ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY (1997) 15: 71-75

Sulphasalazine Therapy in Chronic Uveitis of Children with Chronic Arthritis

Jing-Long Huang, Iou-Jih Hung and Kue-Hsiung Hsieh

SUMMARY **Four children with chronic arthritis (3 juvenile rheumatoid arthritis and 1 juvenile ankylosing spondylitis) and poorly controlled chronic uveitis, were given sulphasalazine (SASP) therapy for a mean period of 3.3 years. Three patients showed an excellent response, as evidenced by a reduction of inflammatory cells in the anterior chamber of the eyes and improvement of visual acuity. The response occurred after a mean of 7.7 weeks. These data suggested SASP therapy may have a role in the treatment of chronic anterior uveitis in children with chronic arthritis.**

Uveitis associated with juvenile rheumatoid arthritis (JRA) is an important cause of vision loss in children.[1-2] Chronic iridocyclitis occurs in approximately 10% of patients with JRA.[1-3] Those patients at greatest risk are young girls, with pauciarticular onset and antinuclear antibody (ANA) seropositivity.[4] One or more ocular complications (synechia, band keratopathy, cataracts or glaucoma) occurs in 33% to 75% of patients with uveitis.[1-5] Factors significantly associated with complicated uveitis were 1) a chronic course of uveitis, 2) juvenile psoriatic arthritis, 3) diagnosis of uveitis prior to, or at the time of arthritis onset, and 4) symptomatic onset. The therapy of iridocyclitis is aimed at suppressing inflammatory activity to preserve vision. Early detection and corticosteroid therapy have been the mainstays in controlling this disease. Fluctuation in disease activity of chronic uveitis and arthritis in patients with JRA may not coincide. Since the introduction of sulphasalazine (SASP) into the treatment of patients with chronic arthritis, SASP has proved its efficacy on synovitis. To our knowledge, there has not been any report of SASP used in the therapy of chronic iridocyclitis to date. In this retrospective study, we reviewed our experience with the use of SASP therapy on chronic iridocyclitis in 4 patients with chronic arthritis (3 with JRA and 1 with juvenile ankylosing spondylitis [JAS]).

PATIENTS AND METHODS

We reviewed the medical records of 36 patients with chronic arthritis. These patients were treated with SASP for at least 3 months in a pediatric arthritis clinic. Four patients had chronic anterior uveitis during their disease courses. The diagnosis of active uveitis, made by an ophthalmologist, was based on finding cells and/or flare in the anterior chamber, or keratitic precipitates on the endothelium of the cornea of lens. The severity of the inflammation was graded subjectively from 1 (mild) through 4 (very severe).[5] The course of the active eye disease was categorized as 1)

From the Department of Pediatrics, Chang Gung Children's Hospital and Chang Gung Medical College, Taoyuan, Taiwan.
Correspondence: Jing-Long Huang, Division of Allergy, Asthma and Rheumatology, Department of Medicine, Chang Gung Children's Hospital, Taoyuan, Taiwan.

acute: (a) single brief episode of less than 4 months, or (b) multiple brief episodes; 2) chronic: (a) single or multiple prolonged (4 months or greater) episodes with remission, or (b) chronic persistent, in which there could also have been acute flares requiring intensification of therapy such as local steroid injections or systemic steroids. Band keratopathy, synechia, cataracts, glaucoma, and phthisis bulbi were recognized as irreversible ocular complications of active uveitis. Significant visual loss was arbitrarily defined as best-corrected visual acuity of 20/200 or less.

Diagnosis of JRA was made according to the criteria defined by the American College of Rheumatology.[6] Ankylosing spondylitis was diagnosed according to the New York criteria.[7]

Sulphasalazine was administered at a dose of 50 mg per kg weight per day to a maximum of 2 gm per day, starting at 500 mg daily and usually increasing by 500 mg weekly until the therapeutic dose was reached. Three of the four children had bilateral eyes involvement. Topic corticosteroids and mydriatics had been administered to all 4 patients with uveitis. Three of 4 patients, whose uveitis followed chronic persistent course, had also received courses of oral corticosteroids, but their treatment efficacy were all limited. Two children had developed posterior synechia and cataract, respectively and had received iridectomy and lensectomy prior to SASP therapy. All these 4 patients were able to discontinue oral prednisolone and previous slow-acting antirheumatic drugs (SAARDs) after commencing SASP; and no patient required additional non-steroid anti-inflammatory drugs during SASP therapy. All patients were regularly followed up in every 1-3 months interval by the same ophthalmologist.

