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Withdrawal of corticosteroids in inflammatory bowel disease patients after dependency periods ranging from 2 to 45 years: a proposed method

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SUMMARY

Background
Even in the biologic era, corticosteroid dependency in IBD patients is common and causes a lot of morbidity, but methods of withdrawal are not well described.

Aim
To assess the effectiveness of a corticosteroid withdrawal method.

Methods
Twelve patients (10 men, 2 women; 6 ulcerative colitis, 6 Crohn's disease), median age 53.5 years (range 29–75) were included. IBD patients with quiescent disease refractory to conventional weaning were transitioned to oral dexamethasone, educated about symptoms of the corticosteroid withdrawal syndrome (CWS) and weaned under the supervision of an endocrinologist. When patients failed to wean despite a slow weaning pace and their IBD remaining quiescent, low dose synthetic ACTH stimulation testing was performed to assess for adrenal insufficiency. Multivariate analysis was performed to assess predictors of a slow wean.

Results
Median durations for disease and corticosteroid dependency were 21 (range 3–45) and 14 (range 2–45) years respectively. Ten patients (83%) were successfully weaned after a median follow-up from final wean of 38 months (range 5–73). Disease flares occurred in two patients, CWS in five and ACTH testing was performed in 10. Multivariate analysis showed that longer duration of corticosteroid use appeared to be associated with a slower wean ($P = 0.056$).

Conclusions
Corticosteroid withdrawal using this protocol had a high success rate and durable effect and was effective in patients with long-standing (up to 45 years) dependency. As symptoms of CWS mimic symptoms of IBD disease flares, gastroenterologists may have difficulty distinguishing them, which may be a contributory factor to the frequency of corticosteroid dependency in IBD patients.

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INTRODUCTION

Corticosteroid (CS) therapy in inflammatory bowel disease (IBD) represents a double-edged sword. On the one hand, it is effective at inducing remission in both Crohn's disease[1, 2] and ulcerative colitis[3] and is regarded by many as the treatment of choice. On the other hand, it has no role in maintaining remission[1, 2] and has many side effects, yet withdrawal of CS from patients whose disease is in remission is often difficult.[4] Many patients who respond to CS become dependent on therapy, with a return of symptoms when treatment is withdrawn.[5, 6] In the era of biologic therapy for IBD, many people will wonder whether chronic CS dependency is a real clinical issue anymore. Yet, a recent audit of IBD care in the UK highlighted that 46% of patients with Crohn's disease were receiving CS therapy for over 3 months.[7] Also, in a large cohort of 547 patients with Crohn's disease treated with infliximab, 29% of patients receiving CS at baseline were unable to stop them completely after 3 months.[8] Chronic CS dependency therefore remains a difficult clinical challenge.

Corticosteroid dependence among IBD patients is difficult to define precisely, but previous investigators have applied the term when a second relapse occurred during attempted CS withdrawal.[9] In a prospective study of CS treatment in 109 patients with Crohn's disease,[10] 36% of patients had developed dependency by 1 year.

Corticosteroids have many adverse effects which can affect virtually every physiological system. They may be particularly deleterious in IBD as they appear to be hazardous in patients with fistulizing disease, an abdominal mass or an abscess.[2] Because of these limitations, 'corticosteroid-sparing' effects of new treatments in IBD have become an important outcome measure in clinical trials.

The underlying aetiology of endocrine withdrawal syndromes is poorly understood.[11] For the corticosteroid withdrawal syndrome (CWS), four aspects are described: (1) relapse of the disease for which the drug was prescribed, (2) suppression of the hypothalamic-pituitary axis (HPA), (3) psychological dependence, (4) a non-specific withdrawal syndrome occurring despite normal circulating cortisol levels. The symptoms of CWS are lassitude (including anorexia, weight loss and fatigue), myalgia, diarrhoea, nausea and abdominal cramps (without vomiting) and headache.[11] A major challenge in the management of IBD patients is that these symptoms can mimic the symptoms of disease flares and hence careful clinical evaluation is required. If CWS is suspected, the dose of CS should remain unchanged and symptoms usually wane after approximately 3 days; if a flare of disease is suspected, CS dose escalation is usually required. The symptoms of adrenal insufficiency are similar to those of the CWS – differentiation from CWS is based on interpretation of adrenal stimulation testing results.

