CLINICAL STUDY

Sulfasalazine in the prevention of anterior uveitis associated with ankylosing spondylitis

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Abstract

Purpose **To assess the effects of sulfasalazine in preventing recurrences and reducing the severity of anterior uveitis associated with ankylosing spondylitis and chronic intestinal inflammation.**

Methods **Twenty-two patients with anterior uveitis associated with ankylosing spondylitis were studied. Ten patients were randomised to receive oral sulfasalazine (group 1) and 12 patients randomised to no treatment (group 2); all were followed for 3 years. Blood–aqueous barrier permeability was determined by fluorophotometry and bowel biopsies were taken.**

Results **A statistically significant difference was observed between the two groups regarding the number of recurrences of uveitis (p = 0.016). The blood–aqueous barrier permeability was significantly higher during acute attacks in group 2 (group 1: 31.3 ± 26.4 × 10^{-4} min^{-1} vs group 2: 66.2 ± 28.5 × 10^{-4} min^{-1}; p = 0.019) but not during the disease-free period. We observed a higher incidence of chronic intestinal inflammation at the end of the study in group 2 (group 1: 3/8 vs group 2: 7/9, p = 0.153). No relation was observed between blood–aqueous barrier permeability and the number of recurrences. The number of patients with severe persistent posterior synechiae at the end of the study was higher in group 2 (group 1: 4 patients before and 4 patients at the end; group 2: 4 patients before and 8 patients at the end; p = 0.65).**

Conclusion **Sulfasalazine may be beneficial in preventing recurrences and reducing the severity of anterior uveitis associated with ankylosing spondylitis.**

Key words Ankylosing spondylitis, Anterior uveitis, Bowel inflammation, Sulfasalazine

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Anterior uveitis is the most common form of uveitis and accounts for approximately three-quarters of cases, with an annual incidence rate of about 8 cases per 100 000 population.[1] Although anterior uveitis is usually the most easily managed form of uveitis, recurrences may result in severe visual loss. Anterior uveitis, as defined by the classification proposed by the International Uveitis Study Group, describes a disease predominantly limited to the anterior segment of the eye.[2] Acute cases of uveitis usually have a sudden onset and last up to 6 weeks. The inflammation is characterised by conjunctival hyperaemia, posterior synechiae, peripheral anterior synechiae and anterior chamber cell and flare. These cells and flare represent extravasated inflammatory cells and protein as a result of a breakdown of the blood–aqueous barrier.

Fluorophotometry is a non-invasive, sensitive and reproducible method that allows a quantitative determination of blood–aqueous barrier permeability.[3] We have previously studied blood–aqueous barrier permeability by fluorophotometry in HLA-B27-associated anterior uveitis, and have demonstrated a 10-fold increase in permeability during an acute attack as well as loss of the integrity of the barrier during the disease-free period.[4]

Anterior uveitis is a prominent manifestation of spondyloarthropathies, including ankylosing spondylitis, Reiter's syndrome and arthritis associated with inflammatory bowel disease.[5,6] The pathogenetic relationship between anterior uveitis and spondyloarthropathies remains undetermined, but the link of HLA-B27 antigen supports a common pathway and/or trigger for the two processes. Bowel inflammation has been shown to play an important role in the pathogenesis of spondyloarthropathies.[7–9] We have previously demonstrated a clear relationship between anterior uveitis and bowel inflammation and a close relation between the recurrence of uveitis and the presence of chronic intestinal inflammation.[10] This finding might have important therapeutic implications in that sulfasalazine, the principal drug used in the therapy of inflammatory bowel disease, could be useful to prevent flare-ups of uveitis.

In this study we used fluorophotometry and ileocolonoscopy to determine whether sulfasalazine could be useful to prevent flare-ups of uveitis associated with ankylosing spondylitis.

Patients and methods

Patients

Twenty-two patients with anterior uveitis associated with ankylosing spondylitis were recruited prospectively from the Instituto de Investigaciones Oftalmologicas Ramon Castroviejo. All patients gave informed consent and the study was approved by the local ethics committee. Patients were included if they had had at least two recurrent acute attacks of uveitis in the last year, chronic intestinal inflammation determined by biopsy and normal bowel habits (the presence of blood in the stool or a frequency of more than three times per day was considered abnormal). Patients who were using oral non-steroidal anti-inflammatory drugs and eyedrops for reasons other than for an acute iritic attack, patients with glucose phosphate dehydrogenase deficiency and sulfamide allergy were not included. All patients were HLA-B27 antigen positive. A sacroiliac radiographic study was performed, classifying the presence of sacroiliitis grade III–IV as abnormal. For the diagnosis of ankylosing spondylitis the New York modified criteria were used.[11] Severe persistent posterior synechiae were defined as those extending more than 90° that persist during the disease-free period.

Patients were assigned randomly to receive either sulfasalazine (group 1; $n = 10$) or no treatment (group 2; $n = 12$). The duration of the study was 36 months in all patients. Patients were included in the treatment group (group 1) if their birth month was an odd-numbered month.

