# LETTERS

## Renal involvement in Chinese patients with rheumatoid arthritis

It was generally admitted that there was no specific rheumatoid lesion in the kidney and that most renal disease in patients with rheumatoid arthritis (RA) was usually linked to amyloid or secondary effects of drugs. Nevertheless, the necropsy study of Boers *et al* had shown that 19.7% of RA patients had a glomerulonephritis (GN) at death.[1] Recent review of renal biopsy findings in RA patients showed that the most common histopathological finding was mesangial GN followed by amyloidosis and membranous GN.[2 3] To evaluate the renal involvement in Chinese patients with RA, a short retrospective clinical study was performed from data of 1468 inpatients of a rheumatology section from 1984 to 1996. Patients having transient mild proteinuria, haematuria or both were not included in the current analysis. Only RA patients with persistent abnormality of haematuria (at least 4 RBC/high power field in two consecutive urine samples), increased proteinuria (daily urinary protein more than 1.0 g) or renal function insufficiency for at least three months (total 14 patients), or all three, had a renal biopsy. The specimens were then examined under light microscope. Immunohistological examination revealed linear IgG deposition along base membrane, IgA deposition in mesangium in patient 5, and non-specific finding in some of the patients taking Chinese herb drugs.

Two categories of patients were found (table 1). Group 1: nephrotic syndrome (NS) with daily protein more than 3.5 g after receiving gold salt or D-penicillamine (D-PC) treatment. Membranous GN in these three patients (patients 1–3) was thought to be related to the drugs themselves. The rest of the patients in this group developed NS or increased proteinuria after receiving disease modified anti-rheumatic drugs (DMARDs) other than gold or D-PC (patients 4–8). Renal biopsy had shown NS with membraneous GN in three patients, IgA nephropathy in one patient, and focal proliferative GN in one patient. Few reports have supported the association between methotrexate, antimalarial drugs, sulphasalazine, and renal disease. It was supposed that renal pathogenesis might be related to RA itself. Serum IgA was comparatively high with positive ANA in this patient group. It was deduced that RA patient with increased IgA is a marker of RA subset with tendency of renal involvement. The relation between IgA, IgA-RF and renal disease in patients with RA was not clear, but the affinity of IgA for mesangium, skin, and synovium might explain the particular clinical presentation of RA with high serum concentration of IgA.[4–8] A similar association was also noted in a patient with Henoch-Schonlein purpura and ankylosing spondylitis with IgA nephropathy. Group 2: Chinese herbs instead of the traditional DMARD treatment (patients 9–14). Distinctive changes in renal biopsy (chronic tubulointerstitial nephritis with renal insufficiency, focal segmental global sclerosis, and diffuse global sclerosis with chronic renal failure) were found in contrast with mesangial proliferative or membraneous GN in most of the patients in the DMARD group. Patients in this group denied having received non-steroid anti-inflammatory drugs (NSAIDs) and any form of DMARDs. Unfortunately, the regimens of herbs were too heterogeneous to draw any meaningful conclusion.

In agreement with the data of Helin, NSAID induced nephropathy (chronic interstitial nephritis and ischaemic change) and systemic rheumatoid vasculitis (necrotising vasculitis) were rare in our RA patients.[2] Renal amyloidosis was not found in our patients, in contrast with that reported in a white population in whom renal amyloidosis was a common finding in longstanding RA patients.[2] Recent reports with special reference to pathological aspects of rapidly extensive interstitial fibrosis with atrophy and loss of tubules in young women with use of slimming regimen including Chinese herbs (*Stephania tetrandra* and *Magnolia officinalis*) have pointed out the potential hazard of renal damage by herbs.[9 10] The glomeruli were relatively spared. Thickening of Bowman's capsule was the rule. Although not found in our biopsy samples, many patients used herbs to treat synovitis. The events highlight the dangers of continuously uncontrolled use of herbs in Chinese patients with RA. Repeat biopsies were not performed in our patients. Irreversible renal damage was noted through the disease course in the group of patients taking Chinese herbs. Proteinuria and haematuria improved after the drugs were withdrawn in the other two groups. Finally, these results of a retrospective study cannot be generalised to reflect the prevalence of renal disease in Chinese patients with RA as a whole because of the material analysed. Renal disease occurring in RA patients may be under-represented in this review.