RESULTS

At the time of commencing SASP therapy, the mean age of these 4 patients was 14.3 years (range, 9.8 to 21.1 years). The mean duration of chronic iridocyclitis before starting SASP was 7.3 years (range, 3.1 to 11.2 years). The duration between onset of arthritis and uveitis was 1.9 years (range, -1.8 to 7 years). The mean duration of follow-up after SASP therapy was 3.3 years (range 2.2 to 4.4 years).

In three patients, 2 pauciarticular onset JRA and 1 JAS, uveitis improved after addition of SASP to their regimen. This improvement was evidenced by a reduction of inflammatory cells in the anterior chamber and improved visual acuity (Table 1). Improvement in the eye inflammation began after a mean of 7.7 weeks of SASP therapy, with a continued decrease in inflammation intensity over a period of two to four months (Fig. 1).

Case 1

This boy, born in 1981, developed pauciarticular onset JRA at the age of 2 years. Initially right knee was involved and later he developed left knee and ankle arthritis. At the age 3 years 1 month, he developed severe bilateral chronic anterior uveitis which caused band keratopathy, posterior synechia and cataract. The intramural inflammation responded poorly to intensive treatment with topical and courses of systemic corticosteroid therapy. He received left iridectomy and lensectomy in 1985 and 1986, respectively. In an effort to obtain better control of joints disease, he was given SASP since October, 1991. During the 29 months of therapy, the uveitis was still very active which further resulted in cataract and significant visual loss of his right eye.

Case 2

This 11 years old boy had severe bilateral chronic anterior uveitis at the age of 2 years. Two years later, he developed pauciarticular onset JRA and has been receiving naproxen therapy since then. The intraocular inflammation, followed a chronic persistent course, was unresponsive to topical, intraocular dexamethasone injections and multiple courses of systemic oral corticosteroids. As an effort to treat synovitis, SASP was given since December, 1992. One month later, not only synovitis but uveitis became quiet. He did not have any more flare of uveitis eversince. When last examined in October 1994, both eyes were quiet with a visual acuity of 20/20 even though in the left eye a tiny bandshaped keratopathy was found.

Case 3

This 18 years old girl, developed pauciarticular onset JRA at the age of 3 years 3 months and right chronic anterior uveitis at the age of 5 years. After treatment with topical corticosteroid and mydriatic eye drops for 11 years, she still suffered from recurrent uveitits with flares, frequently with grade 2 inflammatory cells in the anterior chamber of her right eye. After 3 weeks therapy of SASP, her eye inflammation became quiet with much

Table 1. The clinical response of chronic arthritis in children with chronic anterior uveitis after suphasalazine therapy

Patient	1	2	3	4
Type of arthritis onset	Pauci-JRA	Pauci-JRA	Pauci-JRA	JAS
Sex	M	M	F	M
Age at arthritis onset	2y3m	4y	3y3m	11y
Age at uveitis onset	3y1m	2y	5y	18y
Age at commencing SASP therapy	10y1m	9y9m	16y2m	21y1m
Course of uveitis prior SASP therapy	Chronic persistent	Chronic persistent	Chronic multiple	Chronic multiple
Involved eye(s)	Bilateral	Bilateral	Right	Bilateral
Prior therapy for uveitis	Oral P * Iridectomy Lensectomy	I.O.D.I. ~ Oral P.*	T#	I.O.D.I. ~ Oral P.*
Duration of SASP to onset of uveitis improvement	No response	4 weeks	3 weeks	16 weeks
Duration of follow-up after SASP therapy	3y5m	2y3m	3y2m	4y5m
Last examination				
Uveitis activity	Severe	No	No	No
Visual acuity (corrected)	Near blindness	20/20 o.u.	20/20 o.u.	20/30 o.u.

*: Oral predinosolone; ~: Intraocular dexamethasone injection;
#: Topical steroid and atropine eye solutions.

decrease in inflammatory cells. When last examined in October, 1994, her both eyes had a visual acuity of 20/20.

Case 4

This 25 years old boy, a case of JAS, developed bilateral chronic anterior uveitis, followed a chronic persistent course, at the age of 18 years. The intraocular inflammation did not respond to intensive treatment including topical and systemic oral corticosteroids, which resulted in bilateral cataract formations. Although his joint inflammation became quiet since July 1990, he was given SASP for his active and recurrent flares of uveitis. After 4 months SASP therapy, there was dramatic decrease in the severity and course of his uveitis. In recent 4 years, he had flare of uveitis only once. When last examined in December, 1994, his visual acuity was 20/30 with correction.