Exogenous CS suppress the HPA axis through a negative feedback mechanism that acts on the hypothalamus and pituitary gland. Activation of the HPA axis occurs during periods of inflammatory stress and is mediated in part by the pro-inflammatory cytokine interleukin-1,[12] a cytokine which is important in the pathogenesis of IBD.[13, 14] The process and outcomes of CS withdrawal may therefore depend on the underlying disease process.

For clinicians who wish to withdraw CS from dependent patients, there are very few published guidelines for reference. The standard protocol for CS withdrawal is over 30 years old and is not specific to IBD patients.[15] A PubMed search (using keywords 'corticosteroid withdrawal', 'Crohn's disease', 'ulcerative colitis' and 'inflammatory bowel disease' in November 2008) revealed no more recent publications. We herein describe the process and outcomes of patients with long-standing CS dependency attending a single gastroenterology practice who were weaned using a specific treatment protocol at a single endocrinology practice.

METHODS

Patients and study design

This was a retrospective study of consecutive patients with IBD and CS dependency attending a single gastroenterology practice with extensive experience in the management of patients with IBD. Patients were eligible for inclusion if they could not be successfully weaned by the gastroenterologist and required referral to an endocrinologist for weaning. The study period was from October 1998 (the year when this service first became available in the endocrinology practice consulted) to June 2006. For inclusion in the study, patients had to be in clinical remission from IBD. Corticosteroid withdrawal was undertaken to reduce the side effect burden from continued CS usage. Corticosteroid dependency was defined as continued usage

despite multiple attempts at weaning by a gastroenterologist at the practice using conventional methods of slow reductions in prednisone dosing. Patients were then referred to a single endocrinologist (JIM) for further evaluation. Patients were excluded from the study if they were not compliant with the withdrawal regimen.

Endocrine evaluation

Patients were transitioned from their current CS dosing regimen to an equivalent dose of dexamethasone as a twice daily (BID) regimen (0.75 dexamethasone = 5 prednisone = 5 prednisolone = 4 methylprednisone = 20 hydrocortisone = 25 cortisone acetate). They were provided with 0.5 mg tablets and dose reductions were generally performed at 1–4 week intervals, beginning with 0.25–0.5 mg decrements. At each office visit, CS withdrawal vs. active IBD was determined based on symptoms and examination. In addition, when adrenal insufficiency was suspected as potentially playing a role in a patient's failure to wean at the planned rate, stimulation testing (low dose ACTH) was performed.

Table 1. Determination of corticosteroid weaning times

	CWS	No CWS
Adrenal reserve	Moderate wean (2–3 months)	Rapid wean (1–2 months)
No adrenal reserve	Very slow wean (6–12 months)	Slow wean (3–6 months)

CWS, corticosteroid withdrawal syndrome.

Corticosteroid weaning times were determined based on symptoms and estimates of adrenal reserve deduced from stimulation testing (see below and Table 1). Once patients were at low doses approximating 0.5 mg BID or less, decrements were 0.125 to 0.25 mg every 3–14 days based on symptoms. Patients were repeatedly educated about the expected and typical symptoms of CWS (nausea, headache, fatigue, muscle pains and diarrhoea). They were instructed that these symptoms would occur shortly after each dose reduction, typically last 3 days and that following this period, they could reduce the dose further in the 3–7 day window after each dose decrement (Figure 1). They were explicitly told to 'plan' to experience these symptoms as above. Patients were instructed to call the endocrinologist with any symptoms beyond those described above, specifically, 'hitting a wall' or 'having no energy', low blood pressure, severe diarrhoea or abdominal pain, or inability to keep down the pills because of nausea and/or vomiting. In the weeks prior to complete discontinuation of CS, dosing regimens frequently included an every other day, every 3 days and twice weekly schedule. Patients were also allowed to 'chip' the pills to have 0.125 mg (one-fourth pill) reductions. Patients were informed that the CS dose reductions would be relatively greater and faster at the beginning and more subtle and slower towards the end.

