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SUMMARY

Background
Oral corticosteroids are the mainstay treatment for induction of ulcerative colitis remission in patients failing or intolerant to aminosalicylate therapy, but the poor tolerability profile of these drugs limits their usefulness. Second-generation, gut-selective corticosteroids may offer a safe alternative to systemic agents.

Aim
To review the efficacy and safety of systemic and second-generation oral corticosteroids for the induction of remission in ulcerative colitis.

Methods
The PubMed database was searched for randomised, controlled, and open-label trials of orally administered corticosteroids published between January 1950 and September 2015. Additional trials were identified from review of citation lists. Trials that compared oral corticosteroids with non-oral agents or in combination with agents other than aminosalicylates were excluded.

Results
Of the 240 studies identified, 21 were eligible for inclusion. Few trials directly compared oral systemic and second-generation corticosteroids (n = 4). Some second-generation corticosteroids had questionable efficacy vs. placebo or mesalazine (mesalamine), but beclomethasone dipropionate and budesonide MMX demonstrated a comparative benefit. Only beclomethasone dipropionate was similar to conventional corticosteroids for induction of remission and other clinical endpoints. Direct comparative trials for budesonide MMX were unavailable. Second-generation corticosteroids had an overall favourable safety profile, with minimal adverse effects on cardiovascular and metabolic parameters and a low incidence of adverse events.

Conclusion
Beclomethasone dipropionate and budesonide MMX provide greater induction of remission in ulcerative colitis than placebo or mesalazine but additional active-comparator trials are needed to firmly establish the efficacy profile vs. systemic corticosteroids. Second-generation corticosteroids have a more favourable safety and tolerability profile than systemic corticosteroids.

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INTRODUCTION

Ulcerative colitis (UC) is a prevalent colonic inflammatory disease characterised by relapsing and remitting symptoms of bloody diarrhoea, rectal urgency, and tenesmus.[1] First-line therapy for mild-to-moderate UC consists of oral and/or topical mesalazine[1, 2]; however, based on data from a meta-analysis of 11 randomised, placebo-control clinical trials, only 60% of patients with mild-to-moderate UC (887 of 1470 total patients) achieve remission with mesalazine.[3] For those who do not respond to mesalazine, treatment with systemic oral corticosteroids (e.g. prednisone) is recommended[1, 2] based on their beneficial effects on disease activity compared with placebo.[2] However, a substantial percentage of patients (up to 90%)[4] who receive conventional oral corticosteroids experience adverse events, including skin thinning, ophthalmic disorders, and infections.[5] The most commonly reported adverse events associated with low-to-medium doses of oral corticosteroids (i.e. ≤30 mg prednisolone equivalent dose except for the first month of treatment when doses ≤60 mg may have been used) are psychological and behavioural disruptions (e.g. mood disturbances) and gastrointestinal adverse events (e.g. peptic ulcer disease).[6] Other adverse events, such as neurological (e.g. dizziness) and endocrine and metabolic disruptions (e.g. weight gain), may also be evident in patients with inflammatory bowel disease.[6] Corticosteroids may increase bone resorption and remodelling, thereby reducing bone mineral density and increasing fracture risk.[5] In addition, patients receiving systemic corticosteroids are more likely to experience hyperglycemia and to develop diabetes as a result of corticosteroid-related increases in gluconeogenesis and insulin resistance.[5, 7]

Second-generation oral corticosteroid therapies (e.g. fluticasone propionate, prednisolone metasulphobenzoate, beclomethasone dipropionate and budesonide) target delivery of steroids to the site of inflammation (i.e. distal small bowel and colon),[8–11] thereby providing local (topical) anti-inflammatory effects and potentially reducing systemic corticosteroid concentrations.[8] With the exception of fluticasone propionate (a poorly absorbed, synthetic corticosteroid that undergoes extensive first-pass metabolism),[12] all of the second-generation corticosteroids use novel drug technologies to ensure colonic targeting. A gastrointestinal-targeted formulation of prednisolone metasulphobenzoate, a poorly absorbed corticosteroid, uses pH-sensitive Eudragit technology (Evonik Industries, Essen, Germany) to provide release of active drug in the distal colon.[13, 14] Targeted colonic release of beclomethasone dipropionate, a synthetic derivative of beclomethasone, has been achieved through development of a multiple methacrylic polymer coating formulation that allows drug distribution at a pH ≥6.4.[8] Budesonide, which has a high ratio of topical-to-systemic activity and low oral bioavailability,[11] is available in pH-controlled formulations that target budesonide to the small intestines and proximal colon (pH >5.5), and as a Multi Matrix (MMX; Cosmo Technologies, Ltd., Dublin, Ireland) controlled-release formulation that allows release of budesonide throughout the colon.[8, 11]

Although second-generation corticosteroids are becoming available and may represent well-tolerated and effective alternatives to conventional oral corticosteroids for inductions of remission of UC, the extent of their potential benefit compared with traditional corticosteroid regimens still remains unclear. This article reviews the current literature regarding the efficacy and tolerability of conventional oral systemic and second-generation corticosteroid therapies for induction of remission in patients with UC.