Sulfasalazine treatment

The drug was started at a dose of 500 mg b.i.d. and then increased daily by 1 g until the therapeutic dose was achieved (3–4 g/day). This dose was administered for 6 months and then tapered to 1 g b.i.d. Regular laboratory measurements (blood complete count and creatininaemia) were performed monthly for the first 3 months and then every 3 months.

Flurophotometry

A Fluorotron Master (Coherent, Palo Alto, CA) was used to perform the blood–aqueous barrier permeability study. A detailed report of its technical characteristics has been published elsewhere.[12] This fluorophotometer has a detection threshold of less than 0.5 ng/ml and an axial resolution of 1.5 mm. Four different measures of the background autofluorescence in the anterior chamber were performed using the anterior segment ocular. The average result (AC0; ng/ml) was obtained and subtracted from the values obtained after injection of the tracer. Thereafter 14 mg/kg body weight of 20% sodium fluorescein was injected intravenously. Blood samples were drawn into EDTA tubes at 7, 15 and 55 min after the injection from a heparinised catheter in the contralateral arm. Samples were centrifuged (10 min at 1500 r.p.m.) and the supernatants ultrafiltrated in CF2 tubes (Amicon, Danvers, MA). The value of the protein-unbound fluorescein was assessed in three samples using a fluorophotometer-adapted container. These values were used to obtain the time integral of the plasma free fluorescein decline (NPBF; ng/ml/min) using a power of time regression procedure. The measure of the anterior chamber fluorescein was performed at 30 min after the injection (AC30; ng/ml). The diffusion coefficient (K_d) was assessed from the ratio between the anterior chamber fluorescein concentration and the time integral of the plasma free fluorescein decline.[3]

$$K_d = \frac{\text{AC30} - \text{AC0}}{\text{NPBF}} \ (min^{-1})$$

Blood–aqueous barrier permeability was determined during an acute attack and in the disease-free period in all patients. The fluorophotometric analysis was performed by an ophthalmologist who was unaware of the treatment.

Endoscopic and histological study

The endoscopic study was carried out using a Pentax EC-380 IL videocolonscope, without premedication, with four to ten gut mucosa specimens of terminal ileum, colon, or both, obtained by random biopsy though the mucosa was macroscopically normal. The histopathological analysis was carried out by a pathologist who was unaware of the clinical diagnosis. Biopsy specimens were fixed in formalin, dehydrated, mounted in paraffin, and tissue sections routinely stained with haematoxylin and eosin. In each biopsy sample several variables were analysed. First, the epithelial status was classified as normal, atrophic or ulcerated. Second, the presence of chronic inflammatory infiltrates was classified semiquantitatively as mild, moderate or severe. A tissue sample was considered to show chronic intestinal inflammation when a moderate to severe plasma lymphocytic infiltrate was evident in the lamina propria, or when the cellular infiltrate was mild and there was epithelial atrophy with marked villous flattening in the small bowel or a reduced number of glands and distortion of the crypts in the colon. Mild oedema or congested vessels in the lamina propria were not considered as inflammation. Ileocolonoscopic and bowel biopsy was performed before treatment on all patients, and at the end of the study in 8 patients of group 1 and 9 patients in group 2.

Statistical analysis

For statistical analysis of the data from the two groups continuous variables were compared using Student's *t*-test for two samples and the Mann–Whitney rank sum test, and dichotomous data using Fisher's exact test (two-tailed). The results were considered significant at $p < 0.05$.

Table 1. *Mean number of attacks of uveitis per patient per year for each group*

Group 1			Group 2		
First year	Second year	Third year	First year	Second year	Third year
0.50 ± 0.53	0.60 ± 0.84	0.30 ± 0.67	1.33 ± 1.23	0.83 ± 0.94	1 ± 1.04

Values are the mean ± SD.
Mann–Whitney test, $p = 0.016$.

Results

During this prospective cohort study, 22 patients were enrolled in two groups. In group 1 there were 8 men and 2 women, mean age 37.5 ± 5.5 years. In group 2 there were 9 men and 3 women, mean age 35.6 ± 4.9 years. There were no significant differences between the groups as regards age or gender. There was no statistically significant difference between group 1 and group 2 in pre-operative visual acuity ($p = 0.8$). The 3 year mean post-treatment visual acuity was 0.8 in group 1 and 0.6 in group 2 ($p = 0.05$).

No differences were found in the number of recurrences of uveitis and the results of biopsies at the onset of the study. The data relating to the number of recurrences after treatment are summarised in Table 1. A statistically significant difference was observed between the two groups regarding the number of recurrences ($p = 0.016$). The blood–aqueous barrier permeability, measured as the diffusion coefficient (K_d), was significantly higher during acute attacks in group 2 (group 1: 31.3 ± 26.4 × 10^{-4} min^{-1} vs group 2: 66.2 ± 28.5 × 10^{-4} min^{-1}; $p = 0.019$) but not during the disease-free period (group 1: 3.9 ± 2.4 × 10^{-4} min^{-1} vs group 2 5.3 ± 2.6 10^{-4} min^{-1}; $p = 0.191$) (Table 2). We observed a higher incidence of chronic intestinal inflammation at the end of the study in group 2 (group 1: 3/8 vs group 2: 7/9; $p = 0.153$). No relation was observed between blood–aqueous barrier permeability and the number of recurrences. There was no statistically significant relationship between blood–aqueous barrier permeability during acute attacks and disease-free periods. The number of patients with severe persistent posterior synechiae at the end of the study was higher in group 2 (group 1: 4 patients before and 4 patients at the end, group 2: 4 patients before and 8 patients at the end; $p = 0.65$).