Low dose (1 mcg) cosyntropin (Synthetic ACTH, Synacthen) stimulation testing was performed to detect subtle neuroendocrine recovery to help guide the pace of subsequent tapering and/or stopping of CS when it remained unclear whether further reductions would be possible. We interpreted an increase of ≤2 μg/dL as indicative of low adrenal reserve, an increase of >2

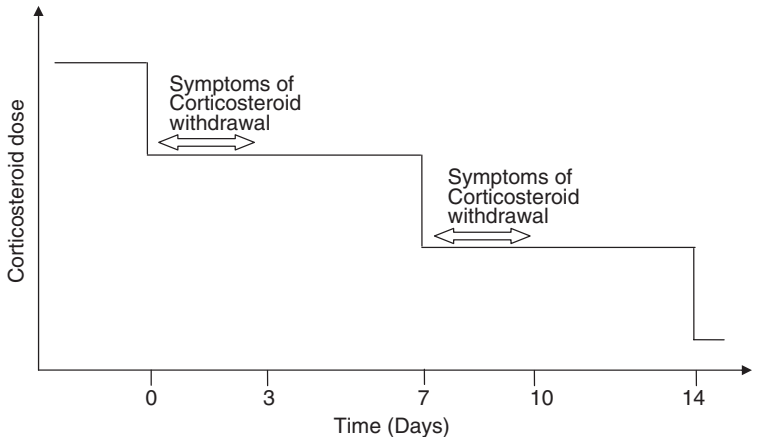


Figure 1. Schematic diagram to show process of corticosteroid dose reduction. Symptoms of the corticosteroid withdrawal syndrome typically occurred after dose reduction and lasted 3 days. If symptoms abated after this time, patients were instructed to reduce the dose further in the 3-7 day window after each dose reduction.

but <8 μg/dL indicative of moderate adrenal reserve, and an increase of >8 μg/dL indicative of intact adrenal function. Final office visits were scheduled 3–6 months following discontinuation of CS. Success was defined as withdrawal from CS after a minimum of 3 months' follow-up.

Data analysis

Patients and outcomes were characterized using descriptive statistics. Continuous variables were described by means and categorical variables by percentages. Linear regression was used to identify factors predictive of weaning time including age, gender, body mass index, drug dose, drug duration and 'drug dose times duration'. All data analysis was performed using STATA 9.1 (Stata Corp., College Station, TX, USA).

Study approval

Institutional review board approval was granted for this study.

RESULTS

Baseline characteristics

Fourteen patients were referred for CS withdrawal during the study period; two patients were excluded from the study because of non-adherence to the prescribed withdrawal regimen. Twelve patients were eligible for inclusion and are described here.

There were 10 men and 2 women, (6 ulcerative colitis, 6 Crohn's disease), with a median age of 53.5 years (range 29–75) and an average body mass index (BMI) of 23.6 (range 17.7–30.7) (Table 2). The median duration for disease and CS dependency was 21 (range 3–45) and 14 (range 2–45) years respectively, and the median daily dose of prednisone over this time period was 12.5 mg (range 5–22.5). Ten patients (83%) were successfully weaned (Table 2). Of these 10 patients, three required temporary retreatment with CS either for presumed IBD disease flares or other reasons, but had remained off CS by the end of the study period. Duration of follow-up from final CS usage was a median 38 months (range 5–73). The median weaning time in successful patients was 15 months (range 4–49) and median number of hospital visits was 8.5 (range 3–37).

Two patients were not weaned: one was suspected to have psychological dependence on CS and was lost to follow-up after three visits; the other developed an unknown autoimmune disease (suspected as Sjogren's syndrome/Sicca syndrome), which necessitated continued CS use.