METHODS

Prospective, controlled and uncontrolled clinical trials that evaluated the efficacy and safety of oral second-generation corticosteroids and/or conventional oral corticosteroids for the induction of remission in patients with UC were reviewed. Studies of oral corticosteroid treatments were identified from a search of the PubMed database using the search terms "steroid," "corticosteroid," "fluticasone propionate," "budesonide," "prednisolone," "hydrocortisone" and "beclomethasone dipropionate" in combination with the phrase "ulcerative colitis" and exclusion of the terms "foam," "enema," "intravenous," and "rectal." Searches were limited to human clinical trials published in English between 1950 and September 23, 2015. Bibliographies of the publications identified from the PubMed search were reviewed to potentially identify additional trials. Of the publications identified, trials that compared oral corticosteroid therapies to non-oral therapies (e.g. infliximab, adsorptive granulocyte and monocyte apheresis) and those that evaluated corticosteroids in combination with therapies (e.g. antibiotics) other than aminosalicylates were excluded. Trials were also excluded if they were conducted in paediatric populations or did not provide efficacy and safety data for patients with UC.

RESULTS

A total of 183 studies were identified from initial PubMed searches for review and a further 57 studies were selected from publication bibliographies. Of these

240 studies identified, 219 were excluded. Most (77%) of the identified studies were excluded because they did not evaluate the efficacy and safety of steroids (e.g. evaluated cost effectiveness) or did not provide adequate efficacy and safety data specifically for patients with UC. The remaining articles were excluded because they: evaluated non-oral delivery systems (17 studies; 7%); were conducted in paediatric populations (17 studies; 7%); evaluated corticosteroids in combination with other therapies (five studies; 2%); or were review articles (five studies; 2%). A total of 21 clinical trials (8%) were extensively reviewed for inclusion: six trials for conventional oral corticosteroids (e.g. prednisolone, prednisone, or cortisone),[15–20] two trials for fluticasone,[10, 12] four trials for prednisolone metasulphobenzoate,[9, 13, 14, 21] four trials for beclomethasone dipropionate[22–25] and nine studies for budesonide.[26–34]

Conventional oral corticosteroids for induction of UC remission

Uncontrolled and active-comparator studies of the oral corticosteroid, prednisone, with doses ranging from 20 to 60 mg/day for 2–5 weeks have demonstrated symptomatic and/or endoscopic improvement from baseline in patients with active UC.[12, 35, 36] Supportive efficacy data from controlled clinical trials of conventional oral corticosteroids for the induction of remission in patients with UC are limited to two older clinical trials, but both demonstrated a benefit of systemic corticosteroid therapy for induction of remission compared with placebo.[17, 19]

In 1955, Truelove *et al.*[19] reported the results of a placebo-controlled, double-blind clinical trial of oral cortisone in patients with an initial flare or relapse of chronic UC. The severity of UC at baseline was not reported, but only patients who had chronic UC that 'would normally be expected to require at least 6 weeks' treatment in hospital' were included. Patients received cortisone (n = 109) or placebo (n = 101) for up to 6 weeks.[19] The cortisone dose and treatment duration were at the discretion of the healthcare provider but most patients received cortisone ≤100 mg/day (84%) for the full 6 weeks (85%). At the end of the 6-week treatment period, 40% of patients who received cortisone achieved clinical remission [defined as <1–2 nonbloody stools per day, no fever or tachycardia, and haemoglobin and erythrocyte sedimentation rates (ESR) that were at or returning towards normal levels] compared with <17% of patients who received placebo. In a placebo-controlled trial of nonhospitalised patients, individuals with left-sided colitis received either placebo (calcium lactate) or once-daily doses (40–60 mg/day) of prednisone for 3–4 weeks.[17] Clinical remission (defined as normal bowel functioning without bleeding or discharge and the presence of normal or inactive mucosa on sigmoidoscopy) was obtained in a greater percentage of patients who received prednisone [68% (13/19)] compared with placebo [17% (3/18)].

The overall safety and tolerability profile of conventional oral corticosteroids are generally well known. Adverse effects, such as weight gain,[17] pyogenic complications (e.g. ischiorectal abscess),[19] eye complications (e.g. iridocyclitis),[19] moon face,[12, 17, 36] acne,[17, 21] facial flushing,[12, 17] blood pressure effects or palpitations,[12, 17, 36] dyspepsia,[17] confusion,[12] hair growth,[12] hyperglycemia[12] and suppression of cortisol concentrations[12] were observed in controlled and uncontrolled trials of conventional oral corticosteroids. Higher doses appeared to be more efficacious for induction of remission than lower doses, but were also associated with an increased incidence of adverse events (e.g. weight gain, hypertension, and oedema).[36] An effort to improve the tolerability profile of oral corticosteroids by altering the dosing schedule of prednisone 20–120 mg from daily to every other day failed to adequately induce remission[20]; patients in the trial were subsequently switched to daily dosing and no safety data from the alternate dosing schedule were reported.

Second-generation oral corticosteroids for induction of UC remission

Fluticasone propionate. Fluticasone propionate is a poorly absorbed, synthetic corticosteroid that undergoes extensive first-pass metabolism.[12] Inhaled forms of fluticasone propionate, either as a nasal spray or as an orally inhaled powder, are currently approved in the USA for the treatment of perennial non-allergic rhinitis and asthma, respectively. However, the efficacy of orally administered fluticasone propionate for UC is questionable despite its enhanced availability in the gastrointestinal tract. In a small (N = 60), randomised, placebo-controlled trial, oral fluticasone propionate tablets 20 mg/day (in combination with stable noncorticosteroid therapies) were not significantly more efficacious than placebo at inducing remission in patients with mild-to-moderate UC proximal to the splenic flexure: 47% of patients improved or achieved remission (overall physician's impression score of '0' based on symptoms, clinical signs and endoscopic findings) with fluticasone vs. 45% with placebo (P = 0.89).[10] In addition, a similar percentage of patients in the placebo (17%) and fluticasone propionate (18%) groups achieved remission (i.e.

