Zidovudine in primary Sjögren’s syndrome

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Abstract

Objective. To evaluate the efficacy of the administration of zidovudine (AZT), an antiretroviral drug, in patients with primary Sjögren’s syndrome (SS).

Methods. Seven female patients (age 57 ± 8.6 yr) with primary SS were enrolled in an open, uncontrolled trial of AZT (250 mg b.i.d.) for the treatment of primary SS. The efficacy variables were oral and ocular dryness symptoms, fatigue, tender points, physician's and patient’s global assessments (GA), ocular function tests (fluorescein tear break-up time, Schirmer’s test, Rose Bengal staining) and laboratory parameters [erythrocyte sedimentation rate (ESR), serum IgG, IgA and IgM].

Results. A significant improvement was observed in all subjective manifestations, as well as the objective parameters of ocular dryness. The treatment was well tolerated, except for mild and transitory gastrointestinal disturbances in 6/7 patients. Laboratory parameters did not change significantly. The clinical benefit persisted in 5/7 patients 1 month after the end of therapy.

Conclusion. AZT seems to be effective and well tolerated in patients with primary SS.

Key words: Zidovudine, Sjögren’s syndrome, Retrovirus.

Sjögren’s syndrome (SS) is a chronic, systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands [1]. The salivary and lacrimal glands are primarily involved, leading to glandular hypofunction and the clinical presentation of dry mouth (xerostomia) and eyes (keratoconjunctivitis sicca) [1]. It can occur alone (primary SS) or in association (secondary SS) with various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus or myositis [1]. About 30% of primary SS patients exhibit extraglandular manifestations including non-erosive arthritis, Raynaud’s phenomenon or involvement of thyroid, lungs, kidneys and liver. Five to 10% of the patients will develop a malignant lymphoproliferative disease [1].

Retroviruses have been implicated in the aetiology of various autoimmune diseases [2, 3]. Evidence for a pathogenic role for retroviruses in the initiation and maintenance of autoimmunity in SS includes: (a) the presence in SS patients of antibodies which are cross-reactive with retroviral gag proteins [4–6]; (b) the detection of retrovirus antigens in SS patients [7]; (c) the occurrence of SS-like conditions in human immunodeficiency virus (HIV) patients [8] and human T-lymphotropic virus Type I (HTLV-1)-associated disease [9, 10]; (d) the description of intracisternal A-type retrovirus particles in salivary gland cells from SS patients [11, 12]; (e) the demonstration of a reverse transcriptase activity in salivary glands of SS patients [12]; (f) the identification of an exogenous retroviral sequence from salivary gland tissue of an SS patient [13]. Animal models also provide supportive evidence: Green et al. [14] described a sialadenitis in the HTLV-1-tax transgenic mouse and MAIDS mice develop a salivary gland lymphocytic infiltration [7, 8].

Zidovudine, the first antiretroviral agent approved for clinical use, is a thymidine analogue that inhibits retroviral replication by interfering with the viral reverse transcriptase and elongation of the viral DNA chain [15]. The administration of zidovudine (AZT) in some patients with diffuse infiltrative lymphocytosis syndrome (DILS) and HIV infection led to a diminution of salivary gland enlargement and improvement in the associated discomfort [16]. Despite the development of symptomatic therapy, no systemic treatment is still available for SS [17]. The aim of the present study was to determine the possible effects of AZT administration on primary SS disease-related signs and symptoms.

Patients and methods

Study design and patient population

We designed an open-labelled, uncontrolled longitudinal trial for the treatment of primary SS by AZT over 3 months. Inclusion criteria were: (1) fulfilment of both...
the European Community [18] and the San Diego [19] classification criteria for primary SS; (2) disease duration (defined from diagnosis) of <1 yr; (3) evidence of active disease requiring treatment based on ocular and oral dryness complaints, extraglandular symptoms (including fatigue, arthralgias, myalgias) and the presence of an active inflammatory process such as an elevated erythrocyte sedimentation rate (ESR) of >25 mm/h or hypergammaglobulinaemia; (4) a 3 month wash-out period of any systemic treatment capable of interfering with the condition process. Exclusion criteria were HIV1-2, HTLV-1 and hepatitis C (HCV) infection, and the presence of any other connective tissue disease. Only modifications in the symptomatic treatment, such as artificial tears (AT), were allowed during the study.

Approval was obtained from the local ethical board and written informed consent from the patients. Seven female patients (age 57 ± 8.6 s.d. yr) were included in the study. Their clinical, immunological and histological characteristics are summarized in Table 1.

Treatment
Zidovudine was administered orally, at constant dose (250 mg b.i.d.) for 3 months. The dose of AZT was selected from the recommended dose in antiretroviral therapy [20].

Assessment and outcome measures
Clinical, ophthalmological and biological evaluations were performed monthly for the 3 months of treatment and 1 month after the discontinuation of therapy. Clinical assessment was carried out by the same physician (SDS) and consisted of: (1) a general physical examination; (2) a dry mouth evaluation (0–4 scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe); (3) the need for water during speaking and the need to awaken for water drinking; (4) the speech test (number of repeated ‘Puttica’ during 2 min; presented by P. J. Shirlaw at ‘New Advances in Basic Science, Diagnosis and Treatment of Sjögren’s Syndrome’, London, January 1997); (5) an ophthalmological evaluation (0–4 scale: 0 = no symptom, 1 = mild symptoms partially relieved by AT, 2 = moderate symptoms partially relieved by AT, 3 = severe symptoms partially relieved by AT, 4 = severe symptoms unrelieved by AT); (6) the frequency of AT use; (7) the fatigue evaluation test by a 0–100 mm visual analogue scale (VAS); (8) the tender joint count (maximum 24); (9) a muscle tender point count (maximum 18); (10) psychological status by the Hamilton scale.

