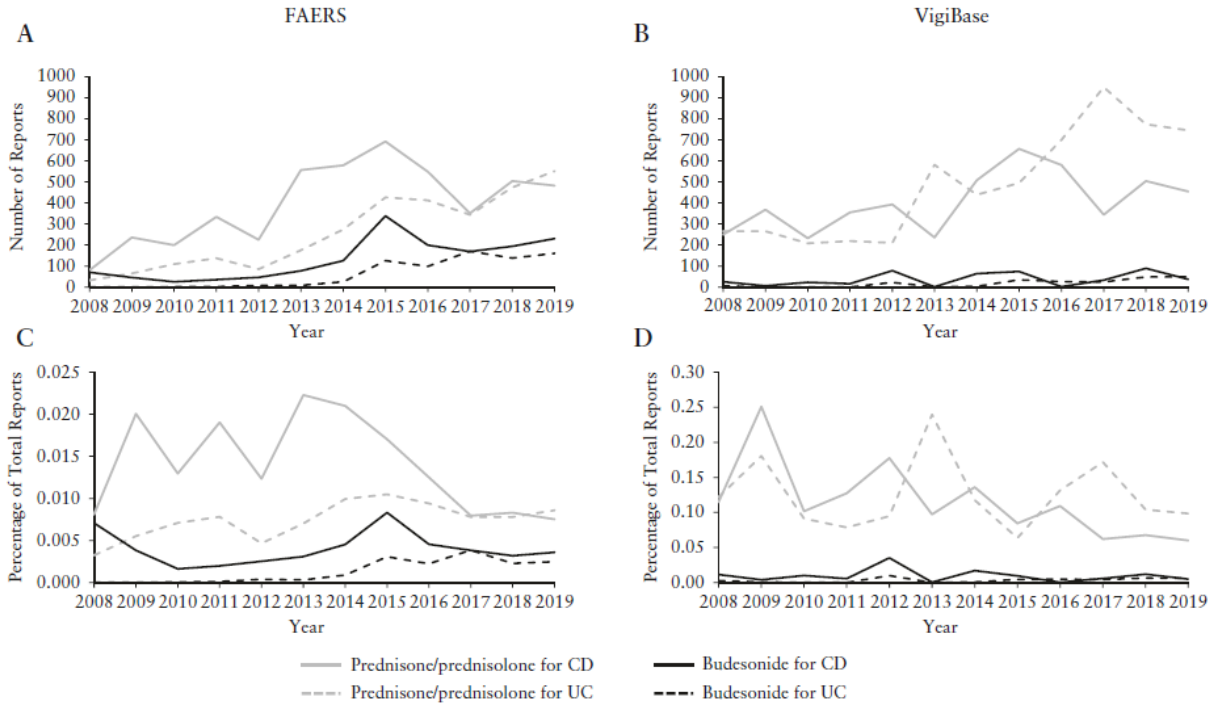


In the FAERS and VigiBase databases, IBD-related AEs (eg, abdominal pain, diarrhoea, nausea and fatigue) were common (Supplementary Figures S3 and S4). To test whether specific AEs of concern were reported more frequently for prednisone/prednisolone and budesonide than for other drugs in the databases, PRRs were calculated for AESIs based on frequency of reports for specific AEs associated with corticosteroids compared with reports of the same AESIs for all other drugs in the databases. Across both databases, AESIs reported more frequently in patients exposed to prednisone/ prednisolone vs all other drugs included adrenal insufficiency, Cushingoid complications, osteonecrosis, osteoporosis, and pancreatitis (Figure 2). For patients exposed to budesonide, adrenal insufficiency, Cushingoid complications, diabetes, and osteoporosis were again disproportionately reported.

3.1.1. Impact questionnaire study

Between November 2019 and September 2020, questionnaires were sent to 18 900 patients from the UK IBD BioResource. Among the 9229 (48.8%) patients who returned questionnaires, 47.7% were diagnosed with CD and 52.3% were diagnosed with UC or unclassified IBD (Table 1). Overall, 69.7% of patients reported exposure to corticosteroids since diagnosed with IBD, with 66.0% reporting exposure to prednisolone and 13.7% reporting exposure to budesonide (Supplementary Table S3). Among patients