endoscopic evidence of quiescent disease and the absence of symptoms). The authors speculated that poor efficacy results may be attributable to disease location: most patients had active disease in the rectosigmoidal region with no patients having UC proximal to the splenic flexure.[10] This may indeed be the case, as a randomised, double-blind trial ($N = 206$) reported that fluticasone propionate 20 mg/day for 4 weeks showed similar efficacy to prednisolone (10–40 mg/day) for induction of remission in patients with at least left-sided UC; however, the percentage of patients who had improvement in individual clinical symptoms (e.g. number of formed stools, nonbloody stools, and <3 bowel movements per day) was significantly smaller with fluticasone propionate than with prednisolone (Figure 1).[12]

Oral fluticasone propionate has a favourable tolerability profile, but is not without some systemic effects (e.g. altered glucose concentration). In a placebo-controlled trial of fluticasone propionate tablets 20 mg/day for 4 weeks, no alterations in haemoglobin, platelet count, ESR, C-reactive protein, orosomucoids, serum albumin or morning salivary cortisol concentrations were observed with either treatment.[10] However, one nondiabetic patient in the fluticasone propionate group developed glycosuria and an elevated plasma glucose level after 2 weeks of treatment.[10] Blood glucose concentrations returned to normal within 2 days after treatment

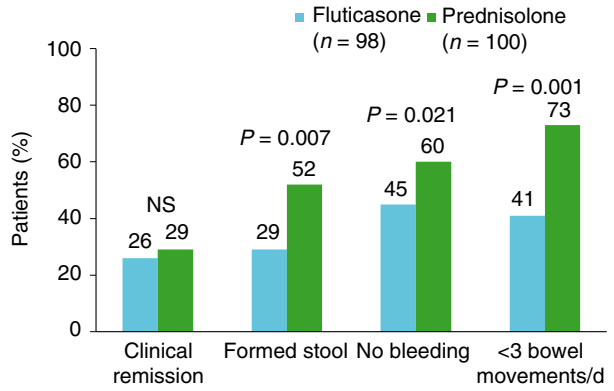

Figure 1 | Efficacy of fluticasone propionate.[12] Patients with at least left-sided ulcerative colitis were randomised to receive either oral fluticasone propionate 20 mg/day or oral prednisolone (10–40 mg/day) for 4 weeks. A significantly greater percentage of patients who received prednisolone experienced an improved number of formed stools or nonbloody stools and <3 bowel movements/day compared with fluticasone propionate. Data from Hawthorne *et al.*[12] NS, not significant.

discontinuation, suggesting that the adverse event was related to systemic effects of fluticasone propionate.[10] Compared with other oral steroids such as prednisone, potential systemic corticosteroid-related adverse events are lower with fluticasone propionate.[12] In a randomised, double-blind trial in patients with UC, fewer potential corticosteroid-related adverse events were observed with oral fluticasone propionate 20 mg/day at the end of 4 weeks of treatment compared with prednisolone.[12] Facial swelling, facial flushing, mental confusion and increased hair growth were reported with prednisolone but not with fluticasone propionate.[12] In addition, mean changes in blood pressure levels were significantly reduced with fluticasone propionate vs. prednisolone ($P < 0.05$), and fewer patients who received fluticasone propionate experienced alterations in plasma glucose concentrations.[12] In addition, mean morning plasma cortisol levels were generally unaltered with fluticasone propionate, whereas they were substantially suppressed with prednisolone ($P < 0.001$ vs. fluticasone propionate).[12]

Prednisolone metasulphobenzoate. Although compelling clinical data are lacking, prednisolone metasulphobenzoate, a Eudragit-coated formulation, appears to induce remission in patients with UC. Small ($N = 13–15$), uncontrolled studies have reported improvements from baseline in UC symptoms or gastrointestinal mucosal inflammation with prednisolone metasulphobenzoate.[14, 21] In a large ($N = 181$), randomised, double-blind study, prednisolone metasulphobenzoate 40 mg/day for 6 months improved global patient- and physician-reported symptoms to a similar extent as a tapering regimen of oral prednisolone (40 mg/day for 2 weeks, tapered to 5 mg/day during an 8-week period) and was statistically non-inferior to prednisolone taper for induction of remission (defined as Powell–Tuck score of ≤2, excluding endoscopic scores; Figure 2a).[13] However, time to response and the rate of mucosal healing were slower with prednisolone metasulphobenzoate compared with prednisolone taper.[13]

In general, prednisolone metasulphobenzoate was well tolerated. In an active-comparator trial, the percentage of patients who reported drug-related adverse events was lower with prednisolone metasulphobenzoate 40 mg/day (56%) and prednisolone metasulphobenzoate 60 mg/day (66%) than a prednisolone taper regimen (80%).[13] For prednisolone metasulphobenzoate, the most common corticosteroid-related adverse events specifically evaluated in the study were sleep changes (15–18%), insomnia (8–13%), flushing (8–15%), moon face (13–15%), and mood alterations (10–13%); only the incidence of mood

