LETTERS TO THE EDITOR

Survey of artificial tear and saliva usage among patients with Sjögren’s syndrome

Sjögren’s syndrome (SS), a chronic immune mediated disease associated with xerostomia and keratoconjunctivitis sicca, may occur alone (primary SS) or with other autoimmune diseases (secondary SS). The benefits of substitution treatment for dry eyes and mouth seem very variable. This survey assessed patients’ experience of the wide variety of tear and saliva substitutes available. Patients with SS, from Cannock Chase Hospital, University Hospital Birmingham, City Hospital Birmingham, or Birmingham Heartlands and Solihull Hospitals, completed a questionnaire, returned at their clinic visit or by prepaid post. SS was defined by the presence of four from six EC diagnostic criteria, with the modification that patients with primary SS must have anti-Ro antibodies (by enzyme linked immunosorbent assay (ELISA) or countercurrent immunoelectrophoresis) and/or have had a lip biopsy demonstrating features typical of SS. The questionnaire asked patients to identify, from a comprehensive list, all tear and saliva substitutes that they had ever heard of, had ever used, or were currently using, to identify useful source(s) of information about substitution treatment, and to rate the effectiveness of any treatments they had ever used, on 10 cm visual analogue scales (VAS). The duration of any substitute treatment was not recorded. Demographic, clinical, and laboratory data for each patient were obtained by chart review. The Mann-Whitney U test was used to compare results between groups. Research ethics committee approval was obtained for this survey.

Fifty patients (two male), including 40 with primary SS, were included in the survey. Mean age (range) was 57 (33–82) years and disease duration 5 (0–14) years. Forty three patients had symptomatic dry eyes, 36 had gritty eyes, and 31 patients used tear substitutes three or more times each day. All complained of a dry mouth, 42 had difficulty swallowing dry food, and 23 patients had recurrent or persistent salivary gland swelling. Thirty two patients had positive anti-Ro antibodies and 39 patients had undergone a diagnostic labial salivary gland biopsy. On a 10 cm VAS, the mean rating of disease severity was 6.2 cm (range 0.0–9.8).

Non-proprietary, hypromellose eye drops and Viscontears were the most widely known and used tear substitute treatments (table 1). Four patients had never heard of any of the tear substitutes listed, despite two having symptomatic dry eyes; six had never used any and 11 were not currently using any. Oralbalance, Glandosane spray, Saliva Orthaana spray and lozenges, and Salivax pastilles were the most widely known and used saliva substitute treatments. Eight patients had never heard of any of the saliva substitutes listed, despite all having a symptomatic dry mouth; nine had never used any and 22 were not currently using any. Patients’ rated the effectiveness of any replacement product they had used (fig 1). The median (range) VAS score for all tear products was 5.35 (0.25–9.8), which was significantly higher than for saliva products where the median (range) was 3.15 (0.2–9.5) (p<0.002). There was no significant difference between the effectiveness ratings of any of the tear or saliva products, except that Salivax pastilles were rated significantly higher than Glandosane spray (p<0.05). Seventeen patients viewed their general practitioner as a good source of information about substitution treatments, 34 highlighted the important role of hospital staff, 16 nominated local and national patient support groups, and smaller numbers had received information from their dentist (seven subjects), optician (two), and pharmacist (three).

This survey has shown that a relatively select number of replacement products are regularly used in SS. Only two tear replacement products were widely used, though most patients had heard of other products and had tried some. It seems likely that patients have continued to use the product that they found most effective. Some patients were taking no tear replacement treatment, including two who denied ever hearing about such treatment, despite having dry eyes. In these patients, there is a concern that their health professionals might have failed to advise of potential symptom relieving treatments. A wider variety of saliva replacement products were used, but by a smaller proportion of patients. This may suggest that they were less helpful overall, because many were known to and tried by the patients though clearly not continued. Reports on the effectiveness of these products comprise small placebo controlled studies and an occasional comparison of two active treatments. A survey of their use in routine clinical practice has not previously been described. Although it has limitations, this study suggests that patients need better information about the products available. There are few published guidelines even for medical personnel, though the internet may help to remedy this for doctors and patients (http://www.dry.org/ss95gui.html). This study has also shown the gulf remaining between the many available tear and saliva replacement products and their use by patients.

We thank Dr L Rankin, Dr P Johnaputra, and Dr R Jubb for allowing us to survey their patients at Selly Oak Hospital, Birmingham.