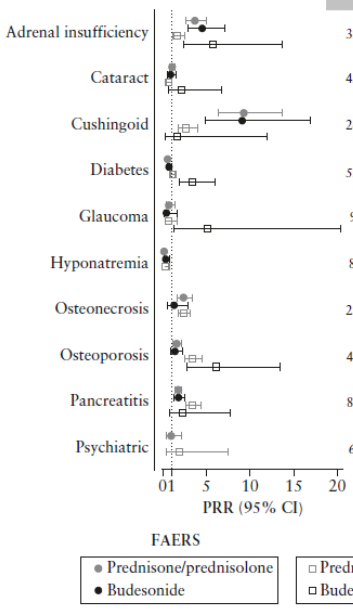
who recalled exposure to prednisolone, 31.4% reported receiving at least 1 course longer than 12 weeks in duration, while no patients who recalled exposure to budesonide reported receiving a course longer than 12 weeks in length.

Table 1 *Demographics and disease characteristics of patients who completed the impact questionnaire.*

Characteristic	Patients N = 9229
Age, years	
16–49	3662 (39.7)
50–60	3773 (40.9)
≥70	1794 (19.4)
Sex, male	4202 (45.5)
Smoking status	
Current	540 (5.9)
Former	3465 (37.5)
Type and behavior/extent of IBD[a]	
Crohn's disease	4405 (47.7)
Nonstricturing, nonpenetrating	2587 (58.7)
Stricturing	1048 (23.8)
Penetrating	496 (11.3)
Ulcerative colitis or unclassified IBD	4824 (52.3)
Proctitis	56 (1.2)
Left-sided	227 (4.8)
Extensive	4104 (87.2)
Disease duration, years, median (IQR)	14 (8–24)
History of IBD-related surgery[b]	2087 (22.6)
Stoma	334 (3.6)
Mental health disorders	139 (1.5)

Data are presented as patients, *n* (%) unless otherwise specified.
[a]Behavior/extent percentages based on the number of patients with each IBD type.
[b]Any surgery for IBD (perianal or abdominal).
Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range.

Figure 2 *Proportional reporting ratios for adverse events of special interest reported to the FAERS database and VigiBase for prednisone/prednisolone and budesonide vs all other drugs. PRR signal indicated by values in bold text. PRRs were not calculated for adverse events with no reports for the drug of interest. Time of data retrieval: FAERS, November 11, 2020; VigiBase, November 26, 2021. FAERS, FDA Adverse Event Reporting System; N/A, not applicable; PRR, proportional reporting ratio.*



	FAERS						VigiBase					
	Prednisone/prednisolone N = 7870	Other drugs N = 37 438 241		Budesonide N = 2287	Other drugs N = 37 823 072		Prednisone/prednisolone N = 10 696	Other drugs N = 4 520 090		Budesonide N = 660	Other drugs N = 5 064 266	
	n (%)	*n* (%)	PRR (95% CI)	*n* (%)	*n* (%)	PRR (95% CI)	*n* (%)	*n* (%)	PRR (95% CI)	*n* (%)	*n* (%)	PRR (95% CI)
Adrenal insufficiency	39 (0.5)	50 282 (0.1)	**3.69 (2.70, 5.05)**	18 (0.6)	52 032 (0.1)	**4.52 (2.85, 7.16)**	23 (0.2)	5699 (0.1)	1.70 (1.13, 2.57)	5 (0.8)	6707 (0.1)	**5.72 (2.39, 13.70)**
Cataract	45 (0.6)	198 787 (0.5)	1.08 (0.80, 1.44)	14 (0.5)	202 082 (5.0)	0.90 (05.4, 1.53)	14 (0.1)	9187 (0.2)	0.64 (0.38, 1.09)	3 (0.5)	10 490 (0.2)	2.19 (0.71, 6.79)
Cushingoid	26 (0.3)	13 334 (0.0)	**9.28 (6.32, 13.62)**	10 (0.3)	14 372 (0.0)	**9.09 (4.89, 16.88)**	23 (0.2)	3644 (0.1)	**2.67 (1.77, 4.02)**	1 (0.2)	4576 (0.1)	1.68 (0.24, 11.89)
Diabetes	59 (0.7)	501 392 (1.3)	0.56 (0.43, 0.72)	28 (1.0)	508 304 (1.3)	0.72 (0.50, 1.04)	56 (0.5)	21 014 (0.5)	1.13 (0.87, 1.46)	11 (1.7)	25 151 (0.5)	**3.35 (1.87, 6.03)**
Glaucoma	9 (0.1)	60 193 (0.2)	0.71 (0.37, 1.37)	2 (0.1)	61 133 (0.2)	0.43 (0.11, 1.71)	4 (0.0)	2613 (0.1)	0.65 (0.24, 1.72)	2 (0.3)	3008 (0.1)	5.10 (1.28, 20.37)
Hyponatremia	8 (0.1)	221 012 (0.6)	0.17 (0.09, 0.34)	6 (0.2)	223 055 (0.6)	0.35 (0.16, 0.78)	6 (0.1)	7531 (0.2)	0.34 (0.15, 0.75)	0	7981 (0.2)	NA
Osteonecrosis	29 (0.4)	57 940 (0.2)	**2.38 (1.66, 3.42)**	6 (0.2)	59 911 (0.2)	1.31 (0.59, 2.91)	45 (0.4)	7985 (0.2)	**2.38 (1.78, 3.19)**	0	9825 (0.2)	NA
Osteoporosis	49 (0.6)	146 122 (0.4)	1.60 (1.21, 2.11)	16 (0.6)	149 575 (0.4)	1.40 (0.86, 2.28)	49 (0.5)	6140 (0.1)	**3.37 (2.55, 4.46)**	6 (0.9)	7570 (0.1)	**6.08 (2.74, 13.49)**
Pancreatitis	86 (1.1)	228 063 (0.6)	1.79 (1.45, 2.21)	32 (1.1)	230 406 (0.6)	1.81 (1.29, 2.56)	67 (0.6)	8252 (0.2)	**3.43 (2.70, 4.36)**	3 (0.5)	9208 (0.2)	2.30 (0.81, 7.73)
Psychiatric	6 (0.1)	29 303 (0.1)	0.97 (0.44, 2.17)	0	29 615 (0.1)	N/A	2 (0.0)	456 (0.0)	1.85 (0.46, 7.43)	0	526 (0.0)	NA