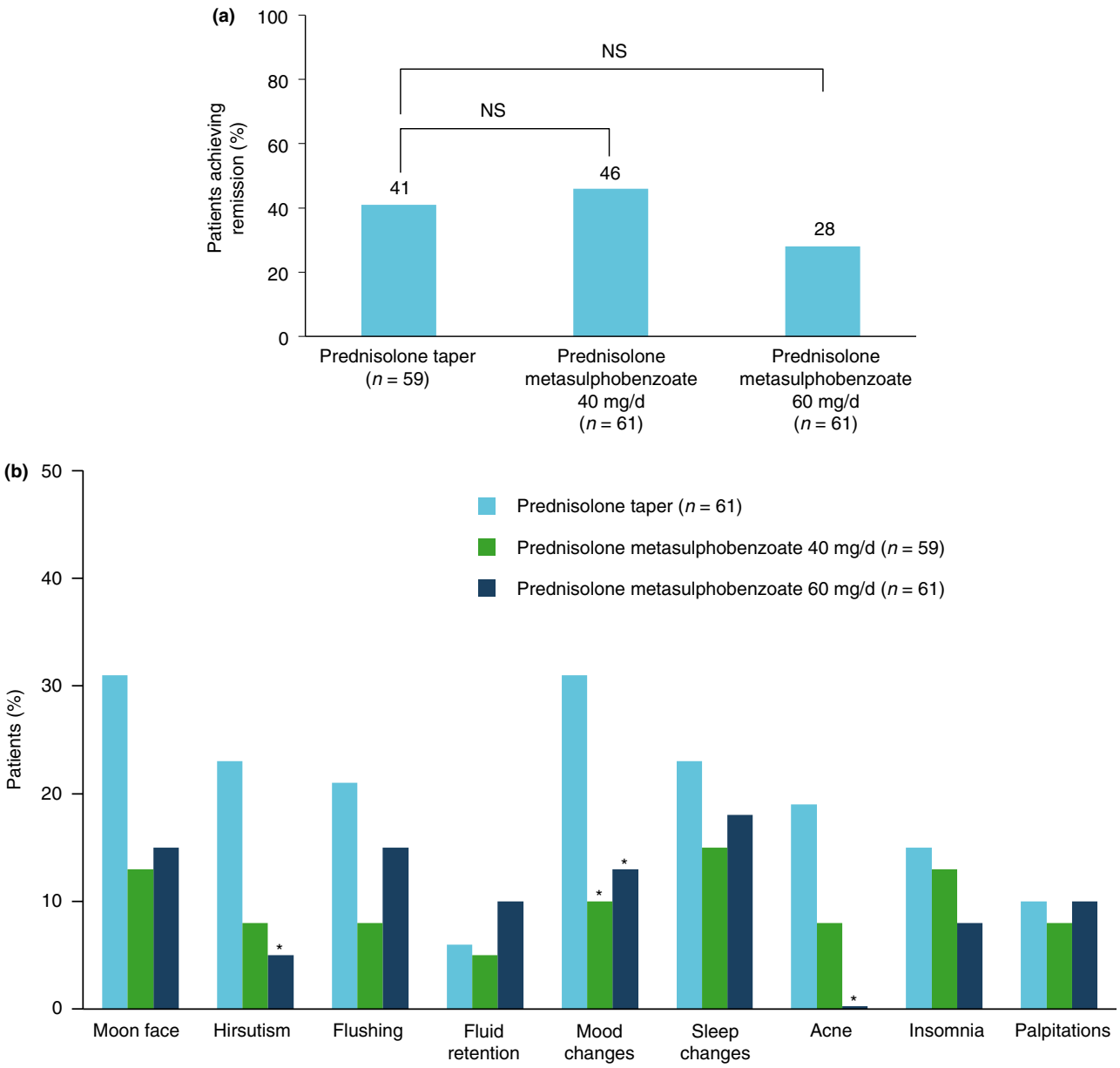

Figure 2 | Efficacy (a) and corticosteroid-related adverse event profile (b) of prednisolone metasulphobenzoate.[13] In a randomised, double-blind trial, patients with UC extending to at least the descending colon/sigmoid colonic junction and a Baron sigmoidoscopy score of ≥1 (i.e. at least erythema or granularity) received either prednisolone taper, prednisolone metasulphobenzoate 40 mg/day or prednisolone metasulphobenzoate 60 mg/day for at least 2 months. Prednisolone metasulphobenzoate 40 mg/day was statistically non-inferior to prednisolone taper for the induction of UC remission (i.e. Powell–Tuck score of ≤2, excluding endoscopic scoring) after 2 months of treatment (a), and displayed a more favourable safety and tolerability profile than prednisolone (b). *$P \leq 0.04$ vs. prednisolone taper. Data from Rhodes *et al.*[13] NS, not significant; UC, ulcerative colitis.

changes, acne, and hirsutism were significantly lower than with prednisolone taper (Figure 2b).[13] Haemoglobin A1c levels were significantly higher at month 2 in the prednisolone taper group vs. prednisolone metasulphobenzoate ($P < 0.0001$).[13] Overall, patients reported less disruptive adverse effects with prednisolone metasulphobenzoate vs. prednisolone taper.[13] In addition, bone-related adverse effects (e.g. fractures) might be less prevalent with prednisolone metasulphobenzoate compared with systemic corticosteroids, due to the former's

lack of apparent substantial adverse effects on bone formation and bone mineral density in patients with UC (12-week study).[21]

