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CONCISE COMMUNICATIONS

Induction therapy with an intravenous loading dose of azathioprine for treatment of refractory, active rheumatoid arthritis

Since 1974, azathioprine (AZA) has been approved for use as a disease-modifying antirheumatic drug (DMARD) in rheumatoid arthritis (RA). Intravenous (IV) AZA has been found to be effective as induction therapy for Crohn's disease, an inflammatory bowel condition (1). Based on this experience, we designed a study with the primary aim of evaluating the safety and utility of a single IV loading dose of AZA, followed by maintenance oral AZA, in patients with active, refractory RA.

This was an open-label, single-center study involving 10 adult patients with treatment-resistant RA (1 man, 9 women; mean age 47.6 years). All were in functional class I, II, or III as defined by the American College of Rheumatology (ACR) (2). Patients had active disease at the time of enrollment, as evidenced by ≥9 joints that were painful or tender on motion, ≥6 swollen joints, morning stiffness of ≥45 minutes, and an elevated C-reactive protein level. The protocol was reviewed and approved by the Institutional Review Board, and informed consent was obtained from all patients before screening and treatment. Two patients who were homologous low for thiopurine methyltransferase activity were excluded from enrollment because of prior reports of severe neutropenia in such patients following AZA treatment (3).

A total of 1,800 mg (22.5–36.0 mg/kg body weight) of IV AZA was administered as a constant-rate infusion. A 1,800-mg loading dose of IV AZA would be comparable with an oral AZA loading dose of at least 3,600–4,390 mg, given an oral bioavailability of 41–50% (1). Following the single-dose IV administration, oral AZA was given to patients beginning at 50 mg/day; after 4 weeks, the dosage was increased to as much as 150 mg/day (range 1.7–2.5 mg/kg/day). Followup visits with clinical assessments occurred at weeks 2, 4, 8, 16, and 24. Total red blood cell 6-thioguanine nucleotide (RBC 6-TGN) concentrations were measured based on the conversion of 6-TGN to the free 6-thioguanine base (4).

Treatment failure was recorded if another DMARD had to be substituted or added, or prednisone or equivalent at a dosage of >10 mg/day had to be administered, during the followup period. The ACR core set of disease activity measures for at least 20% improvement (5) was used to assess clinical response. Success of the treatment was defined at the outset as clinical improvement, by the ACR 20% criteria, in at least 7 of the 10 patients who received IV AZA, without subsequent disease relapse by week 24 when compared with baseline.

Enrolled patients had been receiving stable doses of glucocorticoids in the 2 weeks prior to screening, not exceeding 10 mg/day of prednisone. Patients taking nonsteroidal antiinflammatory drugs (NSAIDs) were receiving stable doses in the 2 weeks prior to screening. The mean number of DMARDs previously taken was 4.2 per patient. DMARD use immediately prior to enrollment included methotrexate (MTX) alone (1 patient), sulfasalazine (SSZ) + MTX (2 patients), hydroxychloroquine (HCQ) + MTX + SSZ (1 patient), SSZ alone (2 patients), cyclosporin A (CSA) + AZA (1 patient), HCQ alone (2 patients), HCQ alone (2 patients), and intramuscular gold alone (1 patient). HCQ and SSZ were discontinued 2 months prior to the initial dose of IV AZA, and MTX, CSA, and oral AZA were discontinued 2 weeks prior to the initial dose of IV AZA. At the time of the IV AZA administration, 9 patients were taking prednisone, 5 were taking an NSAID, and 5 were taking other analgesics.

At week 24, only 3 of the 10 patients met the definition of response (ACR 20% improvement criteria). An "induction effect" of marked improvement, which might have been expected soon after infusion of the high-dose AZA, was not seen in the initial 4–8 weeks of the study. We found no correlation between the initial IV dose of AZA (in mg/kg) and patient response, or in the subsequent dosage of AZA (in mg/kg/day up to a maximum of 150 mg/day). There was also no correlation between clinical response and RBC 6-TGN concentrations at the AZA doses studied.

In general, the drug was well tolerated. Adverse events included a flare of arthritis (1 patient), low-grade fever during the AZA infusion (1 patient), nausea during the infusion (1 patient), nausea during and several weeks after the infusion (3 patients), leukopenia to a nadir of 2,600 white blood cells/mm^3 (at week 8) (1 patient), and vaginal candidiasis (at week 8) (1 patient). No abnormalities in serum aspartate aminotransferase levels were seen during the followup period.

Despite the fact that MTX was discontinued only 2 weeks prior to the administration of IV AZA in the 4 patients taking it at screening, only 1 flare of disease was noted during the initial 8 weeks of the study in this subset of patients. This design was chosen to minimize patient discomfort, and was believed to most closely parallel actual clinical practice with respect to decision-making regarding changes in DMARD therapy in patients in whom these therapies have been unsuccessful. It remains a matter of speculation whether the design biased against detection of a greater rate of response.