Significantly more patients who were exposed to prednisolone recalled selected AEs compared with those who were ex- posed to budesonide (61.9% vs 27.4%, $p = 0.0001$; Figure 3). The most commonly recalled AE was weight gain that affected self-esteem (prednisolone, 39.3%; budesonide, 13.0%). Other AEs recalled by patients exposed to prednisolone and budesonide included sleep problems (32.6% and 10.7%, respectively), mood disturbance (29.2% and 12.2%) and skin changes that affected self-esteem (21.0% vs 7.6%). Suicidal thoughts or attempts were reported by 4.8% and 2.1% of patients who received prednisolone and budesonide, respectively. Recalled AEs among patients who selected 'Other' (prednisolone, 16.2%; budesonide, 8.9%) and entered free text are visualized by frequency in Supplementary Figure S5. For both prednisolone and budesonide, the strongest correlations ($r > 0.4$) between AEs occurred between mood disturbance, sleep problems, and weight gain affecting self-

esteem (Supplementary Figure S6).

Patient characteristics associated with increased likelihood of reporting any AEs are presented in Figure 4. Female patients were significantly more likely to recall AEs associated with corticosteroid use compared with male patients (prednisolone, OR [95% CI] 2.20 [1.97, 2.53], $p < 0.001$; budesonide, OR [95% CI] 1.40 [1.09, 1.80], $p \leq 0.01$). Older patients were significantly less likely than younger patients to report AEs with corticosteroid use (prednisolone, OR [95% CI] 0.86 [0.85, 0.88], per 5-year increment; $p < 0.001$; budesonide, OR [95% CI] 0.95 [0.91, 0.99], per 5-year increment; $p \leq 0.05$). Patients were also significantly more likely to recall AEs associated with prednisolone if they had a history of mental health disorders (OR [95% CI] 2.30 [1.20, 4.13], $p \leq 0.01$) or received longer vs shorter durations of corticosteroid courses (OR [95% CI] 1.002 [1.001, 1.003], per week of treatment duration; $p < 0.001$). However, these factors were not associated with increased recall of AEs related to budesonide exposure.

Suicidal thoughts or attempted suicide was more likely to be reported by patients who had a history of mental health disorders (OR [95% CI] 1.96 [1.00, 4.83], $p \leq 0.05$) and less likely to have occurred among older vs younger patients (OR 95% CI] 0.92 [0.87, 0.96], per 5-year increment; $p < 0.001$; Figure 5).