Beclomethasone dipropionate. Oral beclomethasone dipropionate uses gastro-resistant film coatings to target delivery to the distal small intestine and throughout the colon.[23] An oral formulation (e.g. Clipper tablets; Chiesi Limited, Manchester, UK) is only available in a few European countries and is not currently available in the USA.[8] In combination with mesalazine, beclomethasone dipropionate has been shown to induce remission and reduce inflammation in patients with extensive or left-sided UC.[22, 23] In a randomised, single-blind study, beclomethasone dipropionate tablets 5 mg once daily for 4 weeks improved clinical and endoscopic parameters from baseline in patients with extensive or left-sided UC[23]; however, the extent of this improvement was similar to that observed with mesalazine 2.4 mg/day alone.[23] In a separate randomised, double-blind, placebo-controlled trial in patients with extensive or left-sided UC, beclomethasone dipropionate 5 mg once daily for 4 weeks in combination with mesalazine 3.2 g/day improved clinical symptoms and endoscopic lesions compared with mesalazine 3.2 g/day alone.[22] The clinical remission rate [disease activity index score (DAI) <3] at week 4 was also greater with combination therapy (58.6%) than with mesalazine alone (34.4%; $P = 0.02$).[22] In a randomised, double-blind trial in patients with mild-to-moderate UC ($N = 297$), beclomethasone dipropionate 5 mg once daily was statistically non-inferior to prednisone taper (40 mg/day for 2 weeks followed by 10-mg dose reductions during an 8-week period) for induction of clinical response (DAI score <3 or a ≥ 3 point reduction in DAI score in patients with moderate disease) after 4 weeks of treatment; in the beclomethasone dipropionate group, 64.6% of patients achieved response vs. 66.2% of patients in the prednisone group [difference, −1.6; 95% confidence interval (CI), −13.0 to 9.9].[25] Endoscopic healing, rectal bleeding scores, and the percentage of patients who achieved clinical remission (DAI score ≤1) were also similar with beclomethasone dipropionate and prednisone taper at week 4.[25]

Beclomethasone dipropionate is generally associated with fewer adverse events and clinical laboratory abnormalities and, in randomised trials, the percentage of patients who reported adverse events with oral beclomethasone dipropionate (1.1–3.4%) was similar to that reported with placebo (1.1–6.5%) or mesalazine (1.1%).[22, 23] The most common adverse events occurring during 4 weeks of beclomethasone dipropionate treatment were constipation and menorrhagia.[22, 23] In addition, the incidence of potential corticosteroid-related adverse events (excluding reduced cortisol concentrations) was statistically similar with beclomethasone dipropionate 5 mg/day (5.8%) and prednisone taper (10.3%; $P = 0.18$) after 4 weeks of treatment (Figure 3).[25] However, the percentage of patients who achieved clinical response without a potential corticosteroid-related adverse event was numerically greater with beclomethasone dipropionate (51.2%) than prednisone taper (37.8%), potentially indicating a more favourable efficacy vs. tolerability profile overall (Figure 3).[25] No clinically relevant changes in mean blood pressure levels,[22, 23, 25] heart rate[22, 23, 25] or weight[22, 23] have been reported with oral beclomethasone dipropionate,[22, 23]but significant alterations in plasma glucose levels (from 4.9 mmol/L at baseline to 4.7 mmol/L after 4 weeks of treatment; $P = 0.004$) and platelet count (276.3×10^9 cells/L to 262.3×10^9 cells/L; $P = 0.036$)

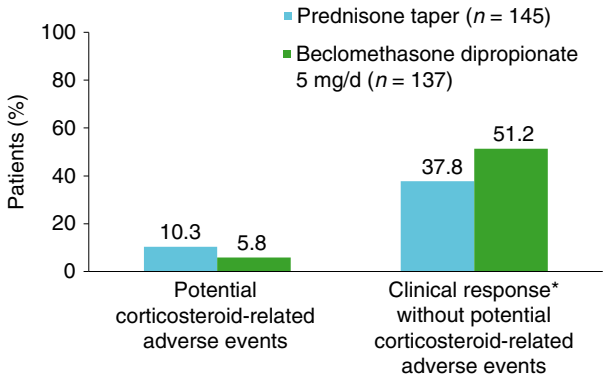

Figure 3 | Potential corticosteroid-related adverse events in patients with and without clinical response after beclomethasone dipropionate or prednisone.[25] In a randomised, double-blind clinical trial, patients with mild-to-moderate UC (DAI score, 3–9) were randomised to receive either beclomethasone dipropionate 5 mg/day tapered to every other day, or prednisone taper (40 mg/day starting dose tapered by 10 mg every 2 weeks during an 8-week period). Corticosteroid-related adverse events were not significantly reduced with beclomethasone dipropionate vs. prednisone ($P = 0.18$); however, a numerically higher percentage of patients achieved clinical response without a corticosteroid-related adverse event with beclomethasone dipropionate than with prednisone. Data from van Assche *et al.*[25] *Clinical response defined as either a ≥3-point decrease in DAI score (for patients with baseline DAI scores of 7–9) or a DAI score <3. DAI, disease activity index; UC, ulcerative colitis.

have been observed.[22] Reductions in mean plasma cortisol concentrations have been observed with beclomethasone dipropionate, but levels remained within normal limits[22, 23] or were ≥150 nmol/dL[25] for most patients, and there were no clinical signs of pituitary–adrenal dysfunction.[22, 23, 25]

