Sulphasalazine and regression of rheumatoid nodules

H J ENGLERT,¹ G R V HUGHES,² AND M J WALPORT¹

From the ¹Rheumatology Unit, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London; and the ²Rheumatology Unit, St Thomas's Hospital, London

SUMMARY The regression of small rheumatoid nodules was noted in four patients after starting sulphasalazine therapy. This coincided with an improvement in synovitis and also falls in erythrocyte sedimentation rate (ESR) and C reactive protein (CRP). The relation between the nodule regression and the sulphasalazine therapy is discussed.

Sulphasalazine (Salazopyrin), an azo compound of sulphapyridine and 5-aminosalicylic acid, was introduced in 1941 for the treatment of rheumatoid arthritis and ulcerative colitis.¹ Its effectiveness in the treatment of ulcerative colitis remains undisputed. It quickly fell into disfavour as a treatment for rheumatoid arthritis, however, after a report by Sinclair and Duthie showed that it had no disease modifying effect.² It was reintroduced in 1978 by McConkey *et al*³ and has been subsequently found to exert a disease modifying effect in the treatment of rheumatoid arthritis.⁴ There have been no reports on its use in modifying extra-articular features of rheumatoid disease.

During a prospective trial of sulphasalazine we followed the clinical course of 19 patients, five of whom had small rheumatoid nodules. We now report regression of rheumatoid nodules in four and relate this to remission of rheumatoid disease induced by sulphasalazine.

Case reports

CASE 1

A 64 year old man with a four year history of seropositive erosive rheumatoid arthritis developed a polyarticular flare and was entered into a prospective trial of sulphasalazine. At entry his joint score was 15 and he was noted to have a 10 mm nodule over the left olecranon; ESR was 120 mm/1st h; CRP 68 µg/ml; RA latex 1/1280; platelets 529×10¹²/l. After 12 weeks of therapy the rheumatoid nodule had disappeared and the joint score had fallen to 5;

ESR was 38 mm/1st h; CRP 28.5 µg/ml; RA latex 1/1280; platelets 401×10¹²/l.

CASE 2

A 66 year old man with an 18 year history of seropositive rheumatoid arthritis started treatment with sulphasalazine in July 1985. At entry he had an 8 mm rheumatoid nodule over the left olecranon and marked polyarticular synovitis; ESR was 22 mm/1st h; CRP 35.5 µg/ml; RA latex 1/40; platelets 441×10¹²/l. After eight weeks of therapy the nodule had disappeared and the synovitis improved; ESR was 10 mm/1st h; CRP 1 µg/ml; RA latex 1/80; platelets 304×10¹²/l.

CASE 3

A 64 year old woman with a two year history of seropositive rheumatoid arthritis and a polyarticular flare started treatment with sulphasalazine in September 1985. At entry she had a joint score of 8 and two rheumatoid nodules 6 mm and 3 mm in diameter were noted over the left olecranon; ESR was 64 mm/1st h; CRP 1 µg/ml; RA latex 1/320. Within 12 weeks the joint score had fallen to 3, both nodules had disappeared, and the synovitis settled; ESR was 39 mm/1st h; CRP 1 µg/ml; RA latex 1/160.

CASE 4

A 61 year old woman with a 15 year history of seropositive nodular erosive rheumatoid arthritis developed a polyarticular flare for which she started treatment with sulphasalazine in April 1985. Small confluent rheumatoid nodules at her right elbow disappeared, her synovitis improved, and her joint score fell from 15 to 7 over 12 weeks; the ESR fell from 67 to 3 mm/1st h; and CRP from 55.5 µg/ml to 16.5 µg/ml over the same period.

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Correspondence to Dr H J Englert, Rheumatology Unit, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS.

CASE 5

The fifth patient, who at four weeks noted 'softening' of her small decranon nodules, elected to cease therapy after eight weeks. At this stage there was no objective decrease in nodule size.

Discussion

The initial pathogenetic event in the formation of a rheumatoid nodule is thought to be a focal arteriolitis.⁵ This eventually evolves into the characteristic triple layered rheumatoid granuloma with a central core of fibrinoid necrosis, a middle layer of palisading fibroblasts and histiocytes, and an outer layer of granulation tissue, which often, with time, forms a connective tissue capsule.⁵

Rheumatoid nodules occur almost exclusively in patients with circulating rheumatoid factor⁶ and in general are associated with erosive disease and a poorer prognosis.⁷ Unusually rheumatoid nodules regress spontaneously,⁸ but the mechanism by which this occurs is unknown.

