LongoVital® in the treatment of Sjögren’s syndrome

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Abstract
Objective
Sjögren’s syndrome (SS) is a chronic autoimmune disease complex of unknown aetiology. There is no curative treatment for SS, however, in recent years the influence of nutrients on autoimmune processes has attracted increasing attention. LongoVital (LV) (DK. Reg. No. 5178/75) is an herbal-based tablet enriched with the recommended daily doses of vitamins. The purpose of the present study was to investigate whether 4 months’ daily intake of LV as compared to placebo would affect clinical and laboratory disease parameters in patients with SS.

Methods
Forty patients with SS participated in a placebo-controlled, double-blind, randomised, clinical, 8 month cross-over study. Group A (n = 22) received LV during the first 4 months and Group B (n = 18) LV during the last 4 months.

Results
The unstimulated salivary flow rate increased during the LV period in Group A (p < 0.001). The stimulated salivary flow rate increased in Group B during the LV period (p < 0.05), and in Group A during the subsequent 4 months on placebo (p < 0.05). The rose bengal score decreased in Group B during (p < 0.01) and in Group A after the LV intake (p < 0.05). During the last 4 months of the study both groups showed an increase in serum levels of α-amylase (total: Group A, p < 0.01; Group B, p < 0.05; pancreatic fraction: Group A, p < 0.0001; Group B, p < 0.01) and in serum levels of IgM (Group A and B: p < 0.001), while levels of circulating immune complexes decreased (Group A, p < 0.05; Group B, p < 0.001).

Conclusion
It is concluded that LV has a beneficial and prolonged effect on some of the clinical and immunoinflammatory disease markers in SS.

Key words
Herbs, immunomodulation, LongoVital, nutritional supplementation, prophylaxis, Sjögren’s syndrome, vitamins.

**Introduction**

Sjögren’s syndrome (SS) is a chronic autoimmune disease complex of unknown aetiology. SS is characterised by a triad of the clinical conditions keratoconjunctivitis sicca (KCS), xerostomia and a connective tissue disease. Primary SS (SS-1) clinically manifests as KCS and xerostomia with rheumatologic and neurophysiologic features, and secondary SS (SS-2) manifests as KCS or xerostomia, plus an inflammatory connective tissue disease.

There is no curative treatment for SS, but in recent years the influence of nutrients on autoimmunie processes has attracted increasing attention. LongoVital (LV, DK reg. No. 5178/75) is a tablet based on dried and ground herbs from paprika, rosemary leaves, peppermint leaves, milfoil flowers, hawkthorn leaves and flowers, and pumpkin seeds supplemented with the nationally recommended doses of vitamins. LV has been on the market in Scandinavia since 1975 and previous placebo-controlled studies have demonstrated a preventive effect of the tablets on recurrent aphthous ulceration (1, 2) and a reduction of gum bleeding in periodontal patients (Stoltze et al., unpublished observations), in both groups of patients possibly due to a contemporary augmentation of cellular immune competence.

Patients with SS may have increased levels of humoral immunoinflammatory markers (primary disease markers, ref. 3) in the peripheral blood, and the purpose of the present study was to investigate whether 4 months’ daily intake of LV as compared to placebo would affect clinical (secondary) and primary disease parameters in patients with SS.

**Material and methods**

*Patients*

The study population consisted of 40 patients with primary (n = 32) or secondary (n = 8) SS, 39 females and 1 male, mean age 60 years (range 30 - 85 yrs.). The patients had had their SS diagnosis for an average period of 8.3 years (range 0 - 30 yrs.) when the study was initiated. A further description of the patient population is provided in Table I. At the beginning of the trial patients were instructed to keep their intake of drugs, vitamins and/or food supplements as well as smoking habits unchanged during the study.

*Diagnosis of SS*

The diagnosis of primary or secondary SS was based on the criteria for the classification of Sjögren’s syndrome as proposed by Vitali et al. (4).