Active disease

Two patients developed active inflammatory bowel disease during the withdrawal process (Figure 2). One patient (patient no. 2), a 75-year-old man with a 35-year history of Crohn's disease and multiple previous small bowel resections, required treatment with total parenteral nutrition. The other patient (patient no. 9), a 29-year-old woman with a 6-year history of ulcerative colitis, required treatment with intravenous ciclosporin. Both patients were successfully weaned following treatment of active disease. In addition, CS were recommenced or increased in two further patients for spurious flares of IBD.

Corticosteroid withdrawal syndrome

Symptoms of CWS occurred six times in five patients. The dose of CS was continued unchanged until symptoms had abated (Figure 2).

Cosyntropin testing

Low-dose cosyntropin testing was performed 14 times in 10 patients. The pace of subsequent tapering was based on results of these tests (Figure 2).

Multivariate analysis

Multivariate analysis did not show any statistically significant predictive factors for a slow wean (data not shown), including the average daily dose of CS ($P = 0.985$). However, longer duration of CS use was associated with a slower wean, although the results failed to reach standard levels of statistical significance ($P = 0.056$).

DISCUSSION

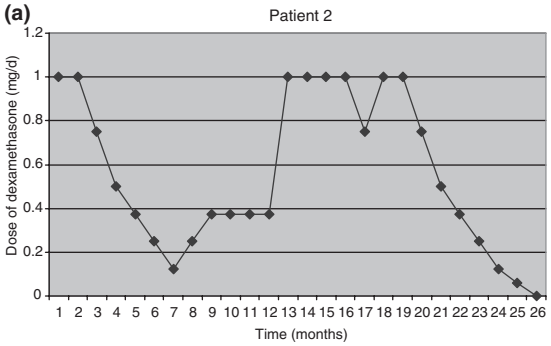
We found that withdrawal of CS in IBD patients who were dependent for as long as 45 years was possible using a method of slow dose reduction with oral dexamethasone under the supervision of an endocrinolo-

Table 2. Baseline details of study patients

Pt	Age	Gender	Year of diagnosis	IBD	Disease location	Previous Surgery	Other medications	BMI	Disease duration (years)	Dependency period (years)	Average prednisone dose (mg/day)	Weaning time (months)	Follow-up duration after final steroid course (months)	Weaning success?
1	75	M	1954	UC	Pancolitis	Left hemi-colectomy (LGD)	Data not available	25.0	45	45	13.5	32	43	Yes
2	75	M	1966	CD	Jejunoileitis, colitis	Multiple ileal and ileocolic resections	Antibiotics Infliximab	19.9	35	10	ACTH 240 units/week	26	39	Yes
3	59	M	1966	CD	Ileitis, perianal	Ileocolic resection ×4	MP	20.6	37	20	10.5	–	–	No
4	49	M	1971	CD	Jejunoileitis, colitis	Ileocolic resection ×3	Antibiotics MP Methotrexate Infliximab	23.2	34	13	12.5	11	15	Yes
5	54	M	1976	CD	Ileitis	Ileal resection ×2	MP Infliximab Adalimumab	17.7	25	21	11	49	31	Yes
6	48	M	1976	CD	Ileocolitis	Ileocolic resection	MP Infliximab	21.9	26	26	15	–	–	No
7	53	M	1982	UC	Left-sided colitis	TPC and IPAA	AZA Infliximab	30.7	17	17	12.5	41	48	Yes
8	54	M	1986	UC	Left-sided colitis	TPC and IPAA; pouch excision and end ileostomy	Antibiotics MP	27.1	17	15	5	18	37	Yes
9	29	F	1997	UC	Pancolitis	–	MP Cyclosporin	28.5	6	5	5	12	43	Yes
10	35	F	1998	CD	Jejunoileitis, colitis	–	Antibiotics MP	22.5	3	3	10	6	73	Yes
11	71	M	2002	UC	Procto sigmoiditis	–	MP Infliximab	25.3	4	4	22.5	7	5	Yes
12	48	M	2003	UC	Left-sided colitis	TPC and IPAA	MP Cyclosporin Infliximab	21.3	4	2	20	4	13	Yes
Mean/ Median	53.5							23.6	21	14	12.5	15	38	