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Table 1  Number of patients (50 patients surveyed) who had ever heard of, ever used, or were currently using tear or saliva substitute treatments available in the United Kingdom

<table>
<thead>
<tr>
<th>Product</th>
<th>Ever heard</th>
<th>Ever used</th>
<th>Currently using</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tear substitute treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypermellose eye drops*</td>
<td>33</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Viscontears</td>
<td>22</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Lactri-Lube</td>
<td>13</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Snee tears</td>
<td>12</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Liquifilm tears</td>
<td>11</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Minims artificial tears</td>
<td>10</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Tears Naturale</td>
<td>9</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Ible</td>
<td>9</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>GEarTears</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Hypotears</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Saliva substitute treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oralbalance</td>
<td>21</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Glandosane spray</td>
<td>20</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Saliva Orthaana</td>
<td>19</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Saliva Orthaana lozenge</td>
<td>15</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Salivax pastilles</td>
<td>15</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Lubranst spray</td>
<td>15</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Salivace spray</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Saliveze</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</table>

*Including Isopto Alkaline and Isopto Plain eye drops.
Y chromosome microchimerism in Sjögren’s syndrome

There are many similarities between graft versus host disease (GVHD) and some rheumatic autoimmune diseases, such as systemic sclerosis (SSc), Sjögren’s syndrome (SS), and primary biliary cirrhosis. Bianchi et al reported that fetal cells could survive in the maternal circulation for up to 27 years after parturition. This phenomenon is called fetal microchimerism.¹

Some observations led the hypothesis that persistent fetal cells in the maternal circulation could mediate a graft versus host reaction, resulting in autoimmune disease. It is known that during a chronic GVHD, a Sjögren-like syndrome, is often observed: a salivary gland biopsy sample from patients with chronic GVHD showed lymphocytic infiltration, similar to that found in SS.²

Nison and colleagues have studied male fetal microchimerism in skin lesions and peripheral blood from women with SSc and at least one male pregnancy. They found that male DNA is more commonly associated with women with SSc than the healthy ones.³

Miyashita and colleagues have recently studied, by a nested polymerase chain reaction (PCR), fetal male microchimerism in peripheral blood from women with SSc, SS, and systemic lupus erythematosus.⁴

They confirmed that male DNA is found more commonly in women with SSc than in normal women, whereas there was no significant difference between patients with SS and healthy women.⁵

Also, Toda and colleagues have examined microchimerism in the circulation of patients with SS. A Y chromosome-specific sequence was detected as a marker for fetal cells by a nested PCR and by DNA hybridisation combined with PCR using specific primers and probes. The authors concluded that circulating fetal cells in patients with SS are uncommon, if they exist, but they may migrate preferentially into target organs of the disease rather than into the circulation.⁶

We have recently searched for male microchimerism in minor salivary glands tissue from six women with SS and at least one male pregnancy or miscarriage (table 1, patients 1–6). A diagnosis of SS was made according to EEC criteria.⁷ As control we used DNA from minor salivary biopsy samples of three women with SS and and SS, with and with a female pregnancy (patients 7–9), one woman with SS without a previous pregnancy (patient 10), and two healthy women, one with a male pregnancy and one with a female pregnancy (patients 11, 12). Table 1 gives details of the patients.

We assayed by PCR for a specific Y chromosome sequence, SRY, and for the homologous gene of amelogenin.⁸ We tested our primers by diluting male peripheral blood DNA with female blood DNA. The sensitivity of our methodology was 10 pg for SRY primers and 100 pg for amelogenin. Given the sensitivity of the method, a cautionary note has to be made about laboratory personnel. When a male operator performed the DNA extraction and PCR a random positive case was obtained.

We have not found any male DNA either in the tissue from women with SS and a male pregnancy or in the controls. As far as we know this is the first study of fetal microchimerism in minor salivary gland tissue from a patient with SS.