The protocol was approved by the local ethics committee, and after providing patients with written information about the trial, their oral and written consent to participate was obtained. Forty-four consecutive patients fulfilling the diagnosis of either SS-1 or SS-2 were included in the study. The inclusion period was 5.5 months. Forty patients completed the trial.

Four patients withdrew before the end of the study, 2 during the placebo period and 2 while on LV. Of the two patients who dropped out while on placebo one had problems with constipation and the other developed a skin rash. Since these problems were suspected to have been induced by the active tablets, the code was broken and the patients withdrawn from the study. One patient withdrew while on LV due to complaints of bloating, and the other due to unrelated major surgery.

The investigation was designed as a clinical, prospective, double-blind, 8-month cross-over study with the intake of LV for 4 months, and placebo for 4 months in randomised order. The LV tablets were coated to make them indistinguishable from the inert lactose, placebo tablets. At the beginning of the trial (Day 0), test tablets were handed out together with written instructions to take three tablets every morning at breakfast. Patients were evaluated after one month (Day 30), 4 months (Day 120, coinciding with the change in medication), 5 months (Day 150), and finally after 8 months (Day 240).

*Clinical evaluations*

All patients were seen between 8.30 a.m. and noon to control for circadian gland function (5). The unstimulated whole salivary flow rate was determined over a 15-minute period and paraffin-stimulated whole saliva for 5 minutes. During the sialometry collection period the pa-
tients were placed in an upright position and, while bending slightly forward, were asked to spit into a cup without swallowing. The amount of saliva collected was measured using a 5 ml syringe.

Ocular signs were determined without local anesthesia. The Schirmer-I test was performed on closed eyes for 5 minutes (Eagle Vision standardised sterile strips, Memphis, Tennessee). Van Bijsterberg scoring was performed after administering 2.5 µl 1% rose bengal with a plunger-operated pipette (Transferpette, Wertheim, Mainen, Germany).

Haematological evaluations
Peripheral blood samples were obtained on days 0, 120 and 240 in order to determine routine haematological parameters, including iron parameters (haemoglobin, plasma iron, serum ferritin and transferrin, MCHC, MCV), vitamin B status (vitamin B12, plasma folic acid), the differential white blood cell count and the erythrocyte sedimentation rate (ESR). Peripheral blood levels of the primary disease activity markers immunoglobulins A, G and M were also determined continuously.

Heparinized plasma samples were stored at -80°C and soluble IL-2R (sIL-2R) were quantified by ELISA (Endogen, TriChem, Virum, Denmark) at the Institute for Inflammation Research, Rigshospitalet. Determinations were carried out bi-monthly. The assay sensitivity was 5 to 10 pg/ml, and the inter- and intra-assay coefficients of variation were less than 15%.

The following parameters were determined simultaneously at the end of the trial from the stored serum samples. Circulating immune complexes (CIC) (stored at -80°C) were assayed at Medilab by particle-enhanced nephelometry using a kit from Behring Diagnostics GmbH (B-35041, Marburg, Germany). The inter- and intra-assay coefficients of variation were less than 9%.

Autoantibodies were determined from serum samples stored at -20°C by the Department of Autoimmunology, Statens Serum Institut. IgG ANA were determined by an indirect immunofluorescence technique using commercially prepared slides of monolayer HEp-2 cells (ImmunoConcepts, Sacramento, CA, USA) and fluorescein isothiocyanate (FITC)-labelled rabbit immunoglobulins against Fc (DAKO, Denmark). Sera were screened at a dilution of 1:40, and positive reactions were categorized according to the nuclear immunofluorescence patterns (6).

Anti-Ro/SSA and anti-La/SSB antibodies (Ab) were determined by Diamet® anti-SSA and anti-SSB kits (SHIELD Diagnostics, Dundee, Scotland), following the manufacturers instructions (normal range below 2 IU/ml). IgM and IgA rheumatoid factors (RF) were determined by an ELISA technique (7).