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*Table 1 Clinical data in RA patients with renal involvement*

| *Patient* | *Age/sex* | *Disease duration** | *Drug/duration** | *RF (IU/ml) initial/nephritis* | *Urine RBC* | *Daily protein* | *IgG/A/M (mg/dl)* | *BUN/Cr (mg/dl)* | *Renal biopsy* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 58/M | 16M | D-PC/9M | 1510/30 | 2–4 | 5.1 | 1712/292/153 | 17/1.1 | MGN |
| 2 | 54/F | 21M | Gold/1285mg | 945/30 | 0–1 | 3.8 | 1980/178/108 | 18/1.2 | MGN |
| 3 | 51/M | 102M | Gold/1310mg | 556/30 | 2–3 | 3.5 | 1690/250/103 | 20/1.2 | MGN |
| 4 | 63/F | 42M | Pla+Sul/38M | 112/96 | 2–3 | 5.4 | 2370/694/184 | 17/0.8 | MGN |
| 5 | 38/F | 46M | MTX+Sul/36M | 1450/88 | 30–40 | 2.6 | 1741/890/266 | 12/0.7 | IgA Nephropathy |
| 6 | 67/M | 80M | Pla+Sul/80M | 994/12 | 5–6 | 3.5 | 2980/652/185 | 35/1.2 | MGN |
| 7 | 36/F | 44M | MTX/40M | 552/40 | 5–6 | 1.7 | 2190/778/247 | 25/0.9 | FPGN |
| 8 | 62/M | 64M | MTX+Sul/26M | 1280/42 | 2–3 | 5.9 | 1280/670/288 | 18/0.9 | MGN |
| 9 | 49/F | 216M | CHD/216M | 668/43 | 4–5 | 1.3 | 1615/156/170 | 20/1.6† | FSGS |
| 10 | 66/F | 108M | CHD/108M | 434/164 | 4–5 | 2.3 | 2100/221/123 | 33/3.5 | FSGS |
| 11 | 45/F | 96M | CHD/96M | 223/36.4 | 3–4 | 0.9 | 1800/199/188 | 50/7.0 | CRF |
| 12 | 51/F | 106M | CHD/106M | 884/320 | 4–6 | 1.1 | 1921/229/101 | 62/8.6 | CRF |
| 13 | 64/M | 72M | CHD/72M | 234/10.1 | 4–6 | 1.5 | 1700/376/89 | 63/3.3 | TIN |
| 14 | 76/M | 228M | CHD/228M | 280/33.2 | 2–5 | 1.4 | 1832/288/112 | 48/4.5 | TIN |

*Duration (months) since diagnosis of RA and prescription of disease modified antirheumatic drugs until diagnosis of nephropathy, total cumulative dose of gold salt was calculated. †Persistent renal insufficiency was noted in patients 4–14. No abnormality in liver function and no significant drug reaction was noted. MTX: methotrexate; Sul: sulphasalazine; D-PC: D-penicillamine; Gold: gold salt intramuscular weekly injection; Pla: hydroxychloroquine; CHD: Chinese herb drug; MGN: membranous glomerulonephritis; FPGN: focal proliferative glomerulonephritis; FSGS: focal segmental global sclerosis; CRF: chronic renal failure in uraemic stage; TIN: tubulointerstitial nephritis; urine RBC as number/HPF and daily urine protein as g/24 h.

# Evaluation of adverse experiences related to pamidronate infusion in Paget's disease of bone

Pamidronate disodium, a second generation bisphosphonate, has been found to be safe as well as effective in the treatment of Paget's disease of bone.[1] It is licensed in the UK and many other countries for the intravenous treatment of Paget's disease. Most units using pamidronate have found the occurrence of flu-like symptoms, fever, and myalgia in 20–30% of patients after the first pamidronate infusion.[2] It therefore became our practice that patients received an initial 30 mg "test dose" of pamidronate before receiving a series of fortnightly infusions of 60 mg and this practice is now recommended by the manufacturers. This protocol however increases the number of infusions in a course of pamidronate treatment and therefore the cost and would only be justified if the adverse reactions were therefore minimised. We have therefore conducted a double blind placebo controlled trial to evaluate the need for this initial low dose "test" dose in patients receiving a course of 60 mg infusions.