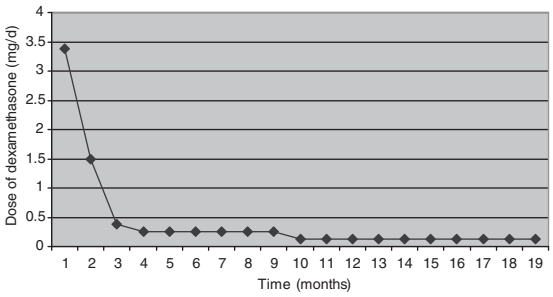
BMI, body mass index; LGD, low grade dysplasia; TPC and IPAA, total proctocolectomy and ileal pouch-anal anastomosis; MP, mercaptopurine.

(a)



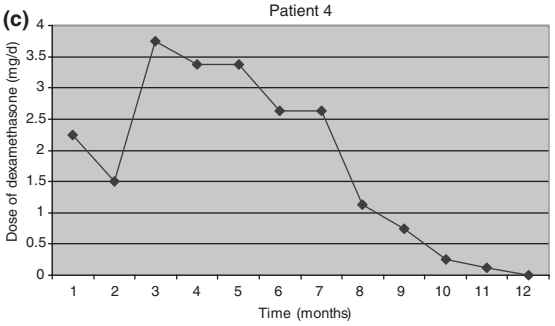
Variable	Results	Interpretation
CWS	0	
Low dose ACTH testing	Month 4: Time 0: 2.0 60: 10.6 Month 7: Time 0: 10.2 30: 19.3 60: 21.9	Delta >8: Wean continued Delta >11 but edema and falling albumin: referred back to gastroenterologist and diagnosed with active IBD
Other comments	Months 12–20: CS for active IBD	

(b)



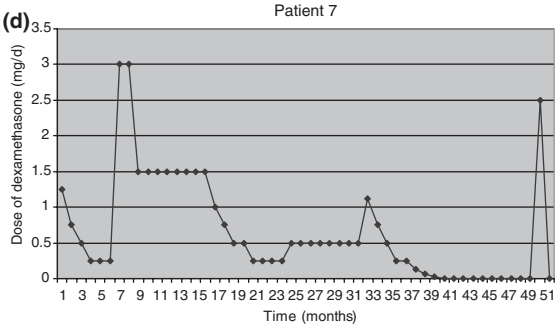
Variable	Results	Interpretation
CWS	0	
Low dose ACTH testing	0	
Comments	Not weaned: diagnosed with unknown autoimmune disease	

(c)



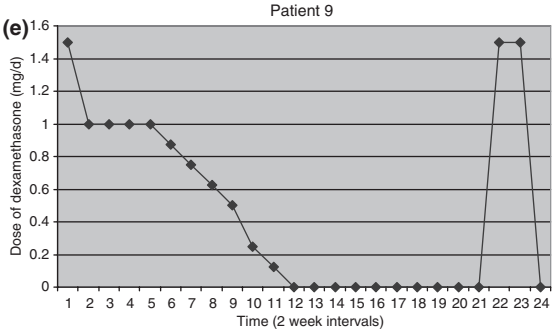
Variable	Results	Interpretation
CWS	1: Mon th 4	Dose of CS continued unchanged
Low dose ACTH testing	Month 9: Time 0: 4.2 30: 7.0 60: 4.3	Delta >2: Wean continued

(d)



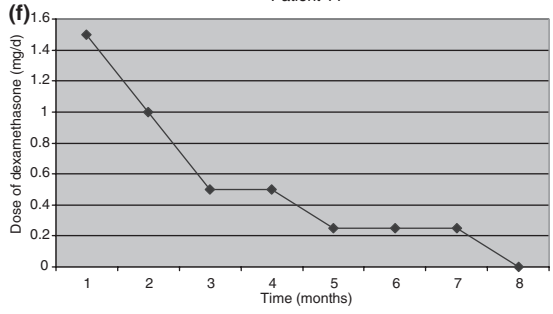
Variable	Results	Interpretation
CWS	0	
Low dose ACTH testing	Month 20: Time 0: <0.2 30: 2.4 60: 2.5 Month 37: Time 0: <0.2 30: 1.7 60: 1.6 Month 40: Time 0: 9.1 30: 11.2 60: 9.3	Delta >2: Wean continued Delta 1.7: Wean slowly Delta >2: Continue final wean
Other comments	Months 50-52: CS for Grave's disease	