Subjective evaluation
At the end of the trial the patients were questioned regarding their preference for either the first or the second 4-month period of treatment. An overall evaluation of symptoms, comparing Day 0, Day 120 and Day 240, was also carried out.

Treatment response
The treatment response was determined from its effect on: 1) secondary disease activity markers (unstimulated and stimulated salivary flow rates, Schirmer-I values and rose bengal score); 2) primary disease activity markers (peripheral Igs, autoantibodies, IL-2R, CIC and α-amy- lase); 3) routine haematological parameters; 4) subjective period of preference; and 5) the patient’s overall evaluation of his/her symptoms at the end of the trial as compared to Day 0 and Day 120.

Statistical analysis
The Friedman and Wilcoxon matched-pair signed rank test was applied for statistical analysis of intra-group param-
etters; intergroup parameters were analysed by the Mann-Whitney U-test. Frequencies were analysed by the sign test (binomial theorem). P-values below 0.05 (two-sided) were considered statistically significant.

Results

Due to the previously demonstrated carry-over effect of LV lasting several months (1), data analysis on the group that had taken LV during the first 4 months (Group A, n = 22) and on the group that received LV during the last 4 months (Group B, n = 18) was done separately. Four patients in each group were diagnosed as having SS-2 and the remaining as having SS-1. The duration of the disease before the trial was not significantly different between the two groups (p = 0.459). Three patients in each group were daily smokers (one SS-2 patient in each group). Two patients in Group A and one in Group B reported a regular intake of evening primrose oil, while bromhexine was used by 2 patients in Group A and 4 in Group B, and LV was already used by one patient in each group.

Secondary disease activity markers

In Group A there was a significant increase in the whole unstimulated salivary flow rate during the 4 months on LV (p < 0.001; Table II), whereas in Group B there were no significant changes in the unstimulated salivary flow rate during either of the treatment periods (Table II).

In Group A the stimulated salivary flow rate did not change significantly during the period on LV, but did increase significantly during the subsequent 4 months on placebo (p < 0.05; Table II).

In Group B the stimulated salivary flow rate increased significantly during the 4 months on LV (p < 0.05; Table II).

There were no significant changes in Schirmer-I values in any of the groups during any of the treatment periods.

The rose bengal score was determined by adding the left and right eye values and dividing by 2. In Group A there was no significant change in the rose bengal score while on LV, whereas the score decreased significantly during the succeeding 4 months on placebo (p < 0.05; Table III). Group B showed a significant decrease in the rose bengal score during the LV period (p < 0.01; Table III).

Primary disease activity markers

Levels of IgA and IgG did not change significantly during any of the treatment periods. The level of IgM, however, decreased in Group A during the 4 months on LV (p < 0.05; Table IV), and increased during the subsequent placebo period (p < 0.001; Table IV). In Group B, the IgM concentration increased in the LV period (p < 0.001; Table IV).

The level of CIC decreased in both groups while on LV (Group A: p < 0.05; Group B: p < 0.001; Table IV), and in Group A there was a further decrease during the placebo period (p < 0.05; Table IV).

There were no significant changes in the salivary α-amylase fraction in either of the groups during either of the treatment periods (Table IV). In contrast, there was a significant increase in the total and in the pancreatic α-amylase fraction in Group B during LV intake (p < 0.05 vs. p < 0.01; Table IV), and in Group A during the last 4 months on placebo (p < 0.01 vs. p < 0.0001; Table IV).

The prevalence and titres/concentration of ANA, IgM or IgA RF and SS-A/SS-B Ab and IL-2R did not change signific-

