Comparative trial of remission prophylaxis in quiescent Crohn's disease with oral 4-aminosalicylic acid versus 5-aminosalicylic acid slow release tablets

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S HOWALDT, A RAEDLER, H-C REINECKER, et al. Comparative trial of remission prophylaxis in quiescent Crohn's disease with oral 4-aminosalicylic acid versus 5-aminosalicylic acid slow release tablets. Can J Gastroenterol 1993;7(2):241-244. 4-Aminosalicylic acid (4-ASA) has been suggested to be effective in the treatment of active ulcerative colitis. Oral slow release tablets containing 4-ASA (1.5 g/day) were compared with those containing 5-ASA (1.5 g/day) in the maintenance treatment of Crohn's disease in a one-year double-blind, randomized study involving 60 patients with ileocolonic or colonic involvement. Patients were enrolled if in stable remission without active drugs for more than two months but less than one year. Total colonoscopy and ileoscopy were performed at enrollment and at the end of the study. The cumulative relapse rates at 12 months were 37% in the 4-ASA and 38% in the 5-ASA group. Clinical relapse, as defined by a rise in the Crohn's disease activity index (CDAI) of more than 100 points to values higher than 150, was accompanied by a statistically significant rise in serum concentrations of soluble interleukin-2 receptor and by an increased percentage of activated peripheral blood T cells. There were no statistical differences between the 4-ASA and the 5-ASA group regarding relapse rates, the rise in CDAI during relapse or the increase of soluble interleukin-2 receptor concentrations. It is concluded that 4-ASA may be as effective as 5-ASA in the maintenance treatment of quiescent Crohn's disease and that there were no differences in the severity of relapse between both treatment groups. (*Pour résumé, voir page 242*)

Key Words: 4-Aminosalicylic acid, 5-Aminosalicylic acid, Crohn's disease, Immune activation, Soluble interleukin-2 receptor, Ulcerative colitis

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4-AMINOSALICYLIC ACID (4-ASA), also named para-aminosalicylic acid (PAS), is regarded as a relatively safe drug, following its use in the therapy of tuberculosis over many years. It is an isomer of 5-aminosalicylic acid (5-ASA), which is the active component of salazosulphapyridine used in the treatment of inflammatory bowel disease (IBD). However, in comparison with 5-ASA, the sodium salt of 4-ASA is a more stable compound (1,2). Animal models led to the conclusion that 4-ASA may have anti-inflammatory properties comparable to those of 5-ASA (1). Numerous clinical studies have shown that 4-ASA is highly effective in the topical treatment of ulcerative proctitis or left-sided ulcerative colitis (2-6). Moreover, 4-ASA slow-release tablets were shown to be effective in active ulcerative colitis (7). The results of a one year, double-blind, randomized and prospective trial are reported in which enterically coated 4-ASA was compared with a dose rate of 5-ASA at 0.5 g tid in the maintenance therapy of patients with inactive Crohn's colitis and ileocolitis.

Essai comparatif d'une prophylaxie sur la rémission dans la maladie de Crohn silencieuse avec des comprimés à libération lente d'acide 4-aminosalicylique versus acide 5-aminosalicylique

RÉSUMÉ: L'acide 4-aminosalicylique (4-AAS) serait efficace dans le traitement de la colite ulcéreuse active. Des comprimés à libération lente renfermant du 4-AAS (1,5 g par jour) ont été comparés au 5-AAS (1,5 g par jour) dans un traitement d'entretien de la maladie de Crohn, dans le cadre d'une étude randomisée à double insu, sur 60 patients porteurs d'atteintes iléo-coliques ou coliques, sur une période d'un an. Les patients ont été admis, s'ils étaient en rémission stable et s'ils n'avaient pris aucun médicament actif durant plus de 2 mois, mais depuis moins d'un an. La coloscopie et l'iléoscopie ont été effectuées au moment de l'admission, puis à la fin de l'étude. Les taux de rechute cumulatifs après 12 mois ont été de 37% dans le groupe 4-AAS et de 38% dans le groupe 5-AAS. La rechute clinique, définie comme une élévation d'un index d'activité de la maladie de Crohn de plus de 100 points pour atteindre des valeurs supérieures à 150, s'est accompagnée d'une élévation significative au plan statistique des concentrations sériques de récepteurs d'interleukine-2 et d'une augmentation du pourcentage de cellules T sanguines périphériques activées. Aucune différence statistique n'a été observée entre le 4-AAS et le 5-AAS au sujet des taux de rechute, de l'élévation de l'indice d'activité de la maladie de Crohn ou de l'augmentation des concentrations de récepteurs solubles de l'interleukine-2. On en conclut que le 4-AAS peut être aussi efficace que le 5-AAS dans le traitement d'entretien de la maladie de Crohn silencieuse et qu'il n'y a eu aucune différence dans la gravité des rechutes entre les deux groupes traités.