Budesonide. Budesonide is a synthetic corticosteroid with a high affinity for glucocorticoid receptors (~200-fold higher vs. hydrocortisone and ~15-fold higher vs. prednisolone).[37] The molecule undergoes extensive (~90%) hepatic first-pass metabolism, forming metabolites with no to minimal activity.[38–40] Multiple oral formulations of budesonide have been evaluated for induction of remission in patients with UC.[41] Budenofalk capsules (Dr Falk Pharma, Freiburg, Germany) and Entocort EC capsules (AstraZeneca, Wilmington, DE, USA) and Entocort CR capsules (AstraZeneca UK Limited, Cheshire, UK), are pH-dependent-release formulations that facilitate release of budesonide in the distal ileum and right colon.[41] Given the restricted release profile in the colon, these pH-dependent–release formulations are only indicated for Crohn's disease of the ileum and/or ascending colon, and not UC. In contrast, the budesonide extended-release tablets formulation [licensed in the USA as Uceris (Cosmo S.p.A, Milan, Italy) and in the European Union/Asia as Cortiment (Ferring Pharmaceuticals, St-Prex, Switzerland)] uses MMX technology (budesonide MMX) to provide extended, targeted release of budesonide throughout the entire colon.[33, 41] It is indicated in the USA for the induction of remission in patients with mild-to-moderate UC and approved in Europe for induction of remission in patients with mild-to-moderate UC when mesalazine treatment has been insufficient.

pH-dependent budesonide. Open-label studies have shown a clinical benefit with pH-dependent budesonide,[26, 29] but data from large, high-quality clinical trials are limited (Table 1).[26, 28–30] Because of this limitation, the potential benefit of pH-dependent budesonide vs. other therapies is unclear. Evidence suggests that clinical improvement with pH-dependent budesonide may be inferior to that observed with mesalazine[30] and prednisolone for UC.[28] A large ($N = 343$), randomised, double-blind study demonstrated that pH-dependent budesonide capsules 9 mg for 8 weeks did not meet statistical non-inferiority vs. mesalazine 3 g/day for induction of UC remission [defined as clinical activity index (CAI) score ≤4 in combination with stool frequency and rectal bleeding subscores of '0'].[30] A smaller ($N = 75$) randomised, double-blind trial in patients with mild-to-moderate UC proximal to the sigmoid colon indicated that pH-dependent budesonide capsules (10 mg/day tapered to 4 mg/day over 9 weeks) exhibited a similar degree of endoscopic improvement as prednisolone (40 mg/day tapered to 5 mg/day over the same period), but histological improvements (particularly in the descending and sigmoid colon) were greater with prednisolone.[28]

Oral pH-dependent budesonide has a relatively favourable safety profile[26, 29] although gastrointestinal disturbances and alterations in the hypothalamic–pituitary–adrenal axis function have been reported.[26, 30] Changes from baseline in cortisol concentrations have been observed with pH-dependent budesonide in some,[26, 30] but not all,[28] UC trials. Based on a single randomised clinical trial, the adverse event profile of pH-dependent budesonide was generally similar to that of mesalazine; 'UC deteriorations' and headache were the most commonly reported adverse events with both pH-dependent budesonide (10.2% and 5.6%, respectively) and mesalazine (3.0% and 5.4% respectively).[30] The incidence of infection-related adverse events (e.g. respiratory tract infection, influenza, fever, urinary tract infection) with pH-dependent budesonide was either similar or lower vs. mesalazine.[30] Compared with prednisolone during a 9-week study, pH-dependent budesonide was associated with fewer central and peripheral nervous system–related adverse events.[28] In addition, no statistically significant changes from baseline were noted for mean morning plasma cortisol concentrations or leucocytes, platelet count and orosomucoid levels with pH-dependent budesonide; however, significant changes from baseline ($P < 0.05$) were observed at various time points with prednisolone.

Budesonide MMX. Compared with other second-generation corticosteroids, the efficacy and safety data for oral budesonide MMX have been studied in a larger, phase 3 UC programme. Pooled data analysis of 2 large ($N = 489$–512) phase 3, randomised, placebo-controlled trials (CORE I and CORE II) conducted in patients with mild-to-moderate UC demonstrated that budesonide MMX 9 mg once daily for 8 weeks induced clinical and colonoscopic remission in a significantly greater percentage of patients (17.7%) compared with placebo (6.2%; $P = 0.0002$).[32] Statistically significant rates of clinical and colonoscopic remission were observed with budesonide MMX 9 mg/day vs. placebo in patients with left-sided disease (20.3% vs. 3.2%; $P = 0.002$) and proctosigmoiditis

Table 1 | pH-dependent oral budesonide capsules for induction of UC remission

Study	Methodology	Disease distribution	Patients, *n*	Medication	Treatment duration	Treatment outcome
Lofberg *et al.*[28]	Randomised, double-blind	Proximal to sigmoid colon	75	pH-dependent budesonide (Entocort; Astra Draco AB, Lund, Sweden): 10 mg/day tapered to 4 mg/day or prednisolone 40 mg/day tapered to 5 mg/day	9 weeks	• Similar reduction in mean endoscopic scores with pH-dependent budesonide vs. prednisolone • Greater reduction in mean histopathological scores with prednisolone vs. pH-dependent budesonide (P = 0.02)
Keller *et al.*[29]	Open-label, observational	Steroid-dependent patients; proctitis, left-sided colitis, or extensive colitis	14	pH-dependent budesonide (Budenofalk; Dr Falk Pharma, Freiburg, Germany): 9 mg	≥6 months	• 78.6% of patients achieved remission (CAI score ≤4)
Kolkman *et al.*[26]	Randomised, open-label	Proctitis, proctosigmoiditis, or left-sided colitis	15	pH-dependent budesonide (Budenofalk): 9 mg (single daily or multiday dosing)	4–8 weeks	• Overall response rate (CAI ≤4 or 30% decrease in CAI) was achieved by 38–71% of patients • Number of stools per day was reduced from baseline in the single-day dosing, and percentage of bloody stools was reduced from baseline in both groups
Gross *et al.*[30]	Randomised, double-blind	Patients with active UC; patients with proctitis limited to 15 cm from the anus were excluded	343	pH-dependent budesonide (Budenofalk): 9 mg/day or mesalazine 3 g/day	8 weeks	• Clinical remission (CAI ≤4 and stool frequency and rectal bleeding subscores of '0': 39.5% with pH-dependent budesonide vs. 54.8% with mesalazine (P = 0.5) • Greater mean improvement in CAI (P = 0.02) and endoscopic index (P = 0.02) with mesalazine vs. pH-dependent budesonide • Greater percentage of patients with endoscopic remission (endoscopic index ≤3; 63.3% vs. 49.7%; P = 0.01) and histological remission (histological index score ≤1; 58.4% vs. 47.5%; P = 0.04) with mesalazine vs. pH-dependent budesonide