| Table II. Salivary flow rates (ml) from 40 patients with Sjögren's syndrome during daily intake of LongoVital® (LV) or placebo in an 8-month, double-blind, crossover trial. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Time of evaluation** | **LV** (n = 22) | **Placebo** | **Placebo** | **LV** (n = 18) | **Placebo** | **Placebo** | **LV** |
| **Unstimulated - 15 min** | | | | | | | | |
| **Median** | 0.3 | 1.0 | 1.0 | 0.5 | 0.8 | 0.2 | 0.3 | 0.9 | 0.7 | 0.8 |
| **95% confidence interval** | 0.0 - 1.2 | 0.1 - 1.2 | 0.1 - 1.5 | 0.1 - 1.8 | 0.1 - 2.0 | 0.0 - 1.5 | 0.0 - 1.2 | 0.2 - 1.9 | 0.1 - 1.0 | 0.0 - 2.1 |
| **Friedman** | [ ————*** ————] | [ ———— NS ———— ] | [ ———— NS ———— ] | [ ———— NS ———— ] |
| **Mann-Whitney** | [ ———— ———— NS ———— ] | |
| **Stimulated - 5 min** | | | | | | | | |
| **Median** | 1.9 | 1.9 | 1.7 | 2.0 | 2.7 | 2.0 | 2.0 | 2.2 | 3.0 | 2.8 |
| **95% confidence interval** | 0.2 - 4.0 | 0.5 - 3.0 | 0.2 - 3.0 | 0.9 - 4.0 | 1.4 - 4.0 | 0.2 - 4.6 | 0.4 - 5.0 | 0.3 - 3.6 | 0.1 - 4.5 | 0.4 - 4.5 |
| **Friedman** | [ ———— NS ———— ] | [ ———— * ———— ] | [ ———— NS ———— ] | [ ———— * ———— ] |
| **Mann-Whitney** | [ ———— ———— NS ———— ] | |

NS: not significant; * p < 0.05; *** p < 0.001.
cantly in group A or group B during either of the treatments.

Routine haematology
In both groups there was a significant decrease in the number of basophils during the 4 months on LV (Group A, Day 0: 0.11 x 10^9/L, Day 120: 0.06 x 10^9/L p < 0.0001; Group B, Day 120: 0.10 x 10^9/L, Day 240: 0.05 x 10^9/L: p < 0.01). No other significant changes in routine haematological parameters were demonstrated.

Subjective evaluations
There was no significant difference in period of preference between the two groups. Twelve patients in Group A and 4 patients in Group B expressed an overall improvement on day 240 as compared with Day 0 (p < 0.05).

Some side effects were experienced by 5 patients during the LV period and by 2 patients during the placebo period. In the LV period 2 had temporary, mild problems with constipation, 1 had pruritus, 1 skin rash, and 1 experienced an exacerbation of her psoriasis during the autumn. While on placebo one complained of nausea and another of mild problems with constipation. During the LV period two patients experienced an improvement of peristalsis.

Discussion
The study demonstrates a beneficial effect of 4 months of LV intake on some of the oral and ocular parameters and favourable changes in some of the immunoinflammatory disease activity markers in the peripheral blood of patients with SS. The inclusion of both SS-1 and SS-2 patients in this study could be criticised. However, there were four SS-2 patients in each group, thus affecting the results evenly in both groups. The unstimulated secretion rate increased during LV intake in Group A without a decrease during the 4 months after LV intake. The stimulated salivary flow rate increased in Group B while on LV and in Group A during the 4 months after the LV treatment had stopped. Therefore, LV appears to have a sustained effect on both the unstimulated and stimulated salivary secretion rates. So far, pilocarpine is the only systemic drug which has been shown to produce a reliable stimulation of saliva production (8, 9). However, the use of pilocarpine is restricted by the high frequency of side effects. LV therefore seems to be the first harmless systemic drug that may improve both unstimulated and stimulated salivary secretion.

The LV intake did not affect the Schirmer-I values significantly. Rose bengal scores, however, decreased significantly in Group B while on LV, and in Group A during the 4 months after the treatment. The rose bengal score appears to be the key parameter in evaluating the degree

Table III. Rose bengal score (according to the van Bijsterfeld scoring system) from 40 patients with Sjögren’s syndrome during daily intake of LongoVital® (LV) or placebo in an 8-month, double-blind, crossover trial (right and left values added and divided by 2).

