HLA-DRB1*0301 and DQA1*0501 in RA

Auranofin is an oral gold preparation used in the treatment of rheumatoid arthritis (RA). During treatment, proteinuria has been reported in approximately 3% of patients. In a few cases in which renal biopsies were performed, a membranous nephropathy was shown to have developed. Several antirheumatic agents have been reported to induce renal manifestations or drug-induced lupus reactions, or both, in patients with RA. In these subjects a genetic predisposition for HLA has been previously suggested.

To determine whether similar genetic factors might be operative in auranofin-induced nephropathy, we analysed the HLA-DRB1, DQA1, and DQB1 alleles using a polymerase chain reaction. Furthermore, we investigated if the renal side effects were associated with serological findings in accordance with systemic lupus erythematosus (SLE), thus indicating the development of a drug-induced lupus reaction.

Six patients (three female, three male) who developed biopsy-proven membranous nephropathy or significant proteinuria (>0.5 g/day) during treatment with auranofin are reported. All patients met the American College of Rheumatology criteria for RA. The median age before onset of auranofin treatment was 72 (52–83) years, 4/6 patients were rheumatoid factor positive and 2/5 patients were antinuclear antibody (ANA) positive. The median duration of auranofin treatment before the onset of proteinuria was 5 (4–10) months.

During auranofin treatment, two patients developed an increased ANA titre (1/200 and 1/1600) but no antibodies against anti-dsDNA, SSA/SSB, Sm, or RNP were detected. None of the patients developed an increased serum creatinine level. After withdrawal of auranofin, proteinuria decreased significantly or disappeared in all cases.

Table 1 presents the HLA alleles.

A high frequency of the alleles associated with SLE—namely, DRB1*0301 (DR3), DQA1*0501, and DQB1*0201, was recorded in the patients developing membranous nephropathy or proteinuria during auranofin treatment. Of these, DRB1*0301 and DQA1*0501 occurred in 4/6 of the patients, and 5/6 patients carried at least one of these alleles.

The importance of DR3 or DQA1*0501 in drug-induced renal manifestations has previously been suggested in patients with penicillamine and sodium aurothiomalate-induced renal side effects. Also, in accordance with these findings, the DQA1*0501 and DRB1*0301 alleles have been recorded in a high frequency in patients developing sulfasalazine-induced nephropathy.

In two cases the development of membranous nephropathy was accompanied by a simultaneous increase in the ANA titre, thus indicating development of a drug-induced SLE reaction. However, both patients had previously presented some sign of an autoimmune reactivity pattern, which may confer a risk factor in the treatment with certain antirheumatic drugs in RA.

Simultaneous treatment with sulfasalazine and auranofin had been given in two cases, but the sulfasalazine treatment period was either limited, or lacked any time relation with the onset of proteinuria, it seems unlikely that the patients developed a drug reaction against sulfasalazine. Further arguments rejecting the possibility of a sulfasalazine-induced drug reaction are the lack of anti-dsDNA antibodies and the rapid onset of proteinuria among the patients, thus contrasting with the findings reported in sulfasalazine-induced SLE.

The mechanism for induction of membranous nephropathy during auranofin treatment is unknown. Interestingly, it has been suggested that gold can bind to and alter major histocompatibility complex-peptide complexes, thus giving a possible explanation of both beneficial effects as well as side effects during treatment. Another possibility is that auranofin may alter the cytokine pattern towards an SLE-like phenotype and thus facilitate the development of SLE associated manifestations in genetically susceptible subjects. In accordance with this hypothesis, auranofin or other gold preparations have been reported to induce the production of interleukin 1 (IL1), tumour necrosis factor α, and IL2. The effects on IL10, a cytokine reported to be increased in both patients with idiopathic SLE and their healthy relatives as well as in patients developing sulfasalazine-induced SLE-like reactions, is unknown, however.

In conclusion, the data suggest that SLE-related HLA alleles, with special focus on DRB1*0301 and DQA1*0501, may predispose to development of renal side effects or drug-induced lupus reactions during treatment with auranofin, as also previously recorded during treatment with other antirheumatic agents. Development of drug-induced SLE, here reported for the first time, may occur during auranofin treatment.

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*No renal biopsy was performed in these patients.

Table 1: HLA DRB1*, DQA1*, and DQB1* alleles in patients with development of renal manifestations during auranofin treatment.

<table>
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<tr>
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