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Once versus three times daily dosing of oral budesonide for active Crohn's disease: A double-blind, double-dummy, randomised trial☆,☆☆

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Abbreviations: 6-MP, 6-mercaptopurine; AE, adverse event; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; GIQLI, Gastrointestinal Quality of Life Index; ITT, intention-to-treat; LOCF, last observation carried forward; OD, once daily; PGA, Physician's Global Assessment; PP, per protocol; SES-CD, Simple Endoscopic Score for Crohn's Disease; SHS, Short Health Scale; TID, three times a day.

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[2] See Appendix A.

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KEYWORDS
Budesonide;
Crohn's disease;
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Dosing

Abstract

Background: Oral budesonide 9 mg/day represents first-line treatment of mild-to-moderately active ileocolonic Crohn's disease. However, there is no precise recommendation for budesonide dosing due to lack of comparative data. A once-daily (OD) 9 mg dose may improve adherence and thereby efficacy.
Methods: An eight-week, double-blind, double-dummy randomised trial compared budesonide 9 mg OD versus 3 mg three-times daily (TID) in patients with mild-to-moderately active ileocolonic Crohn's disease. Primary endpoint was clinical remission defined as CDAI <150 at week 8 (last observation carried forward).
Results: The final intent-to-treat population comprised 471 patients (238 [9 mg OD], 233 [3 mg TID]). The confirmatory population for the primary endpoint analysis was the interim per protocol population (n = 377; 188 [9 mg OD], 189 [3 mg TID]), in which the primary endpoint was statistically non-inferior with budesonide 9 mg OD versus 3 mg TID. Clinical remission was achieved in 71.3% versus 75.1%, a difference of −3.9% (95% CI [−14.6%; 6.4%]; p = 0.020 for non-inferiority). The mean (SD) time to remission was 21.9 (13.8) days versus 21.4 (14.6) days with budesonide 9 mg OD versus 3 mg TID, respectively. In a subpopulation of 122 patients with baseline SES-CD ulcer score ≥1, complete mucosal healing occurred in 32.8% (21/64) on 9 mg OD and 41.4% (24/58) on 3 mg TID; deep remission (mucosal healing and clinical remission) was observed in 26.6% (17/64) and 32.8% (19/58) of patients, respectively. Treatment-emergent suspected adverse drug reactions were reported in 4.6% of 9 mg OD and 4.7% of 3 mg TID patients.
Conclusions: Budesonide at the recommended dose of 9 mg/day can be administered OD without impaired efficacy and safety compared to 3 mg TID dosing in mild-to-moderately active Crohn's disease.

1. Introduction

Systemic glucocorticosteroids are highly effective for inducing remission in patients with active Crohn's disease, but are associated with a high rate of potentially serious side effects.[1] 'Second generation' topical glucocorticosteroids such as budesonide have been developed which preserve efficacy but have lower systemic toxicity and a more favourable safety profile.[2,3] Randomised clinical studies have shown that budesonide therapy leads to remission in 50–60% of patients with active ileocolonic Crohn's Disease.[4–8] The European Crohn's and Colitis Organisation (ECCO) recommends oral treatment with budesonide at a dose of 9 mg/day as first-line treatment of mild-to-moderately active, ileocolonic Crohn's Disease.[9] However, there is no clear recommendation for a precise regimen of budesonide intake, 9 mg/day once daily (OD) or 3 mg three times a day (TID), due to lack of comparative data. It is estimated that 30–45% of patients with inflammatory bowel disease are non-adherent to oral medication schedules[10] and although the causes of non-adherence to medication in inflammatory bowel disease are complex,[10–12] multiple daily dosing is known to discourage adherence.[13]

In a recent double-blind, double-dummy trial, oral budesonide administered either as 9 mg OD or as 3 mg TID was at least as effective as high-dose oral mesalazine (4.5 g/day) in moderately active Crohn's disease.[8] In an exploratory analysis, the primary endpoint of clinical remission was found to be similar with OD or TID budesonide dosing. The objective of the current eight-week, double-blind, double-dummy randomised trial was to compare the efficacy and tolerability of budesonide 9 mg OD versus 3 mg TID in patients with mild-to-moderately active ileocolonic Crohn's disease in a confirmatory manner. In addition to the primary efficacy endpoint of clinical remission, achievement of mucosal healing in each treatment group was also examined.

2. Methods

2.1. Study design and conduct

This was a double-blind, double-dummy, randomised, multicentre, Phase III study in which patients with mild-to-moderately active ileocolonic Crohn's disease received budesonide at a single daily dose of 9 mg or three daily doses of 3 mg. After screening, an eight-week treatment phase was followed by a two-week follow-up period. The study was planned as a three-stage adaptive design with possible sample size adjustment after pre-specified interim analyses. The first patient visit was in November 2009 with the last visit of the treatment phase in April 2012.

The study was undertaken at 50 gastroenterology centres in Bulgaria, Czech Republic, Germany, Hungary, Latvia, Lithuania, Romania, Russia, Slovakia, and Ukraine. It was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki following approval from the relevant independent ethics committee at each centre. Written informed consent was obtained from all participants.