Seventy four patients (40 female, 70.0 (9.4) years (mean (SD); 34 male, 67.5 (9.5) years) with mild to moderate Paget's disease of bone (serum alkaline phosphatase (SAP) <500 IU/l, normal range <130 IU/l) who had never previously received pamidronate were recruited. Patients were randomised in a double blind fashion in to one of two arms A or B and all patients received a total of 210 mg pamidronate (Novartis Pharmaceuticals UK Ltd) in five fortnightly infusions as follows:

(A) Initial 30 mg infusion followed by three infusions of 60 mg pamidronate and a final placebo infusion at fortnightly intervals (n=41, mean SAP 202IU/l (range 85–450 IU/l).

(B) An initial placebo infusion followed by three infusions of 60 mg pamidronate and a final 30 mg pamidronate infusion at fortnightly intervals (n=33, mean SAP 191 IU/l (range 81–512 IU/l).

The frequency and severity of symptoms occurring after each infusion were assessed by questionnaire administered by one investigator (SJM). Unpaired Student's *t* tests were used for statistical analysis.

The commonest symptoms complained of were headache, feeling hot and flushed, shivering and rigors, and each occurred in 20–30% of patients (table 1). These started within 48 hours of infusion and settled within 24 hours. All other symptoms were complained of by less than 5% of patients. There was increased reporting of adverse effects of symptoms in group A compared with group B after the first infusion (1.4 (1.0) versus 0.4 (0.2) (mean (SD)) symptoms, p <0.01, 30 mg pamidronate versus placebo). Likewise there were significantly more adverse effects in group B after the second infusion (60 mg pamidronate) than the first (placebo) (1.7 (1.1) versus 0.4 (0.1), p <0.01). In group A there was a decrease in symptoms between the first (1.4) and second (1.0) infusions (30 mg versus 60 mg pamidronate) despite a larger dose of pamidronate being given in the second infusion. In both groups the maximum number of symptoms occurred after the first pamidronate infusion and was similar whether the first exposure to pamidronate was 30 mg or 60 mg. In both groups the number of reported symptoms decreased thereafter and there was no significant difference between symptoms reported in the two groups after the third, fourth or fifth infusion.

*Table 1 Percentage of patients complaining of the three commonest symptoms in relation to infusion number*

| *Symptoms* | *Infusion number* | | | | |
|---|---|---|---|---|---|
| *Group A (n=41)* | 1 (30 mg) | 2 (60 mg) | 3 (60 mg) | 4 (60 mg) | 5 (placebo) |
| Headache | 22 | 22 | 15 | 5 | 4 |
| Hot/flushed | 38 | 20 | 5 | 7 | 0 |
| Shivering/rigors | 32 | 25 | 7 | 3 | 0 |
| *Group B (n=33)* | (placebo) | (60 mg) | (60 mg) | (60 mg) | (30 mg) |
| Headache | 15 | 31 | 22 | 7 | 0 |
| Hot/flushed | 0 | 22 | 3 | 0 | 0 |
| Shivering/rigors | 0 | 28 | 3 | 0 | 0 |

This study confirms previous findings that 20–30% of patients suffer transient symptoms related to pamidronate infusion.[2 3] In this study we found that 20–30% of patients who had never previously received pamidronate treatment suffered symptoms of feeling hot and flushed, shivering and headaches within 48 hours of their first pamidronate infusion and this lasted for less than 24 hours.

An acute febrile response and haematological changes had been reported after pamidronate infusion.[4–6] Therefore it is likely that the symptoms in our study are similarly related to an acute febrile response to pamidronate infusion.

We found that these symptoms occurred irrespective of whether the dose of pamidronate administered was 30 mg or 60 mg. We therefore suggest that patients with mild-moderate Paget's disease of bone are treated with three infusions of 60 mg without any need for initial low dose "test" dose thereby reducing the cost of treatment and the inconvenience and number of visits to the hospital for the patient.

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