4. Discussion

Results from the impact database and questionnaire studies provide insights into the corticosteroid burden as perceived by patients and as reported in pharmacovigilance databases. Our findings show that AEs patients perceive as meaningfully burdensome, largely those affecting quality of life, differed substantially from the AEs reported in the SRS databases. Approximately half of these AE reports from FAERS and VigiBase were reported by HCPs, which may suggest that HCP perspectives in IBD may not fully align with the patient experience.

The SRS databases showed an increase over time in the number of AE reports associated with corticosteroid use in IBD, which may reflect an increase in prescribing practices of corticosteroids and/or an increase in awareness and reporting of AEs attributable to corticosteroids. When expressed as a percentage of all reports, uptrends in AE reports were only observed in the FAERS database for prednisone/prednisolone and budesonide use in patients with UC. The frequency of all other AE reports for prednisone/prednisolone or budesonide, when expressed as a percentage of total reports, remained constant or decreased over time. Differences in results between CD and UC may be reflective of the more extensive introduction and use of biologic therapies for CD compared with UC, suggesting an increased awareness of the AE burden of corticosteroids.[29] Consequently, this awareness may have led to a decline

in corticosteroid use and a more vigilant approach to reporting AEs in patients with CD.

The types of frequently reported AEs in both SRS databases are consistent with the known safety profile of corticosteroids.[3] Cushingoid complications and adrenal insufficiency were common signals for both prednisone/prednisolone and budesonide. Despite the purported lower rates of systemic AEs associated with budesonide compared with other corticosteroids,[30] systemic AEs can occur with budesonide, particularly with long-term use.[31,32] While budesonide offers a better safety profile than prednisolone as shown by the patient questionnaire data, clinicians should still be mindful of potential systemic exposure with budesonide, which can lead to major AEs. However, the lack of a placebo comparator and uncertainty regarding the use of concomitant medications in our analyses preclude a definitive attribution of systemic AEs to budesonide.

While there is consensus between HCPs and patients to avoid excess corticosteroids, HCP and patient concerns about corticosteroids and rationale for reducing corticosteroid use may be different.[14] Weight gain is frequently reported in the SRS databases and is also the most common AE recalled by patients, with the important additional mention of negative impacts on patient self-esteem. However, the sleep and mental health effects commonly recalled by patients were not frequently reported in the SRS databases. This discrepancy may be partially explained by the breadth of MedDRA preferred terms that are associated with sleep or mental health effects or, more likely, by a lack of physician enquiry about and/or reporting of these AEs. AEs commonly associated with corticosteroid use (eg, adrenal insufficiency, Cushingoid complications, and osteoporosis) were disproportionately reported in the SRS databases but were not fully captured by the options in the impact questionnaire, which were prespecified by the patient focus group according to those outcomes believed to be of the most interest to and have the greatest impact on patients. However, many patients did report these AEs or related terms as free text when selecting the 'Other' category in the survey.

Differences in patient and HCP perspectives were further evidenced in a previous patient survey, which reported that more than 40% of patients with IBD expressed concern about the safety of corticosteroids and had declined corticosteroid treatment because of AEs. In comparison, only 27% of physicians reported concerns about corticosteroid use.[14] The reported differences may also reflect discrepancies between what patients and clinicians consider to be important AEs.

Patients who were young, female and had a history of mental health disorders recalled the highest frequency of corticosteroid-related AEs. Additionally, younger patients and those with a history of mental health disorders were more likely to experience suicidal thoughts or attempt suicide. IBD itself

is associated with an elevated risk of suicidal attempts and complete suicides, with the maximum risk for psychiatric morbidity observed during the initial year following diagnosis,[33] possibly due to the immense stress associated with a new chronic disease diagnosis and disruptions caused by clinical manifestations of the disease. The findings of elevated risk associated with prednisolone use are concerning considering the frequent use of corticosteroids in the treatment of IBD.[1] Notably, the highest use of corticosteroids, including excessive use, typically occurs in the first year following an IBD diagnosis.[34] The occurrence of a period of heightened exposure to drugs associated with suicidal behavior during this vulnerable period represents a potentially toxic combination.