Although this preliminary study does not seem to support the hypothesis that microchimerism has a role in the pathogenesis of Sjögren’s syndrome, we cannot exclude the possibility that the time lag between the last pregnancy and sampling might have influenced the result. On the other hand, Evans and colleagues found male microchimerism in women with scleroderma even up to 38 years after pregnancy.⁹

In conclusion, a larger number of patients, with a more recent pregnancy, should be evaluated in order to confirm or refute the role of fetal microchimerism in women with primary SS.
Pitting oedema in early diffuse systemic scleroderma

The term “puffy skin” is not infrequently noted at initial presentation of patients with systemic scleroderma. However, this is generally described as “non-pitting” oedema. The following case history challenges the latter widely held assumption, showing that its measurement is simple and may offer a more sensitive method of assessing response to treatment than the modified Rodnan skin score.1

CASE REPORT

A premenopausal computer analyst first presented in May 1998 with a two month history of finger stiffness. The next 10 months were spent investigating and treating the cause of her iron deficiency anaemia—gastric ectasia (watermelon stomach). The diagnosis of diffuse systemic scleroderma was made in March 1999. At this time she presented with persisting symptoms of skin stiffness, burning and pruritis, especially in the early morning, affecting the skin of her arms and legs, face, and upper chest. Clinical examination showed finger clawing, sclerodactyly, and scleroderma affecting her arms to the mid-upper arm, the face, neck, upper chest, thighs, and calves. Pitting oedema, noted in the forearms, upper arms, chest, and thighs, had the following characteristics: it occurred in areas of affected skin—typically it occurred in the advancing front of skin involvement, was slow to induce (of bees’ wax consistency), and it affected non-dependent areas. Her skin was also erythematous in parts. Livedoid patterning over the knees was also noted. The rest of the clinical examination, including musculoskeletal cardiac, and respiratory systems, was unremarkable. A skin biopsy specimen from the upper right forearm and dorsum of the left fifth proximal interphalangeal joint was performed. Her antinuclear antibodies (ANA) were positive with a speckled pattern and extractable nuclear antigens were negative for RNP, antitopoisomerase, anticentromere, SSA, SSB, and Sm antibodies.

The diagnosis of diffuse systemic scleroderma was confirmed by positive antinuclear antibodies and extractable nuclear antigens. Lymphocytic inflammation was observed in superficial dermal vessels, consistent with the diagnosis of diffuse systemic scleroderma. Both skin biopsy sites healed with keloid scarring. Her antinuclear antibody titre was 1/640, speckled pattern, and extractable nuclear antigens were negative for RNP, antitopoisomerase, anticentromere, SSA, SSB, and Sm antibodies.

A simple bedside test (the skin pitting oedema time test or “SPOT” test) was devised to quantify the duration of skin pitting and see whether its measurement paralleled response to treatment. A small diameter coin was placed over an area of oedematous skin on the arm, the site being recorded for future reference. A sphygmomanometer cuff was placed over the coin and around the arm, inflated to 100 mm Hg for 60 seconds, and then released. The sphygmomanometer cuff and coin were removed, leaving the coin’s impression in the skin. From this time (time 0) the impression was palpated every minute by two independent observers (patient and author) until it was no longer palpable. This time was noted and recorded as the skin oedema time. Both interobserver and intraobserver variation were assessed over three consecutive days (coefficient of variation 6.8% and 6.8% respectively). The patient’s skin oedema time was compared with that from a similar area of skin on a control matched for age, sex, and menopausal status (24 minutes).

At the patient’s request, treatment with cindamycin over two consecutive days was started on 3 May 1999, at which time the skin oedema time measured 40 minutes. Cindamycin was stopped owing to marked diarrhoea and abdominal tenderness, which settled over five days. The patient was readmitted for pulse methylprednisolone on 13 May, by which time her skin had become increasingly sensitive and pruritic.

Figure 1 outlines her treatment with pulse steroids and cyclophosphamide. Cyclosporin...
was added because of continuing disease activity. Before her first course of intravenous cyclophosphamide bilateral basal crepitations were noted. By 30 June 1999 skin hyperpigmentation and the development of mild dysphagia was noted. Concurrently, she also noted increased hair regrowth on the dorsum of her hands and lateral aspect of the calves. After her final course of cyclophosphamide her hands were no longer clawed into fixed flexion, the skin on the dorsum of the hands was again so supple that the dorsal hand veins were both visible, palpable and protruding from the skin surface; the forearm skin biopsy site was no longer keloid, though that on her finger was still slightly raised and palpable; her skin was much less irritable or pruritic. The most marked areas of skin improvement were those which were still oedematous at the start of treatment and were affected for the least time—upper arms, forearms, hand, thumbs, and anterior chest. The area of skin least responsive to treatment was over the distal phalanges, which remained tethered and immobile.