(e)



Variable	Results	Interpretation
CWS	Month 2: 1 episode	Dose of CS continued unchanged
Low dose ACTH testing	Month 5: Time 0: 0.8 60: 16.7	Delta >16: Wean continued
Other comments	Month 11: Ciclosporin for active IBD Months 21–24: CS for infectious mononucleosis	

(f)



Variable	Results	Interpretation
CWS	2 episodes: Month 3 and month 6	Dose of CS continued unchanged
Low dose ACTH testing	Month 4: Time 0: 0.7 30: 5.0 60: 7.0	Delta >6: Wean continued

Figure 2. (a–f) Corticosteroid withdrawal process for selected patients. Key: CWS: Corticosteroid withdrawal syndrome; CS: Corticosteroid. Units for ACTH testing results are μg/dL.

gist. This method had a high success rate and durable effect, persisting after a median follow-up of greater than 3 years. Also, because the referring gastroenterology practice has a lot of experience with traditional weaning of IBD patients, the patients included in the study represent severely CS-dependent IBD patients. To the best of our knowledge, this is the first study of its kind to describe this withdrawal method in CS-dependent IBD patients.

Even in the current era of biologic therapy in IBD, CS dependency remains a common clinical problem. A recent audit of IBD care in the UK highlighted that 46% of patients with Crohn's disease were receiving CS therapy for over 3 months.[7] This audit examined practice patterns across a wide variety of hospitals in the UK, from district general to large referral hospitals. However, even in centres experienced in IBD care, CS dependency is common. The Leuven group in Belgium recently reported that in a large cohort of 547 patients with Crohn's disease treated with infliximab, 29% of patients receiving CS at baseline were unable to stop CS completely after 3 months.[8] These data highlight the difficulty in weaning IBD patients off CS.

We think that there are two main reasons why CS-dependence in IBD patients remains an important clinical issue. First, the symptoms of CWS manifest in large part as gastrointestinal symptoms,[4, 15] making it difficult for the clinician to distinguish between a genuine flare of disease and CWS. In this study, the protocol for management of this situation was to continue with the same dose of CS for approximately 3 days. If symptoms were because of CWS, they would typically abate after 3 days. If symptoms were because of a disease flare, they would typically continue or worsen beyond 3 days (Figure 1). When the clinical circumstances suggested active disease, the patient was re-referred to the gastroenterologist for further evaluation and treated for active disease as appropriate. Secondly, CWS is difficult to differentiate from adrenal insufficiency. During the study, when we suspected that the latter was occurring (for example, when patients failed to wean despite their IBD remaining quiescent and a slow pace of dose reduction), stimulation testing with low-dose synthetic ACTH was performed. We found that by dissociating the two elements of symptoms caused by CWS (determined by careful clinical evaluation) and adrenal reserve (determined by results of low dose stimulation testing), a more determined approach to weaning could be performed, Table 1. We suspect that several CS-dependent IBD patients are not weaned either because their symptoms of CWS are assumed to be as a result of IBD disease flares or because adrenal insufficiency is not routinely determined.

The CWS remains poorly understood, with 'relative adrenal insufficiency'[5] and 'relative CS resistance'[16]being proposed. It has been proposed that patients developing CWS develop tolerance to CS, with the result that replacement doses are inadequate to allow correct functioning of the central nervous and other systems.[11] Possible mediators of this syndrome include vasopressin, corticotrophin releasing hormone, proopiomelanocortin and central noradrenergic and dopaminergic systems.[11] The '3-day rule' we describe above for differentiating between CWS and disease flare is novel and based on the clinical experience of the endocrinologist in this study (JIM); it is difficult to reconcile this clinical finding with the biological mediators of the syndrome, many of which do not change over the course of several days. Perhaps the time scales of dominant biological factors are shorter than the other mediators, which have longer half lives, but this is purely speculative.