Figure 3 *Frequency of selected adverse events reported by patients on the impact questionnaire.*

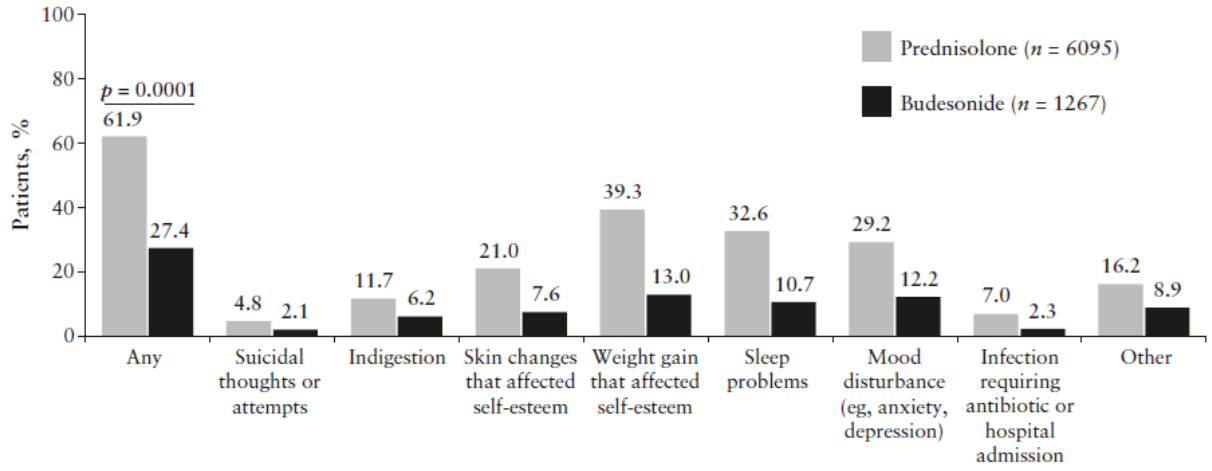


Figure 4 *Significant associations between patient characteristics and any recalled adverse events on the impact questionnaire. ***p < 0.001, **p ≤ 0.01, *p ≤ 0.05. CS, corticosteroid; NS, not significant.*

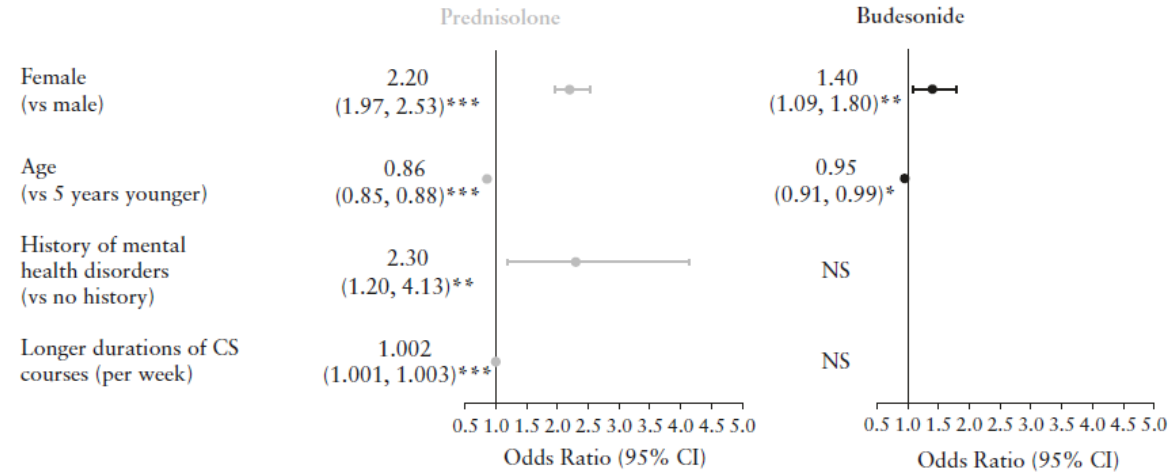
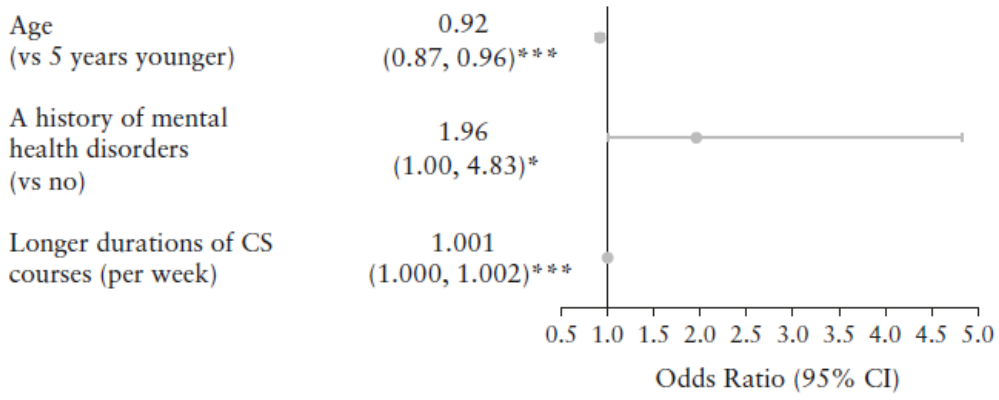