Patient’s and physician’s global assessments were evaluated by a 0–100 mm VAS.

The ophthalmological assessment was made by the same physician (PD) and consisted of fluorescein tear break-up time test (TBUT), Schirmer’s test and corneal evaluation by Rose Bengal staining (0–9 score).

Biological parameters were measured monthly during 4 months: ESR, C-reactive protein (CRP), full blood count, renal and liver function tests, creatine kinase, serum immunoglobulins A, M and G, antinuclear antibodies (ANA) and rheumatoid factor (RF). An indirect immunofluorescence procedure using Hep2 cells was employed to detect the presence and titre of ANA (Immuconcepts, Sacramento, CA, USA). Anti-Ro/SS-A and anti-La/SS-B antibodies were detected by ELISA (INOVA Diagnostics, San Diego, CA, USA). The serum levels of RF were evaluated by laser nephelometry (Behring, Nlatex RF, MA, USA).

Statistical analysis
The significance of differences was evaluated by paired Student’s t-test (intent-to-treat analysis).

Results
Among the seven patients included in the study, all completed the 3 month course of treatment and 6/7 were assessed after an extra month of follow-up free of therapy. During the treatment period with AZT, six improved and one remained unchanged. Clinical and biological results are summarized in Table 2.

Dry mouth
Clinical complaints of dry mouth were improved in 7/7 patients (P < 0.001); this was also supported by a reduc-

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<th>Table 2. Clinical and biological features pre- and post-treatment</th>
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<td>Artificial tears (no./day)</td>
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<td>TBUT (s)</td>
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GA, global assessment; VAS, visual analogue scale; TBUT, fluorescein tear break-up time test.

*P < 0.05; **P < 0.01; †P < 0.001.
tion of water absorption for speaking (3/7 patients at entry and 0/7 after 3 months) and during the night (6/7 to 1/7). In addition, the speech test performance was also ameliorated at 2 min (130 ± 26 to 210 ± 34, P < 0.02).

Dry eyes
Similarly, a subjective improvement (P < 0.0001) was also observed for dry eye manifestations and the daily use of AT was rapidly reduced (P < 0.01). The benefit was confirmed by all tear gland function tests, which improved significantly in six of the seven patients and were unchanged in one (P < 0.02) (Table 2).

General and extraglandular symptoms
Fatigue disappeared after treatment in all patients (P < 0.001), mostly during the second month of treatment. Diffuse muscular pain was reduced in all but one patient. Tender points present at entry in 6/7 patients disappeared after treatment (P < 0.02). Accordingly, global assessments of the disease by the patient (P < 0.001), as well as by the physician (P < 0.001), improved. Dry cough, which was present in 4/7 patients at entry, disappeared in two after the second month. Raynaud’s phenomenon, which was present in 4/7 patients before starting therapy, was not modified. The <10 Hamilton depression scale score at entry remained unmodified at the end of the study.

Laboratory parameters
Biological parameter values did not vary significantly.

Adverse events
No major adverse event occurred during the study. Minor side-effects were reported by 6/7 patients during the first month of treatment (between the second and third week). They comprised gastrointestinal discomfort (5/7) and mild diarrhoea (2/7) for <3 days. A reversible leucopenia was noted in one patient. None of these effects required AZT discontinuation and/or addition of symptomatic treatments.

Discussion
We report here the results of an open-labelled trial with AZT conducted in seven patients with primary SS for 3 months. Antiretroviral treatment was initiated because of their symptoms and evidence of an active inflammatory process. A disease duration of <1 yr was preferred because irreversible damage may exist when overt dryness is noted [1]. All of the patients completed the study. Ocular symptoms and signs (including Schirmer’s test, TBUT and Rose Bengal score), oral symptoms and extraglandular manifestations (fatigue, tender points and arthralgias) improved in all patients. The use of AT was dramatically reduced. The results of this open study need to be analysed with caution since subjective parameters such as eye and mouth dryness, fatigue or tender points may be influenced by the psychological status of the patient, particularly in the case of psychological depression. The latter was improbable taking into account the Hamilton scale (<10).

AZT administration was well tolerated, except for mild and transitory gastrointestinal side-effects. AZT appears to be safe and better tolerated than the other proposed drugs for SS, such as cyclosporin A [22], methotrexate [23] or azathioprine [24]. This is, to our knowledge, the second HIV-unrelated disease which has been treated with AZT. Previously, Gill et al. [25] reported a remission in adult T-cell leukaemia–lymphoma related to HTLV-1 infection treated with a combination of AZT and interferon alpha.

The mechanisms by which AZT exerts a biological action in SS remain unclear. AZT is known to be active against retroviruses, but this drug could also play an immunomodulatory role [26]. In contrast to studies of hydroxychloroquine in SS [27, 28], no fall in ESR or IgG levels in the patients was observed, suggesting that the systemic course was not affected during the short period of treatment.

Many biases can be identified in such an open trial. We cannot rule out a placebo effect. However, it should be emphasized that the beneficial effects were maintained after 1 month follow-up in 5/7 patients, contrasting with very limited placebo effect found in the other trials in SS [20–22]. A flare occurred in one patient after the end of the study and we decided to re-introduce AZT according to the patient’s wishes. All tests improved again significantly. The encouraging results of this study support the need for multicentre randomized trials of AZT in patients with primary SS.

In conclusion, the present study suggests that AZT could be a potentially beneficial and low-risk treatment for primary SS.

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