PATIENTS AND METHODS

Study criteria: In order to be included in the study, patients with Crohn's colitis or ileocolitis had to be in stable remission for more than two months with a Crohn's disease activity index (CDAI) of less than 150 points. Patients were not taking any active drugs, 5-ASA, steroids or other immunosuppressives one week before entry to the study. Patients with less than 30 cm of diseased bowel were excluded from the study, as were patients in stable remission for longer than one year or with bowel resections more than 50 cm. Further exclusion criteria were previous, unsuccessful treatment with 5-ASA, hypersensitivity to 5-ASA compounds, and pregnancy and/or lactation. A medically approved plan of contraception was required for all menstruating females. If it was felt that the medical problems the patient developed during the trial were due to the progressive formation of stenoses, the patient was dropped from the study. Defined endpoints were the end of the study period or a relapse in disease activity, as defined by a rise of the CDAI of more than 100 points to a resulting value greater than 150. The trial was granted prior approval by the institu-

tional review boards of the University of Hamburg and all patients signed an informed consent. A placebo group was not included because of ethical reasons (benefit by 5-ASA, which is licensed for the maintenance of remission therapy in Germany).

Patients: Sixty patients seen at the IBD clinics of University of Hamburg were entered into the trial and were randomized to 5-ASA or 4-ASA. Groups were comparable in age, sex, duration of disease, disease manifestation, length of present remission and previous treatment. Forty patients (19 on 4-ASA and 21 on 5-ASA) reached the predefined study endpoints, three patients developed progressive stenoses and the remaining 17 patients were dropped from the trial because of unreliability in keeping their appointments. None of the patients removed from the trial developed a clinical relapse within four weeks following the exclusion from the study.

Protocol: At the initial visit, history, physical examination, colonoscopy and stool examination for ova, parasites and enteric pathogens was carried out and blood was drawn for electrolyte assessment, differential blood count, sequential multiple analysis (SMA 12),

determination of activated T cells and serum soluble interleukin (IL)-2 receptor concentration. Office visits were repeated at monthly intervals. The patients kept daily diaries in which they recorded the number of bowel movements and scores for blood, mucus, urgency, abdominal pain and the appearance of extraintestinal manifestations. Each office visit included a physical examination, serum electrolytes, differential blood count and SMA 12. Every three months assessment of soluble IL-2 receptor and activated T cells was repeated. Patients were randomly assigned to take either 500 mg 4-ASA tid (Reed and Carnick/Block Drug Co, New Jersey) or 500 mg 5-ASA tid (Claversal; SmithKline Beecham, Pennsylvania). Tablets were coated with Eudragit S/L designed to dissolve at pH 6.8. Colonoscopy and ileoscopy were performed at enrollment and at the study endpoint by an endoscopist unaware of the trial. Endoscopy results were classified by a score shown in Table 1.

Assessment of activated T cells and serum soluble IL-2 receptor concentrations: Peripheral blood mononuclear cells were prepared by density gradient centrifugation as described previously (8). The state of peripheral blood T cell activation was determined by the expression of IL-2 receptors on their plasma membrane (8). In brief, mononuclear cells were labeled with fluorescent antibodies, specifically directed against CD3 (T cells, fluorescein-isothiocyanate conjugated, Becton-Dickinson, California) and 5E9 (transferrin receptor, phycoerythrin conjugated, Becton-Dickinson). Cells were analyzed by two-colour flow cytometry (Facscan, Becton-Dickinson) (8). Serum soluble IL-2 receptor concentrations were assessed by sandwich enzyme-linked immunosorbent assay (ELISA) (T Cell Sciences, Massachusetts) (9).

RESULTS

The patients randomized were comparable with respect to age, sex, duration of disease, disease activity, symptoms and adjunctive medication. Of 60 patients, 21 receiving 5-ASA

TABLE 1

Endoscopy score used to assess disease activity

Score	Criteria
0	Vascular pattern present, normal light reflex
1	No vessels, granulations
2	Contact bleeding, erythema
3	Fibrinous exudate, small ulcers (<5mm, >10/10cm)
4	Spontaneous bleeding, large ulcers (>5mm, >10/10cm)

Endoscopy scores were assessed by an endoscopist not involved in this study in a double-blinded fashion. All endoscopies were carried out by the same examiner

TABLE 2

Cumulative relapse rates under treatment with 4-ASA or 5-ASA

Time point	Relapse rate	
	4-ASA	5-ASA
3 months	4/19 (21%)	3/21 (14%)
6 months	6/19 (32%)	6/21 (29%)
1 year	7/19 (37%)	8/21 (38%)

No statistical differences were seen in cumulative relapse rates at three, six and 12 months between the 4-ASA and 5-ASA groups

and 19 receiving 4-ASA completed the study. The remaining 20 patients were removed from the trial because of progressive stenoses without significant inflammation (three patients) or non-compliance (17). None of them left the study because of relapse. The cumulative relapse rates are shown in Table 2. No statistical difference was found between the 4-ASA and the 5-ASA group.