DISCUSSION

The iridocyclitis of JRA often has an insidious onset with a chronic course and few symptoms. Early detection of eye disease and active treatment with corticosteroids are important in the management of chronic iridocyclitis. Decreasing severity of chronic uveitis in children with chronic arthritis have been reported.[5,8] which may be ascribed to earlier surveillance for ocular disease and more effective treatment. Although there is no relationship between flares of ocular and articular disease in JRA.[9,10] anti-inflammatory medications given to

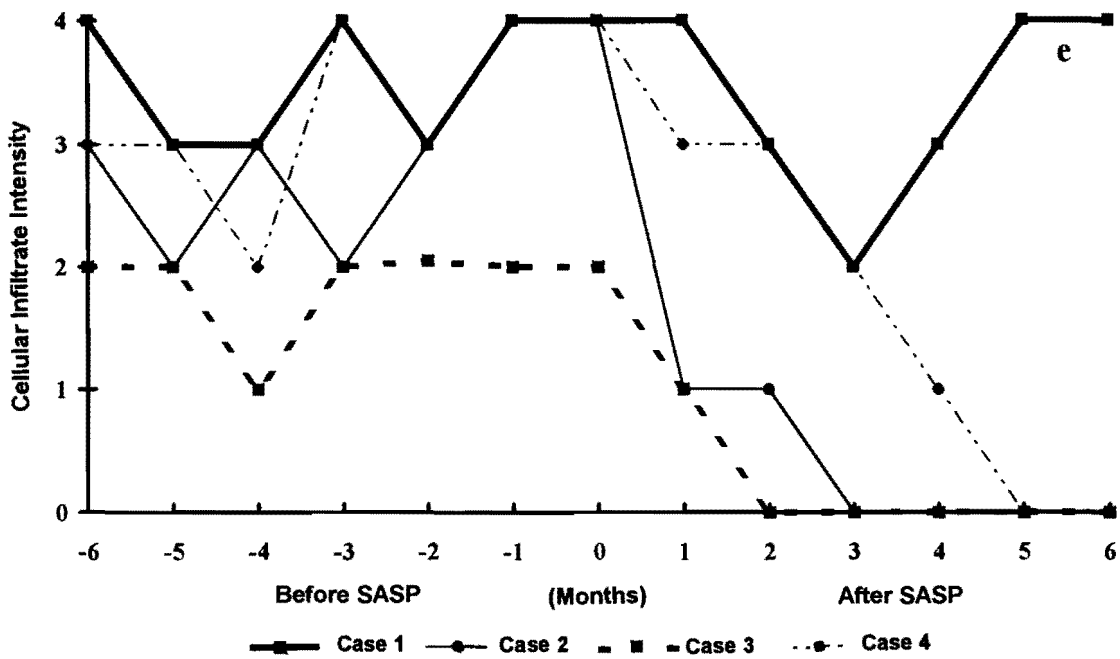

Fig. 1 Chronic uveitis response to sulphasalazine therapy

treat JRA may reduce ocular inflammation.[11]

The etiology and pathogenesis of uveitis associated with JRA are unknown. The demonstration of antibody reactivity to an antigen extracted from the anterior uveal tract (LMW-IA) supports the contention that the pathogenesis of anterior uveitis has an autoimmune basis.[12] Antibodies that react with S antigen[13, 14] and lens BH-crystallin[13] are associated with uveitis in children with JRA.

Sulphasalazine is a SAARD whose mechanism of action is not clear. It seems to have immunomodulatory effects influencing prostaglandin synthesis,[15] neutrophil chemotaxis,[16] lymphocyte function,[17] synovial neovascularization,[18] inhibition of leukocyte adhesion molecule[19] direct immunosuppressive effect of B cell hyperactivity and decreased in the serum immunoglobulin levels.[20, 21] Clinical trials for its use in the management of inflammatory bowel disease and articular manifestation in adult and pediatric patients with chronic arthritis have found it to be beneficial and safe. Dougados *et al.*[22] reported that SASP might prevent attacks of acute anterior uveitis in patients with spondyloarthropathy. To our knowledge, no studies of the effects of SASP therapy on chronic iridocyclitis have been reported to date. In our 4 patients who had poorly controlled chronic uveitis unresponsive to corticosteroids and nonsteroid anti-inflammatory drugs, the addition of SASP therapy resulted in significant improvement of the eye disease in 3 patients over a mean of 7.7 weeks. It seems that immunomodulatory effects of SASP may explain part of its antirheumatic and also anti-uveitis benefits. Prospective controlled studies are needed to confirm these findings.

REFERENCES

1. Key SN III, Kimura SJ. Iridocyclitis associated with juvenile rheumatoid arthritis. Am J Ophthalmol 1975; 80: 425-9.
2. Schaller J, Kupfer C, Wedgewood RJ. Iridocyclitis in juvenile rheumatoid arthritis. Pediatrics 1969; 44: 92-100.
3. Ansell BM, Bywaters EGI, Isdale JC. Comparison of cortisone and aspirin in the treatment of juvenile rheumatoid arthritis. Br Med J 1956; 1: 1075-7.
4. Wolf MD, Lichter PR, Ragsdale CG.

Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology 1987; 94: 1242-8.
5. Cabral DA, Petty RE, Malleson PN, Ensworth S, McCormick AQ, Shroeder M. Visual prognosis in children with chronic anterior uveitis and arthritis. J Rheumatol 1994; 21: 2370-5.
6. Brewer EJ, Bass J, Baum J, *et al.* Current proposed revision of JRA criteria. Arthritis Rheum 1977; 20: 195-9.
7. Bennett BH, Birch TA. New York symposium on population studies in the rheumatic disease: new diagnostic criteria. Bull Rheum Dis 1967; 17: 453-8.
8. Sherry DD, Mellins ED, Wedgwood RJ. Decreasing severity of chronic uveitis in children with pauciarticular arthritis. AJDC 1991; 145: 1026-8.
9. Rosenberg AM, Oen KG. The relationship between ocular and articular disease in children with juvenile rheumatoid arthritis and associated uveitis. Arthritis Rheum 1986; 29: 798-800.
10. Leak AM, Ansell BM. The relationship between ocular and articular disease activity in juvenile rheumatoid arthritis complicated by chronic anterior uveitis. Arthritis Rheum 1987; 30: 1196-7.
11. Olson NY, Lindsley CB, Godfrey WA. Nonsteroidal anti-inflammatory drug therapy in chronic childhood iridocyclitis. AJDC 1988; 142: 1289-92.
12. Hunt DWC, Petty RE, Milar F. Iris protein antibodies in serum of patients with juvenile rheumaotoid arthritis and uveitis. Int Arch Allergy Immuno 1993; 100: 314-8.
13. Petty RE, Hunt DWC. Immunity to ocular and collagen antigens in childhood arthritis and uveitis. Int Arch Allergy Appl Immuno 1989; 89: 31-7.
14. Petty RE, Hunt DWC, Rollin DF, Schroeder ML, Puterman ML. Immunity to soluble retinal antigen in patients with uveitis accompanying juvenile rheumatoid arthritis. Arthritis Rheum 1987; 30: 287-93.
15. Hawkey CJ, Truelove SC. Inhibition of prostaglandin synthetase in human rectal mucosa. Gut 1983; 24: 213-7.
16. Rhodes JM, Bartholomen TC, Jewell DP. Inhibition of leukocyte motility by drugs used in ulcerative colitis. Gut 1981; 22: 642-7.
17. Carter SD, Bacon PA, Hall ND. Characterization of activated lymphocytes in the peripheral blood of patients with rheumatoid arthritis. Ann Rheum Dis 1981; 40: 293-8.
18. Madhok R, Wijelath E, Smith J, Watson J, Sturrock RD, Capell HA. Is the beneficial effect of sulfasalazine due to inhibition of synovial neovascularization? J Rheumatol 1991; 18: 199-202.
19. Greenfield SM, Hamblin AS, Shakoor ZS, Teare JP, Punchard NA, Thompson RPH. Inhibition of leukocyte adhesion molecule upregulation by tumor necrosis factor a: a novel mechanism of action of sulphasalazine. Gut 1993; 34: 252-6.
20. Imai F, suzuki T, Ishibashi T, Tanaka M, Akiyama Y, Dohi Y. Effect of sulfasalazine on B cell hyperactivity in patients with rheumatoid arthritis. J Rheumatol 1994; 21: 612-5.
21. Bird HA, Dixon JS, Pickup ME, *et al.* A biochemical assessment of sulfasalazine in rheumatoid arthritis. J Rheumatol 1982; 9: 36-45.
22. Dougados M, Berenbaum F, Maetzel A, Amor B. The use of sulfasalazine for the prevention of attacks of acute anterior uveitis associated with spondyloarthropathy. Arthritis Rheum 1990; 33(suppl): 145.

INTERNATIONAL CONGRESS ON MELIOIDOSIS

GENERAL INFORMATION

Date	:	22-25 November 1997
Venue	:	Amari Watergate Hotel, Bangkok Thailand
Organized by	:	Chulabhorn Research Institute in collaboration with The Thailand Research Fund, The Infectious Diseases Association of Thailand and Wellcome-Mahidol University-Oxford Tropical Medicine Research Programme
Main topics	:	Epidemiology, Pathogenesis, Immunity, Laboratory Diagnosis, Therapy, Typing, Genomes of *Burkholderia pseudomallei*, etc.
Conference Secretariat	:	The International Congress on Melioidosis Chulabhorn Research Institute Office of Scientific Affairs Vipavadee-Rangsit Highway Bangkok 10210, Thailand
Telefax	:	66 (2) 574 0616
E-mail	:	secretariat@melioidosis.org