Immunomodulator therapy has a CS-sparing effect. In 1980, Present *et al*. showed that treatment with MP enabled 64% of CS-dependent patients with active Crohn's disease to either reduce or discontinue prednisone compared with 15% of patients receiving placebo.[17] A review of five studies of azathioprine/MP demonstrated that a reduction in CS use was possible in 65% of patients receiving these immunomodulators compared to 36% of patients receiving placebo.[18] Put another way, three patients needed to be treated with azathioprine/MP to obtain a CS-sparing effect in one patient. Methotrexate has also been shown to have a CS-sparing effect. In a controlled trial, 39% of patients with active Crohn's disease treated with methotrexate were able to withdraw prednisone therapy completely compared to 19% in the placebo-treated group ($P = 0.025$).[19] Infliximab also has a CS-sparing effect. Although CS-free remission in clinical trials of infliximab in IBD was low, occurring in 24% of patients with Crohn's disease at week 54[20] and 24% of patients with ulcerative colitis at week 30,[21] real-life experience with infliximab from several centres reported better withdrawal rates, with complete CS withdrawal in 54–73% of patients.[22, 23] In the current study, 83% of patients had received azathioprine or MP; 8% received methotrexate and 58% received infliximab. These

figures may represent an underestimate of the actual number of patients who received immunomodulator therapy, as this was a retrospective study spanning as much as 45 years of disease in some patients.

The pace of reducing or tapering CS in patients is important. If the taper is too quick, then the patient may develop frequent withdrawal symptoms and psychologically be more reluctant to persevere; if the CS taper is too slow, then the detriment associated with chronic CS use continues to accrue. Thus, the optimal pace for a CS taper, clinically, is to allow for mild CS withdrawal symptoms. However, the optimal schedule for withdrawal of CS in IBD has not been established. Current US[24, 25] and UK[26] guidelines recommend prednisone 40–60 mg daily until symptoms are resolved and weight gain is resumed (generally 7–28 days). After an initial response is achieved, CS therapy should be tapered gradually, as soon as possible, and under close monitoring for signs of clinical relapse. Current guidelines recommend gradual tapering of the prednisone dosage by 5–10 mg/week to a dosage of 20 mg daily and subsequently by 2.5–5 mg/week until complete withdrawal. Even among endocrinologists, there is considerable variation regarding recommendations for CS tapering.[27]

Historically, alternate-day regimens of CS therapy were devised to alleviate the side effects associated with chronic high-dose CS therapy.[28, 29] These regimens arose because some older studies had suggested that there was a relationship between duration or total dose of CS use and degree of suppression of the HPA axis.[30–32] However, more recent studies using statistical analysis found no significant correlation between the extent of HPA suppression and daily dose, cumulative dose, or duration of CS treatment.[33–36] The regimen used in the current study consisted of twice daily dexamethasone tablets, with no 'rest' days off CS until the later stages of the withdrawal regimen. We found that a longer duration of CS dependency appeared to predict a slower wean, but because of the small sample size, the estimates for factors predictive of a slow wean were unstable. We therefore cannot preclude the possibility that this or other patient characteristics may have had an effect on weaning time. These factors should be investigated in a larger sample of patients.

The strengths of this study are that a standardized protocol for withdrawal was adhered to, and all endocrinological evaluation was performed by a single clinician (JIM). Also, the median follow-up period was greater than 3 years, adding robustness to the findings. The limitations of this study are its retrospective nature and small sample size. The study period was almost 8 years, but the sample size was small because study subjects were carefully selected patients who had failed weaning using traditional methods. Every effort was made by the study gastroenterologists to wean patients off CS using traditional methods, and only patients failing this regimen were referred for withdrawal under endocrinological supervision.

In summary, we found that successful CS withdrawal using a method of slow dose reduction with oral dexamethasone and comprehensive endocrinological supervision had a high success rate and a durable response. We recommend this approach to other units managing IBD patients because of the morbidity associated with chronic CS use in these patients.

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