Figure 5 *Patient characteristics significantly associated with prednisolone use and recall of adverse events of suicidal thoughts or attempted suicide. ***p < 0.001, *p ≤ 0.05. CS, corticosteroid.*



Our findings underscore the importance of integrating patient-reported outcomes into the clinical management of patients with IBD who are receiving corticosteroids. This approach should include routine assessments of patient quality of life and mental health, especially considering the association between corticosteroids and suicidal thoughts or behavior in younger patients and those with a history of mental health disorders. Such evaluations should be part of a holistic approach to treatment management, aiming to reduce corticosteroid exposure where possible and tailoring clinical interventions to meet individual patient needs.

The primary limitation of these analyses is that they are retrospective and descriptive, and causality cannot be established. The impact database study may be limited by potential under- and/or over-reporting of AEs, reporting biases, missing, or inaccurate data and false causality attributions. It is also unknown how the total number of corticosteroid prescriptions changed over time. In addition, some AEs may be related to the clinical manifestations of IBD and not to corticosteroid use. Results of the impact questionnaire study are likewise limited by the need for patient recall and self- reporting and, therefore, a direct relationship between corticosteroid use and reported AEs cannot be established. To some extent, recall bias may have been mitigated by survey prompts to recall specific corticosteroid-related AEs in a standardized manner, while participation bias was avoided by having the corticosteroid questions embedded within a much larger electronic questionnaire that patients were asked to complete. Additionally, most AE reports in the impact data- base study originated from Europe and the United States, and only patients enrolled in the UK IBD BioResource were invited to complete the electronic survey. Consequently, the generalizability of our findings to other populations or regions may be limited.

Taken together, findings from these studies show that the most burdensome AEs recalled by patients differ from those frequently reported in the SRS databases. Results from both studies support limiting corticosteroid use to flare management and escalating other IBD treatments to reduce corticosteroid exposure. Additional consideration should be given to young, female patients and those with a history of mental health disorders before prescribing corticosteroids.

Conflict of Interest

E.A.S. has received speaker fees from AbbVie, Ferring, Janssen, and Takeda. Her current affiliation is with the King Fahad Specialist Hospital in Dammam, Saudia Arabia. E.L. has received educational and research grants from AbbVie, Fresenius- Kabi, Janssen, Pfizer, and Takeda; speaker fees from AbbVie, Bristol Myers Squibb, Celgene, Dr Falk Pharma, Ferring, Galapagos, Janssen, Pfizer, and Takeda; advisory board fees from AbbVie, Arena, Bristol Myers Squibb, Celgene, Ferring, Gilead-Galapagos, Janssen, Lilly, Pfizer, and Takeda; and consulting fees from AbbVie. B.B. has received consulting fees from AbbVie, Allergan, Arena, Biogen, Boehringer Ingelheim, Celgene, Ferring, Galapagos, Hexal, Hospira, Janssen, Movetis, MSD, Pfizer, Shield Therapeutics, Shire, Takeda, and UCB; speaker fees from AbbVie, Arena, Celltrion, Dr Falk Pharma, Ferring, Hoffman-LaRoche, Janssen, Merckle, MSD, Mundipharma, Pfizer, Shield Therapeutics, Takeda and UCB; and research grants from AbbVie, Ferring, Galapagos, Given Imaging, Janssen, Pfizer, Takeda, and UCB. K.B.G. has received grants from AbbVie, Celltrion, Galapagos, and Pfizer; consulting fees from AbbVie, Arena Pharmaceuticals, Galapagos, Gilead, ImmunicTherapeutics, Janssen, Pfizer, Samsung Bioepis, and Takeda; and speaker fees from AbbVie, Celltrion, Ferring, Janssen, Pfizer, Samsung Bioepis, Takeda, and Tillotts. G.C.P. has received unrestricted research grants from AbbVie and Takeda; consulting fees from AbbVie, BMS, Ferring, Galapagos, Janssen, Pfizer, Sorrisopharma, Takeda, and Tillotts; and speaker fees from AbbVie, Dr Falk Pharma, Ferring, Galapagos, Janssen, Pfizer, and Takeda. M.P. has received speaker fees from Janssen. He has received research support from Gilead and Pfizer for the IBD BioResource and is a member of the Crohn's & Colitis UK Research Advisory Group. C.S. has received unrestricted research grants from AbbVie, Janssen, and Warner Chilcott; consulting fees from AbbVie, Arena, Dr Falk Pharma, Fresenius Kabi, Galapagos, Janssen, Takeda, and Warner Chilcott; and speaker fees from AbbVie, Celltrion, Dr Falk Pharma, MSD, Pfizer, Takeda, and Warner Chilcott. M.M., M.L., and J.C. are employees of AbbVie and may hold AbbVie stock and/or stock options. T.F.-H. is a former employee of AbbVie and may hold AbbVie stock and/or stock options. She is a current employee of GlaxoSmithKline. T.R. has received research