DISCUSSION

This case is presented to demonstrate a number of features. The skin of early diffuse disease is often characterised by pitting oedema. The skin pitting oedema time is easily measured and its measurement is reproducible for the least time—upper arms, forearms, hand, thumbs, and anterior chest. The area of skin least responsive to treatment was over the distal phalanges, which remained tethered and immobile.

There are two potential limitations of the “skin pitting oedema time” test. The first relates to its duration, making it impractical to administer in an outpatient department. The second relates to the potential influence of already fibrotic skin on the skin oedema score measurement. The first limitation may be overcome by applying a less compressive force (for example, 50 mm Hg) for a shorter duration (for example, 30 seconds)—both of which independently appeared approximately to halve the skin oedema recovery time, having the patient and/or a relative complete the assessment before leaving the surgery, or devising a mechanical device to monitor skin oedema quantitatively. The role of excess collagen deposition in affecting skin oedema recovery time is uncertain.

In conclusion, the occurrence of pitting skin oedema in early scleroderma is a useful clinical observation, providing information about the underlying pathology and hence the speed of responsiveness of the disease to treatment. It also provides guidelines for the relative usefulness of anti-inflammatory/immunosuppressive drugs rather than the historical antifibrotic “gold standard”, i.e., penicillinamine.

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Parvovirus arthropathy masquerading as the arthritis of Behçet’s disease

Parvovirus B19 is common, with 50–75% of UK adults having evidence of previous infection. Complications, such as arthritis, occur in a small minority. We report a case of parvovirus associated arthritis causing diagnostic confusion in a patient known to have Behçet’s disease.

CASE REPORT

A 34 year old white woman presented with a small joint polyarthritis, low back discomfort, severe heel pain, and patchy sensory disturbance, after a febrile illness with a rash. She had had Behçet’s disease in the age of 3 years, manifest by arthralgia, mouth, nasal and genital ulcers, conjunctivitis, facial swelling, and livedo reticularis. Before her presentation, her Behçet’s disease had been relatively well controlled by 100 mg of azathioprine a day, the only residual symptom being pain and morning stiffness of 45 minutes affecting her fingers, wrists, elbows, and shoulders, and livedo reticularis.

On presentation she was afebrile, with cervical lymphadenopathy. The liver and spleen were palpable. She had mild metacarpophalangeal and wrist synovitis, bilateral knee effusions, and was exquisitely tender bilaterally over the plantar fascia. Her sacroiliac joints were tender. There was subjective symmetrical sensory loss to pin prick and light touch on the dorsum of the feet and the lateral aspect of the hands. Neurological examination was otherwise unremarkable. An x ray examination of the hands, calcaneum, and sacroiliac joints was normal, as was the full blood count, and C reactive protein. Rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and anticardiolipin antibodies were not detected. She was treated initially with ibuprofen and hydrocortisone (12.5 mg hydrocortisone acetate 120 mg intramuscularly and local steroid injections to the plantar fascia (12.5 mg hydrocortisone acetate) brought about rapid improvement. All her symptoms resolved over the following few weeks. Parvovirus B19 IgM was subsequently found to be strongly positive by both enzyme linked immunosorbent assay (ELISA) and radioimmunoassay, indicative of recent infection.

DISCUSSION

Sacroilitis is an unusual feature of Behçet’s disease, and plantar fasciitis has not been previously described in this disorder. Parvovirus arthritis is an uncommon sequela of a common viral exanthem. The usual presentation is of an acute onset polyarthritis, resembling rheumatoid disease, which may follow a flu-like illness and rash. Transient neurologic disease may occur. Parvovirus associated relapse of spondylitis after a symptom-free period of 15 years has been described.

The diagnosis in our case was complicated by superficial similarities to the arthritis of Behçet’s disease. The possibility of neurologic involvement was a new, and worrying, feature. However, there were no "s" features of active Behçet’s disease, such as mouth or genital ulcers, which had been associated with previous exacerbations. The unusual features of seronegative arthritis and prior febrile illness raised the possibility of a coincidental reactive arthritis. Despite the presence of some atypical features, we consider parvovirus B19 to be the most likely cause of this patient’s illness, on both clinical and serological grounds.

This case illustrates the importance of considering the diagnosis of coincidental parvovirus in patients with pre-existing rheumatic diseases where there are unusual features. Because parvovirus associated arthritis is usually self-limiting, this diagnosis may allow a more conservative approach to treatment.

We thank Professor AJ Pinching for allowing us to report on his patient.

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