Because rheumatoid nodules usually cause little in the way of problems, reports on the relation between nodule regression and therapy have been scant. One case has been reported, however, where regression of rheumatoid lung parenchymal nodules was associated with steroid therapy,⁹ and another in which choroidal nodules and an associated retinal detachment improved after prednisolone and cyclophosphamide therapy.¹⁰ Regression of rheumatoid nodules has also been noted in association with gold and penicillamine therapy.¹¹

Although it is possible that nodule regression in four of the five patients occurred spontaneously, the relative infrequency of nodule regression and the temporal relation between introduction of sulphasalazine and the improvement in disease activity strongly suggest that in some way sulphasalazine contributed to both events.

Sulphasalazine has been used for many years in the treatment of ulcerative colitis, but its widespread use as a second line agent in the treatment of rheumatoid arthritis has been relatively recent.³

It is an azo compound of sulphapyridine and 5-aminosalicylic acid (5-ASA): the local action of 5-ASA on the bowel wall is thought to have a predominant role in the drug's activity in ulcerative colitis¹²; in rheumatoid arthritis, however, the sulphapyridine moiety is thought to be more important.¹³ Just how the drug works as a disease modifying agent remains poorly understood. Both sulphasalazine and sulphapyridine are known to have an inhibitory action on polymorph migration

and superoxide production, and 5-ASA and sulphapyridine inhibit polymorph cytotoxicity in vitro.¹⁴ Sulphasalazine has also been noted to inhibit mononuclear cell chemotaxis^{15 16} and to inhibit mast cell degranulation but potentiate basophil histamine release.¹²

None of the above readily explains the mechanism involved in rheumatoid nodule regression, a large component of which would hypothetically require clearance by cellular or enzymatic means, or both, of the large amorphous acellular centre.

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References

- 1 Svartz N. Salazopyrine, a new sulfanilamide preparation. *Acta Med Scand* 1942; **6**: 577-98.
- 2 Sinclair R J G, Duthie J J R. Salazopyrin in the treatment of rheumatoid arthritis. *Ann Rheum Dis* 1949; **8**: 226-31.
- 3 McConkey B, Amos R S, Butler E P, Crockson R A, Crockson A P, Walsh L. Salazopyrin in rheumatoid arthritis. *Agents Actions* 1978; **8**: 438-41.
- 4 Neumann V C, Grindulis K A, Hubbard J, McConkey B, Wright V. Comparison between penicillamine and sulphasalazine in rheumatoid arthritis: Leeds Birmingham trial. *Br Med J* 1983; **287**: 1099-102.
- 5 Sokoloff L, McCluskey R T, Bunion J J. Vascularity of the early subcutaneous nodule of rheumatoid arthritis. *Arch Pathol* 1953; **55**: 475-95.
- 6 Duthie J J R, Brown P E, Truelove L H, Banagar F D, Lowrie A J. Course and prognosis in rheumatoid arthritis. *Ann Rheum Dis* 1964; **23**: 193-202.
- 7 Sharp J T, Calkens E, Cohen A S, Schubart A F, Calabro J J. Observations on the clinical, chemical and serological manifestations of rheumatoid arthritis, based on the course of 154 cases. *Medicine (Baltimore)* 1964; **43**: 41-58.
- 8 Burry H C, Caughey D E, Palmer D G. Benign rheumatoid nodules. *Aust NZ J Med* 1979; **9**: 697-700.
- 9 Beumer H M, Van Belle C J. Pulmonary nodules in rheumatoid arthritis. *Respiration* 1972; **29**: 556-64.
- 10 Hurd E R, Synder U B, Ziff M. Choroidal nodules and retinal detachments in rheumatoid arthritis. Improvement with fall in immunoglobulin levels following prednisolone and cyclophosphamide therapy. *Am J Med* 1970; **48**: 273-8.
- 11 Ginsberg M H, Genant N K, Yu T K, McCarty D J. Rheumatoid nodulosis. An unusual variant of rheumatic disease. *Arthritis Rheum* 1975; **18**: 49-58.
- 12 Barrett K E, Tashof T L, Metcalfe D D. Inhibition of IgE mediated mast cell degranulation by sulphasalazine. *Eur J Pharmacol* 1985; **102**: 279-81.
- 13 Azad Khan A K, Pirijs J, Truelove S C. An experiment to determine the active therapeutic moiety of sulphasalazine. *Lancet* 1977; **ii**: 892-5.
- 14 Pullar T, Hunter J A, Capell H A. Which component of sulphasalazine is active in rheumatoid arthritis? *Br Med J* 1985; **290**: 1535-8.
- 15 Molin L, Stendahl O. The effect of sulfasalazine and its active components on human PMN leucocyte function in relation to ulcerative colitis. *Acta Med Scand* 1979; **206**: 451-7.
- 16 Rhodes J M, Bartholomew T C, Jewel D P. Inhibition of leucocyte motility by drugs used in ulcerative colitis. *Gut* 1981; **22**: 642-7.