support, education grants and/or speaker or consulting fees from AbbVie, Arena, Aslan, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Eli Lilly, Ferring, Galapagos, Gilead, GSK, Heptares, LabGenius, Janssen, MonteRosa, Mylan, MSD, Novartis, Numab, Pfizer, Roche, Sandoz, Takeda, UCB, and XAP therapeutics.

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Author Contributions

M.M., M.L., T.F.-H., and T.R. contributed to conception and design of the study. E.A.S., M.M., and M.L. acquired the data and conducted the statistical analysis. All authors contributed to data interpretation, drafting, and critical review of the manuscript. All authors approved the manuscript for publication.

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Conference Presentation

Part of this work was presented at the United European Gastroenterology (UEG) Week in October 2022 and European Crohn's and Colitis Organisation (ECCO) in July 2021.

Data Availability

AbbVie is committed to responsible data sharing regarding the studies we sponsor. This includes access to study protocols, analysis plans, and other information included in this manuscript. These materials can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal, statistical analysis plan (SAP), and execution of a data sharing agreement (DSA). Requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. These materials will be accessible for 12 months, with possible extensions considered. Data retrieved from the FAERS database are publicly available and can be accessed using the FAERS public dashboard

(https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard). Data from VigiBase and the impact questionnaire are not publicly available due to privacy restrictions. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/, then select “Home.”

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

References

1. Waljee AK, Wiitala WL, Govani S, *et al*. Corticosteroid use and complications in a US inflammatory bowel disease cohort. *PLoS One* 2016;**11**:e0158017.
2. Barrett K, Saxena S, Pollok R. Using corticosteroids appropriately in inflammatory bowel disease: a guide for primary care. *Br J Gen Pract* 2018;**68**:497-8.
3. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. *Otolaryngol Clin North Am* 2010;**43**:753-68.
4. Horita N, Miyazawa N, Morita S, *et al*. Evidence suggesting that oral corticosteroids increase mortality in stable chronic obstructive pulmonary disease. *Respir Res* 2014;**15**:37.
5. Harbord M, Eliakim R, Bettenworth D, *et al*.; European Crohn’s and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;**11**:769-84.
6. Lamb CA, Kennedy NA, Raine T, *et al*.; IBD Guidelines eDelphi Consensus Group. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;**68**:s1-s106.
7. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn’s disease in adults. *Am J Gastroenterol* 2018;**113**:481-517.
8. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol* 2019;**114**:384-413.
9. Torres J, Bonovas S, Doherty G, *et al*. ECCO guidelines on therapeutics in Crohn’s disease: medical treatment. *J Crohns Co- litis* 2020;**14**:4-22.
10. Selinger CP, Parkes GC, Bassi A, *et al*. A multi-centre audit of excess steroid use in 1176 patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**46**:964-73.
11. Selinger CP, Parkes GC, Bassi A, *et al*. Assessment of steroid use as a key performance indicator in inflammatory bowel disease-analysis of data from 2385 UK patients. *Aliment Pharmacol Ther* 2019;**50**:1009-18.
12. Rosiou K, Carbonell J, Dolby V, Monfared N, Raine T, Selinger CP. Sources of excess steroid prescriptions and

clinical adverse outcomes associated with steroid excess in patients with inflammatory bowel disease: the Leeds IBD steroids study. *Aliment Pharmacol Ther* 2022;**56**:501-9.