CAI, clinical activity index; UC, ulcerative colitis.

(23.5% vs. 11.0%; $P = 0.035$) but not in patients with extensive/pancolitis UC (9.4% vs. 3.3%; $P = 0.2$).[32] The two CORE trials also included a comparator arm (mesalazine or pH-dependent budesonide) as a reference treatment arm, but these trials were not powered to detect statistically significant differences between budesonide MMX and these active comparators. However, the percentage of patients who achieved clinical and endoscopic remission with budesonide MMX 9 mg was numerically higher vs. mesalazine (17.9% vs. 12.1%, respectively) in CORE I and vs. pH-dependent budesonide capsules (17.4% vs. 12.6%, respectively) in CORE II,[33, 42] suggesting that budesonide MMX may provide a small therapeutic advantage.

Based on pooled analysis of safety data from five clinical trials (two double-blind, phase 3 trials [CORE I and II]; two placebo-controlled, phase 2 trials, and 1 phase 3, open-label study), budesonide MMX 3–9 mg for up to 8 weeks was well tolerated, with an adverse event profile generally similar to that of placebo.[31] Overall rates of adverse events were similar with budesonide MMX 6–9 mg (54.5–60.6%) and placebo (50.5%)[31]; the most common adverse events reported with budesonide MMX 6–9 mg (vs. placebo) were UC exacerbation (11.8–14.6% vs. 9.6%, respectively), headache (4.5–4.7% vs. 4.1%) and nausea (2.4–4.2% vs. 0.3%).[31] There was no indication that budesonide MMX was associated with an increased rate of infection, and potential corticosteroid-related adverse events occurred in <10% of patients who received budesonide MMX.[31] Mean morning plasma cortisol concentrations significantly decreased from baseline with budesonide MMX vs. significantly increasing in placebo groups, but, on an individual level, cortisol concentrations remained within normal limits for most patients.[31]

Data from CORE I demonstrated that budesonide MMX 9 mg for 8 weeks had an overall safety profile generally similar to that of mesalazine delayed-release tablets 2.4 g/day.[42] The incidence of any adverse event was similar in both groups (budesonide MMX 9 mg, 57.5% vs. delayed-release mesalazine 2.4 g, 63.0%),[42] although a slightly higher percentage (11.8%) receiving budesonide MMX experienced corticosteroid-related adverse events compared with mesalazine delayed-release tablets 2.4 g (7.9%); notably these were changes in sleep and mood and reports of insomnia (Table 2).[42] In CORE II, compared with pH-dependent budesonide capsules, budesonide MMX 9 mg was associated with fewer corticosteroid-related adverse events (6.3% vs. 11.1%, respectively; Table 2[33]), although the overall percentage of patients who reported adverse events was similar between the two groups (55.5% vs. 54.8%). Gastrointestinal adverse events of abdominal pain and flatulence were more prevalent with pH-dependent budesonide capsules (5.6% for both) than with budesonide MMX 9 mg (2.3% and 3.9%, respectively); however, budesonide MMX was associated with more reports of decreased blood cortisol concentration (5.5%) compared with pH-dependent budesonide capsules (3.2%).[33]

Table 2 | Potential corticosteroid-related adverse effects*

	CORE I[42]			CORE II[33]		
Adverse event	Budesonide MMX, 9 mg (n = 127)	Placebo (n = 129)	Mesalazine delayed-release, 2.4 g (n = 127)	Budesonide MMX, 9 mg/day (n = 128)	Placebo (n = 129)	pH-dependent budesonide, 9 mg/day (n = 126)
Moon face	0	0	1 (0.8)	2 (1.6)	4 (3.1)	1 (0.8)
Striae rubrae	0	2 (1.6)	0	NR	NR	NR
Flushing	0	1 (0.8)	2 (1.6)	0	1 (0.8)	1 (0.8)
Fluid retention	2 (1.6)	1 (0.8)	1 (0.8)	0	2 (1.6)	0
Mood changes	5 (4.0)	3 (2.3)	2 (1.6)	2 (1.6)	7 (5.4)	6 (4.8)
Sleep changes	4 (3.2)	7 (5.4)	1 (0.8)	3 (2.3)	4 (3.1)	7 (5.6)
Insomnia	5 (4.0)	6 (4.7)	2 (1.6)	1 (0.8)	2 (1.6)	3 (2.4)
Acne	3 (2.4)	3 (2.3)	4 (3.1)	1 (0.8)	2 (1.6)	3 (2.4)
Hirsutism	0	0	0	0	0	1 (0.8)

Figure adapted with permission from Travis *et al.*[33] and Sandborn *et al.*[42]

MMX, Multi Matrix; NR, not reported.

