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The long-term efficacy of azathioprine does not wane after four years of continuous treatment in patients with steroid-dependent luminal Crohn's disease ☆

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Abstract

Background: The long-term effectiveness of azathioprine, in Crohn's disease (CD) patients remains a matter of debate. This study aims at assessing the effectiveness and safety of azathioprine in patients treated continuously for less or more than 4 years.
Methods: Patients with steroid-dependent Crohn's disease in remission on azathioprine (2–2.5 mg/kg) for between 2 and 8 years were assigned into two groups. Patients in Group A were being treated continuously for 2 to 4 years whereas patients in Group B for 4 to 8 years. Patients were followed every month for 1 year with physical examination and laboratory tests. Compliance with treatment was also assessed every month. Every 3 months the Crohn's Disease Activity Index (CDAI) was calculated and the quality of life (QOL) Inflammatory Bowel Disease Questionnaire (IBDQ) was completed. Colonoscopy with calculation of the Crohn's Disease Endoscopic Index of Severity (CDEIS) was performed at baseline and at the end of the study. The primary end point was relapse after 1 year. Secondary end points were safety of treatment, QOL, and endoscopic healing.
Results: Fifty-eight patients were included in Group A and 42 in Group B. The relapse rates per protocol were 19.6% and 11.9%, respectively (*p*: not significant). There were no significant differences overall and at each time point of the study between the two treatment groups regarding compliance with and safety of treatment, CDAI, IBDQ, and CDEIS scores. Multifactorial analysis did not identify any factor influencing the remission of disease in any patient group.
Conclusions: Long-term treatment with azathioprine of steroid-dependent Crohn's disease is efficacious and safe.

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1. Introduction

Crohn's disease is characterized by a chronic, relapsing or unremitting course with intestinal and constitutional symptoms which deteriorate patients health-related quality of life.[1,2] Steroids are the mainstay of treatment for exacerbations of disease. However, about one third of those who receive corticosteroids for induction of remission become steroid-dependent within 1 year.[3] Moreover, the long-term exposure to systemic corticosteroids is associated with increased risk for developing dangerous and potentially life-threatening complications.[4]

A Cohrane review and a meta-analysis of controlled and uncontrolled clinical trials have documented the efficacy of immunomodulators azathioprine and 6-mercaptopurine both for remission maintenance and as steroid-sparing agents in chronically active, steroid-dependent Crohn's disease.[5,6] However, the duration of this effect remains a matter of debate.[7–11] Three retrospective studies showed contradictory results, one suggesting that the efficacy of azathioprine wanes gradually after 4 years of continuous treatment and the other two showing exactly opposite effects.[7–9] However, a recent double-blind, placebo-controlled withdrawal study suggested that azathioprine is effective and should be continued beyond 3.5 years despite complete remission of Crohn's disease.[10] Another recent retrospective study suggested that azathioprine may be discontinued without the risk of relapse in patients who maintain complete remission for more than 4 years.[11] However, besides effectiveness long-term azathioprine treatment carries a substantial risk for adverse events including bone marrow toxicity, infections, and malignancy.[12–14] On the other hand, adherence to treatment may be compromised by patients' excellent quality of life and concerns for safety of the drug.[15]

Thus, the aim of this study was to assess whether the effectiveness of azathioprine extends beyond 4 years of continuous treatment. Furthermore, the long-term safety of treatment was assessed.

2. Materials and Methods

2.1. Selection of Patients

Eligible patients were at least 18 years and less than 65 years of age and had purely luminal (inflammatory) steroid-dependent Crohn's ileitis, ileocolitis, or colitis. Steroid-dependency was defined as two flares of Crohn's disease within the past 6–12 months which were treated effectively with intravenous or oral corticosteroids (conventional or budesonide) with a relapse of disease upon tapering or soon after withdrawal of corticosteroids. Patients had achieved remission of disease with a combination of corticosteroids, azathioprine, and aminosalicylates; however, once remission had been achieved corticosteroids and aminosalicylates were tapered off and patients were maintained in clinical remission only on azathioprine (maintenance dose 2–2.5 mg/kg/day) and oral folic acid (5 mg every other day). Therefore, at the time of enrollment, patients should be maintained in complete clinical remission only on azathioprine for between 2 and 8 years. Remission was defined as the absence of symptoms of active Crohn's disease and maintenance of a Crohn's Disease Activity Index (CDAI) value of less than 150.[16]

Patients who consented to participate in this study were included in two groups: Group A which included patients who had been treated continuously for more than 2 but less than 4 years, and Group B which included patients who had been treated for more than 4 and less than 8 years. Patients with primary fibrostenotic or fistulizing disease, active Crohn's disease as defined by a CDAI score higher than 150, surgically induced remission or remission maintained on combination treatment with azathioprine and steroids, planned pregnancy, regular use of nonsteroidal anti-inflammatory drugs, insulin-dependent diabetes mellitus, active peptic ulcer disease, chronic renal, hepatic, or heart failure were excluded from this study.

2.2. Study Medication

Commercially available generic azathioprine (tablets 50 mg) was given at a daily dose ranging between 2.0 and 2.5 mg/kg of body weight. All patients received folic acid supplementation (Filicine®, 5 mg tablets, one tablet every other day).

2.3. Study Design

This was a prospective, investigator-blind study which was performed at a single center during a 5-year period (1998–2003) according to the Declaration of Helsinki (as revised in Hong Kong, 1983). Patients were not blinded as to the treatment they were receiving but they were unaware that there was another arm in the study. All patients gave written informed consent. The study was approved by the Ethics Committee in our Institution. Our center is a tertiary referral center for patients with inflammatory bowel diseases; however, there is also open access of individual patients to the outpatient IBD Clinic in person or via a telephone line to the outpatient clinic secretariat office. In fact, at least 40% of the patients attending the Clinic are self-referrals.

Patients fulfilling the entry criteria were evaluated during a 14-day screening period (Fig. 1). During screening the following parameters were recorded: a detailed medical history, physical examination, haematological and biochemical tests, calculation of a CDAI score, completion of the Inflammatory Bowel Disease Questionnaire (IBDQ) regarding quality of life,[17] and an ileocolonoscopy, which was performed after the calculation of the CDAI. At ileocolonoscopy, all endoscopic lesions were recorded and the Crohn's Disease Endoscopic Index of Severity (CDEIS) was calculated according to GETAID.[18] In summary, the following 9 lesions, namely pseudopolyps, healed ulceration, frank erythema, frank oedema, aphthoid ulcers, superficial/shallow ulcers, deep ulcers, non-ulcerated stenosis, and ulcerated stenosis were recorded and graded. The average segmental area, diseased and ulcerated, was separately calculated and the CDEIS was calculated for all ileocolonic lesions. In addition, 6 mucosal biopsy specimens were obtained from four parts of the colon (rectum, left colon, transverse colon, and right colon) and the terminal ileum, if entered. Histology was assessed by an experienced gastrointestinal pathologist (KP) who was unaware of the study protocol or treatment group