All patients in group 1 completed treatment. During the study there were no adverse reactions reported or observed.

Table 2. *Blood–aqueous barrier permeability during an attack and the disease-free period (× 10^{-4} min^{-1})*

Acute attack		Disease-free period	
Group 1	Group 2	Group 1	Group 2
15.3	–	1.23	2.15
16.4	54.3	1.49	6.23
83.2	70.1	2.51	8.19
–	94.5	4.60	9.26
–	45.6	2.51	4.14
15.8	87.8	8.30	1.71
–	32.2	6.25	1.97
12.8	72.3	1.49	8.22
51.2	53.7	6.25	6.81
24.9	18.1	4.19	5.09
	112.8		6.08
	87.2		4.23
31.3 ± 26.4[a]	66.2 ± 28.5[a]	3.8 ± 2.4[b]	5.3 ± 2.6[b]

Values are the mean ± SD.
(–), no attacks.
[a]Student's *t*-test, $p = 0.019$.
[b]Student's *t*-test, $p = 0.191$.

Discussion

Anterior uveitis is the most common form of uveitis, and its association with the HLA-B27 haplotype in the white population has been estimated to be approximately 50%.[13] Patients with HLA-B27-positive anterior uveitis frequently present with unilateral alternating, non-granulomatous, recurrent iridocyclitis usually in association with a seronegative spondyloarthropathy.[1] Power *et al.*[14] have recently found that HLA-B27-positive patients have a more severe clinical course and, hence, a higher incidence of ocular complications than do patients with a negative HLA-B27 haplotype. In the study by Power *et al.*[14] the percentage of legally blind eyes in HLA-B27-positive patients was 11%. Rothova *et al.*[1] have shown that patients suffering from anterior uveitis in whom an HLA-B27 association is found have a significantly higher rate of recurrent inflammatory attacks and, hence, a higher likelihood of severe ocular complications. The unfavourable clinical course in HLA-B27-positive patients supports the need for more aggressive therapeutic strategies to control inflammation in this group of anterior uveitis patients.

We have previously reported a 60% incidence of chronic intestinal inflammation in patients with ankylosing-spondylitis-related uveitis and normal bowel habits.[10] Bowel inflammation has been shown to play an important role in the pathogenesis of spondyloarthropathies. Clinical features of spondyloarthropathies frequently complicate the course of inflammatory bowel diseases and can occur in 20% of patients with Crohn's disease.[6] Several authors have reported an increased incidence of bowel inflammation in patients with spondyloarthropathies and have analysed the relationship of this disease complex with HLA-B27 antigen, vertebral involvement and extra-articular manifestations.[8,9,15] The reason for the association remains unknown. Intestinal inflammation may be responsible for the occurrence of a transgression of oral tolerance and an increase in bowel permeability. This would lead to the absorption of exogenous antigens into the general circulation, initiating vertebral and anterior uveal inflammation in genetically predisposed patients (HLA-B27 antigen).

In the current study, the statistically difference in the rate of recurrences and the decrease in blood–aqueous barrier permeability during acute attacks experienced by patients on sulfasalazine suggest a beneficial role for this drug in anterior uveitis associated with ankylosing spondylitis and chronic bowel inflammation demonstrated by ileocolonoscopy (normal bowel habits). Sulfasalazine, the principal drug used in the treatment of inflammatory bowel diseases, consists of a sulfonamide (sulfapyridine) chemically bound to a salicylate (5-aminosalicylate). It undergoes bacterial cleavage the colon. The salicylate moiety is thought to exert its action through inhibition of prostaglandin synthesis. Reversing the increased bowel permeability found in anterior uveitis associated with ankylosing spondylitis may be the mechanism by which sulfasalazine prevents flare-ups of uveitis. Sulfasalazine has been used for many years in the therapy of inflammatory bowel disease and chronic arthritis. The safety of this regimen has been shown in large number of patients including children and women who are, or may become, pregnant. Most adverse effects (anaemia, hypercreatininemia and gastrointestinal discomfort) are minor and tend to occur within 3 months of starting therapy. Mielants *et al.*[16] have proved that sulfasalazine is beneficial in HLA-B27-related pauciarticular arthritis and enthesopathies resistant to non-steroidal anti-inflammatory drugs. In conclusion, sulfasalazine may be beneficial in the prevention of recurrences and reduction of severity of anterior uveitis associated with ankylosing spondylitis.

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