* Prespecified adverse events of special interest.

DISCUSSION AND CONCLUSIONS

Conventional corticosteroids (e.g. prednisone) are efficacious in inducing remission in patients with Crohn's disease,[43] and UC; however, studies have also reported multiple glucocorticoid-related side effects with these drugs.[17, 19] In parallel to recent developments in the treatment of chronic airway inflammation, second-generation oral corticosteroids were also designed to deliver topically acting corticosteroids directly to the site of colonic inflammation. As a consequence, systemic bioavailability is lower than that observed with traditional corticosteroids, resulting in fewer corticosteroid-related adverse events and limited alterations in weight, blood pressure levels or heart rate.[9, 22, 23, 28] However, all corticosteroids are absorbed systemically to some extent and this may underlie the adverse events that continue to be reported with several agents in the second-generation class (e.g. alterations in glucose concentrations, cortisol concentrations, and haematological parameters).[8, 22, 26, 30, 31] Because of these adverse effects, second-generation corticosteroids should not be considered "steroid-sparing" agents.[8]

Few head-to-head comparative studies with second-generation vs. conventional corticosteroids have been conducted; therefore, it is difficult to definitely ascertain the degree to which second-generation corticosteroids may be more efficacious or tolerable vs. conventional steroids. In separate clinical trials, fluticasone propionate, prednisolone metasulphobenzoate and pH-dependent budesonide were not as efficacious as conventional corticosteroids for the induction of UC remission, although their overall safety and tolerability profiles were generally favourable.[12, 13, 28] Although trials have been smaller with less robust outcome measures vs. other agents in the class, beclomethasone dipropionate is the only second-generation corticosteroid, to date, to demonstrate clinical efficacy for UC similar to that of conventional oral corticosteroids.[25] Of note, oral formulations of beclomethasone dipropionate are not currently available in the USA.[44] Budesonide MMX is approved for the induction of remission for mild-to-moderate UC in multiple countries. Differences in the efficacy profiles of pH-dependent budesonide capsules and budesonide MMX in UC are likely related to the release mechanism of active drug, whereby budesonide MMX is released throughout the colon and pH-dependent budesonide capsules restrict release of budesonide to the ileum and ascending colon.[8] The tolerability profile of budesonide MMX for up to 8 weeks is also generally similar to that of placebo, mesalazine,[32] and pH-dependent budesonide,[33] which may prompt use in patients who would be contraindicated for conventional corticosteroids or beclomethasone dipropionate. pH-dependent budesonide is indicated for the treatment of Crohn's disease of the ileum and/or ascending colon and has been shown to be efficacious in multiple trials for the induction of remission in patients with Crohn's disease (reviewed in Rezaie *et al.*[45]). However, data are lacking for other second-generation corticosteroids, such as budesonide MMX, for treatment of Crohn's disease and one can only speculate at this point on their potential role in this condition.

In conclusion, there is an overall lack of high-quality evidence comparing the efficacy and safety of conventional vs. second-generation corticosteroids; however, it is well established that long-term use of systemic corticosteroids is inadvisable,[8] and there is accumulating evidence to suggest that second-generation agents, though not entirely steroid-sparing,[8] have a more favourable safety profile than conventional oral corticosteroids.[12, 13, 25, 28] Because of this, second-generation corticosteroids may be advisable in patients refractory to first-line 5-ASA therapy (Figure 4),[1,2] although additional active-comparator, controlled UC trials are needed to firmly establish the efficacy profile of second-generation corticosteroids vs. systemic corticosteroids. This would allow refinement in identifying

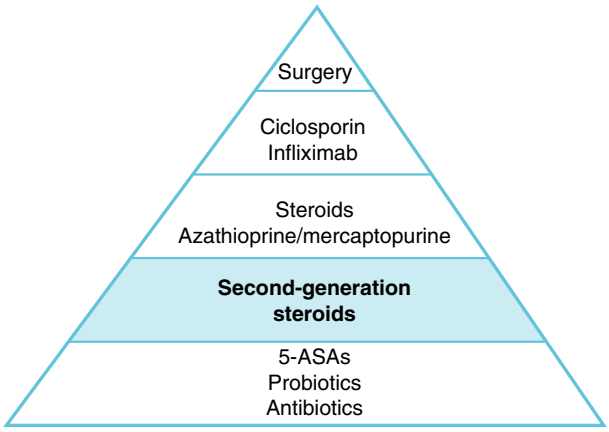

Figure 4 | Recommended placement of second-generation corticosteroid therapies within current treatment paradigm for mild-to-moderate UC. Treatment paradigm based on recommendations from the American College of Gastroenterology[1] and the European Crohn's and Colitis Organization.[2] Most patients with mild-to-moderate UC should receive 5-ASA treatment. Additional therapies (i.e. those higher up on the pyramid) should be reserved for patients who are unresponsive or intolerant of the treatments listed below them on the pyramid. 5-ASA, 5-aminosalicylic acid; UC, ulcerative colitis.

patient populations most likely to benefit from this class of corticosteroids and optimisation of treatment dosage and duration for induction of UC remission.

AUTHORSHIP

Guarantor of the article: Geert D'Haens.
Author contributions: Dr D'Haens provided concept and scientific content for the development of the manuscript, critically reviewed and edited all drafts of the manuscript, and approved the final version of the manuscript.

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