Although generally well tolerated in these patients with active, refractory RA, IV AZA at the doses studied did not appear to enhance control of disease enough to warrant a controlled clinical trial of this regimen (it had been determined that improvement in at least 70% of the patients would be required in order to trigger such a trial). Certainly, this standard of improvement may be too stringent. The pilot nature of the study precludes more definite conclusions about the efficacy of this treatment approach. In an ongoing study by 2 of the authors (WJS and JJL), IV AZA has been administered to patients with inflammatory bowel disease in a dose of 40 mg/kg as induction therapy. It is possible that higher doses of IV AZA could be used in RA with better success.

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Lack of occurrence of severe lupus nephritis among anti-C1q autoantibody–negative patients

Renal involvement is a frequent and serious feature of systemic lupus erythematosus (SLE). Approximately 50% of patients with SLE develop clinical nephritis defined by persistent proteinuria. The most severe histologic changes are focal segmental proliferative and diffuse proliferative glomerulonephritis (WHO class III and IV). The occurrence of autoantibodies against complement component C1q has been described in many patients with SLE and has been shown to correlate with the occurrence or worsening of lupus nephritis (1). However, the positive predictive value has been reported to be only ~50%. In contrast, in the same study (1), the negative predictive value was 96.5%. Most often, autoantibody determinations are performed to assess the presence of a disease or a specific complication. In the case of antibodies to C1q, though, the absence of antibodies may be more informative for the clinician, since it might indicate the absence of a specific complication, i.e., renal disease.

In a retrospective study of 48 patients with SLE, we focused on the negative predictive value of anti-C1q autoantibodies. All patients fulfilled at least 4 of the American College of Rheumatology criteria for the classification of SLE (2). Anti-C1q autoantibodies were measured by enzyme-linked immunosorbent assay, as described by Siegert et al (3). The serum of a patient with hypocomplementemic urticarial vasculitis syndrome was established as reference serum with an arbitrary value of 1,000 units/ml. Values of <80 units/ml corresponded to the background of the assay and were considered to be negative. Two of 47 normal blood donors were positive (87 units/ml and 219 units/ml). All samples were also tested for anti–double-stranded DNA (anti-dsDNA), by the Farr assay. Urinalysis and creatinine measurements were available for all patients for a period of 6 months before to 6 months after anti-C1q autoantibody determination. In 17 of the 48 patients, anti-C1q autoantibody was serially measured for up to 56 months.

Table 1. Anti-C1q autoantibodies in systemic lupus erythematosus patients with versus those without active nephritis (n = 48)*

Active renal disease	Anti-C1q autoantibodies	
	Positive	Negative
Yes	14	0
No	10	24

* Difference between groups was significant at $P < 0.00001$.

Absence of lupus nephritis was defined as normal urinalysis results and creatinine levels. Inactivity of preexisting lupus nephritis was defined as either normal or continuously decreasing or stable values for proteinuria, erythrocyturia (<20 erythrocytes/field), and creatinine for the entire 12-month period. Statistical analyses were performed by Fisher's exact test.

Twenty-one of the 48 patients had anti-C1q autoantibodies at the time of first sampling. Of these 21, 9 had active, ongoing nephritis and 2 developed a renal flare during followup. Three additional patients who were initially negative for anti-C1q autoantibody became positive, after which acute nephritis developed. Thus, we observed a total of 14 patients with active renal involvement, all of whom had anti-C1q autoantibodies at the time of nephritis (Table 1). A renal biopsy was performed in 11 of these 14 patients before or at the time of serum sampling. It showed proliferative lupus nephritis in all 11. The positive predictive value of anti-C1q autoantibodies for nephritis was 14/24 (58%), which was similar to that in previous reports.

Of particular interest was the finding that none of the remaining 24 patients who were negative for anti-C1q autoantibodies in 1 or multiple samples had or developed active nephritis (Table 1). This corresponds to a negative predictive value of 100%. In addition, we observed 3 patients who became negative during followup, after an initially positive test result. None of these 3 developed active nephritis, although 2 of them had a previous history of renal involvement. These data suggest that severe lupus nephritis does not occur in the absence of anti-C1q autoantibodies. Anti-dsDNA autoantibodies were less helpful in predicting lupus nephritis since 45 of the 48 patients were positive at the time of first sampling.

Although our data are very similar to the findings of the only previously reported prospective study (1), the results presented in other reports suggest a lower negative predictive value for anti-C1q autoantibody (4–7). However, most of these other reports contained no description of the time course of lupus nephritis versus anti-C1q autoantibody measurements. It is possible that many of the anti-C1q autoantibody measurements were from serum samples that were not obtained shortly before or during the nephritic episode. Others (1,7) and we

have seen patients in whom anti-C1q autoantibodies disappeared at the time of remission. In addition, some investigators have set a very high upper limit for determination of a negative anti-C1q autoantibody result. This "eliminates" so-called false-positive results in normal subjects, but reduces the sensitivity of the assay and may explain the recording of false-negative anti-C1q autoantibody results in patients with lupus nephritis.

Anti-C1q autoantibodies appear to be necessary but not sufficient for the development of severe lupus nephritis. This observation suggests the possibility of new treatment strategies based on the elimination of these autoantibodies. Most importantly, the absence of anti-C1q autoantibody may help the clinician to decide whether immunosuppressive treatment for renal involvement is required.

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