13. Yasir M, Goyal A, Sonthalia S. *Corticosteroid Adverse Effects*. In: Sonthalia S (ed.), *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
14. Rubin DT, Sninsky C, Siegmund B, *et al*. International perspectives on management of inflammatory bowel disease: opinion differences and similarities between patients and physicians from the IBD GAPPS survey. *Inflamm Bowel Dis* 2021;**27**:1942-53.
15. U.S. Food and Drug Administration. *FDA Adverse Event Reporting System (FAERS) Public Dashboard.* Silver Spring, MD; 2023. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse- event-reporting-system-faers/fda-adverse-event-reporting-system- faers-public-dashboard Accessed May 30, 2023.
16. Foltz AT, Gaines G, Gullatte M. Recalled side effects and self-care actions of patients receiving inpatient chemotherapy. *Oncol Nurs Forum* 1996;**23**:679-83.
17. Love RR, Leventhal H, Easterling DV, Nerenz DR. Side effects and emotional distress during cancer chemotherapy. *Cancer* 19 89;**63**:604-12.
18. Lindquist M. VigiBase, the WHO Global ICSR database system: basic facts. *Drug Inf J* 2008;**42**:409-19.
19. About VigiBase. Uppsala Monitoring Centre. https://who-umc.org/ vigibase/ Accessed May 30, 2023.
20. Raine T, Bokemeyer B, Finney-Hayward T, Munsaka M, Liu M, Louis E. P468 analysis of international spontaneous reporting system databases for safety of corticosteroids in inflammatory bowel disease: the determinants, incidence and consequences of corticosteroid excess (DICE)-impact study. *J Crohns Colitis* 2021;**15**:S458-9.
21. Timeus S, Hofmann R. P402 Systemic steroids vs. local acting steroids: relative risk for corticosteroid-related adverse events. *J Crohns Colitis* 2019;**13**:S309-S309.
22. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. *Clin Pharmacol Ther* 2013;**93**:539-46.
23. Jiao XF, Pu L, Lan S, *et al*. Adverse drug reaction signal detection methods in spontaneous reporting system: a systematic review. *Pharmacoepidemiol Drug Saf* 2024;**33**:e5768.
24. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Saf* 2001;**10**:483-6.
25. Cutroneo PM, Sartori D, Tuccori M, *et al*. Conducting and interpreting disproportionality analyses derived from spontaneous reporting systems. *Front Drug Saf Regul* 2024;**3**:1323057.
26. Parkes M; IBD BioResource Investigators. IBD BioResource: an open-access platform of 25 000 patients to accelerate research in Crohn's and colitis. *Gut* 2019;**68**:1537-40.
27. Harris PA, Taylor R, Minor BL, *et al*.; REDCap Consortium. The REDCap Consortium: building an international community of software platform partners. *J Biomed Inform* 2019;**95**:103208.

28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;**42**:377-81.
29. Targownik LE, Bernstein CN, Benchimol EI, *et al*. Trends in corticosteroid use during the era of biologic therapy: a population- based analysis. *Am J Gastroenterol* 2021;**116**:1284-93.
30. Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. *Gut* 1997;**41**:209-14.
31. Lichtenstein GR, Bengtsson B, Hapten-White L, Rutgeerts P. Oral budesonide for maintenance of remission of Crohn's disease: a pooled safety analysis. *Aliment Pharmacol Ther* 2009;**29**:643-53.
32. Tursi A, Giorgetti GM, Brandimarte G, Elisei W. Safety and effectiveness of long-term budesonide treatment in maintaining remission in patients with mild-to-moderate Crohn's disease. *Inflamm Bowel Dis* 2007;**13**:1184-6.
33. Ludvigsson JF, Olén O, Larsson H, *et al*. Association between inflammatory bowel disease and psychiatric morbidity and suicide: a Swedish nationwide population-based cohort study with sibling comparisons. *J Crohns Colitis* 2021;**15**:1824-36.
34. Raine T, Finney-Hayward T, Clark R, *et al*. P488 Trends in corticosteroid (CS) use over time and following diagnosis in patients with inflammatory bowel disease (IBD), using IBM® MarketScan®. *J Crohns Colitis* 2022;**16**:i454-i5.