To determine whether the clinical severity of relapse was different between patients treated with 4-ASA and those on 5-ASA, the average rise in CDAI scores before and after relapse was assessed in both groups. The CDAI values (mean $\pm$ SEM) of the relapsing patients treated with 4-ASA increased by 132 $\pm$ 36, whereas the 5-ASA group showed an average rise of 147 $\pm$ 40. Moreover, average endoscopic scores (mean $\pm$ SEM) in patients relapsing were not different between treatment groups (3.1 $\pm$ 1.2 for 4-ASA and 3.5 $\pm$ 0.9 for 5-ASA treated patients). There was also little difference in the disease activity of patients maintaining remission with 4-ASA (83.3 $\pm$ 29) in comparison with those receiving 5-ASA (60.9 $\pm$ 23.4).

Immunological parameters including serum soluble IL-2 receptor concentrations and activated peripheral blood T cells can be used to monitor

disease activity in IBD (8-14). A difference in the immunological degree of activation would be indicative for differences in disease activity during relapse in either of the treatment groups. However, both the rise of serum soluble IL-2 receptor concentrations (mean $\pm$ SEM) during relapse (286 $\pm$ 48 U/mL and 242 $\pm$ 54 U/mL) and of activated T cells (10.1 $\pm$ 3.4% and 13.5 $\pm$ 4%) were similar in the 4-ASA and the 5-ASA group, respectively. The increase in soluble IL-2 receptor concentrations during relapse was statistically significant ($P<0.01$) compared with clinically quiescent patients reaching the one-year study end point.

DISCUSSION

This pilot trial indicates that oral 4-ASA may be as effective as 5-ASA in maintaining remission in quiescent Crohn's disease. Relapse rates were not different between patients treated with 4-ASA and those treated with 5-ASA. Moreover, the relapse rates observed under 1.5 g/day 5-ASA were similar to those observed in another trial studying maintenance of remission under 2.4 g/day 5-ASA and using similar study inclusion criteria (15). This trial also included a placebo group, showing a spontaneous relapse rate of more than 50%. The height of the relapse rate is best explained by the selection criteria

used in the trial by Pallone et al (15) and in the present study including only patients who had reached remission recently.

It is possible that the severity of relapse would be different under treatment with 4-ASA compared with 5-ASA. However, neither by clinical (CDAI, endoscopic score) nor by immunological parameters (serum soluble IL-2 receptor, activated T cells) could any difference in disease activity during relapse be found. Moreover, clinical disease activities (CDAI) of patients maintained in remission were similar whether treated by 4-ASA or by 5-ASA.

4-ASA differs from 5-ASA in that it is more stable than 5-ASA, which is substituted in the meta position and therefore breaks down more rapidly in a watery solution (1,2). In contrast to 5-ASA no nephrotoxicity related to 4-ASA has been reported. The only other study which compared these two compounds examined the response to topical treatment in left-sided colitis and showed that 4-ASA and 5-ASA were equally effective (6).

The anti-inflammatory mechanism by which the aminosalicylates exert their therapeutic action is unknown. 5-ASA is a potent inhibitor of arachidonic acid metabolism, decreasing the synthesis of both leukotrienes and prostaglandins (16-18). Moreover, 5-ASA is a potent scavenger of free radicals (19-21). In contrast, 4-ASA does not seem to have an inhibitory effect of the lipooxygenation of arachidonic acid and is ineffective as a radical scavenger (22). However, both drugs inhibit in vitro activation of T and B lymphocytes by pokeweed mitogen in a dose-dependent manner (8,23). Animal models suggest that 4-ASA may be as effective as 5-ASA in terms of in vivo anti-inflammatory properties (1). These observations suggest that the use of either drug in IBD may decrease the heightened state of lamina propria lymphocyte activation as a part of their therapeutic action. Moreover, mechanisms not affecting arachidonic acid metabolism and superoxide release may contribute to the therapeutic potential of both drugs in IBD.

4-ASA, which has been previously

named para-aminosalicylic acid, has been used in the treatment of tuberculosis using resorbable oral doses ranging from 8 to 12 g/day. Consequently, considerable data on the drug's side effect profile have been generated from a large number of patients. The most common side effects include nausea, vomiting and epigastric pain. In a small number of cases, fever, joint pains, skin eruptions and hepatitis have been

reported, which all may be attributed to hypersensitivity reactions (24). Very rarely seen are more serious side effects such as leukopenia, thrombocytopenia and agranulocytosis (22). It may, therefore, be possible to use 4-ASA at much higher doses in a slow release formulation, perhaps resulting in greater therapeutic efficacy.

It is concluded that oral 4-ASA therapy may be as effective as 5-ASA in

the maintenance of remission in Crohn's disease. Moreover, several studies have shown that 4-ASA may be effective in the treatment of active Crohn's disease or ulcerative colitis both as a topical formulation (enema) or as an oral slow release tablet. Additional placebo controlled trials, involving a large number of patients, are warranted to investigate further this promising compound.

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