<table>
<thead>
<tr>
<th>Time of evaluation</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Day 120</th>
<th>Day 150</th>
<th>Day 240</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Day 120</th>
<th>Day 150</th>
<th>Day 240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>3.8</td>
<td>4.5</td>
<td>5.0</td>
<td>4.0</td>
<td>3.5</td>
<td>6.0</td>
<td>4.8</td>
<td>7.5</td>
<td>5.5</td>
<td>3.5</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>3 - 7</td>
<td>2 - 9</td>
<td>4 - 7</td>
<td>4 - 7</td>
<td>3 - 7</td>
<td>4 - 7</td>
<td>4 - 8</td>
<td>5 - 8</td>
<td>3 - 8</td>
<td>3 - 8</td>
</tr>
<tr>
<td>Friedman</td>
<td>[----- NS -----]</td>
<td>[----- * -----]</td>
<td>[----- NS -----]</td>
<td>[----- * -----]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mann-Whitney</td>
<td>[----- NS -----]</td>
<td>[----- NS -----]</td>
<td>[----- NS -----]</td>
<td>[----- NS -----]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS: not significant;  * p < 0.05;  ** p < 0.01

Table IV. Some immunoinflammatory (primary) disease activity markers (medians) from 40 patients with Sjögren’s syndrome during daily intake of LongoVital® (LV) or placebo in an 8-month, double-blind, crossover trial.

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Day 0</th>
<th>Day 120</th>
<th>Day 240</th>
<th>Day 0</th>
<th>Day 120</th>
<th>Day 240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM (mmol/L)</td>
<td>0.3 - 3.7</td>
<td>1.27</td>
<td>1.25*</td>
<td>1.95***</td>
<td>1.35</td>
<td>1.25</td>
</tr>
<tr>
<td>Circulating immune complexes(mg/L)</td>
<td>0 - 5</td>
<td>2.5</td>
<td>2.4*</td>
<td>1.9*</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>α-amylose, total (IU/L)</td>
<td>50 - 220</td>
<td>118.5</td>
<td>113.0</td>
<td>118.0**</td>
<td>134.0</td>
<td>114.0</td>
</tr>
<tr>
<td>Saliva fraction (IU/L)</td>
<td>17 - 120</td>
<td>58.0</td>
<td>53.5</td>
<td>47.0</td>
<td>51.5</td>
<td>53.0</td>
</tr>
<tr>
<td>Pancreas fraction(IU/L)</td>
<td>32 - 110</td>
<td>64.0</td>
<td>62.5</td>
<td>66.0****</td>
<td>77.0</td>
<td>64.3</td>
</tr>
</tbody>
</table>

* p < 0.05;  ** p < 0.01;  *** p < 0.001;  **** p < 0.0001: Values significantly different from the preceding measurement, Wilcoxon.
of KCS patients (10-12). The results thus indicate that LV improves the ocular surface condition and therefore seems to be of benefit in the prevention of epithelial damage. Systemic bromhexine and evening primrose oil have been shown superior to placebo in improving tear secretion (13-16) without any effect on the ocular surface condition as evaluated from rose bengal staining (14, 15). However, bromhexine responders may improve in rose bengal score in the course of time (16). In the present investigation, 6 patients had used bromhexine and 3 patients evening primrose oil on a regular basis before and during the whole study. Therefore, these ongoing treatments should not have affected the results of the present study. The results indicate that LV is superior to both bromhexine and evening primrose oil in preventing epithelial damage. However, bromhexine responders may benefit from supplementation with LV in order to prevent ocular damage. Objective clinical parameters indicated a sustained effect of LV on the stimulated salivary secretion rate, and on the rose bengal score. The presence of a prolonged effect was supported by the subjective overall evaluations at the end of the study where more patients in Group A than in the Group B evaluated their overall condition to be improved as compared with Day 0. The concentration of CIC decreased significantly in both study groups while on LV, and in Group A there was a further decrease during the 4 months after LV intake had stopped. The decreased levels of CIC apparently induced by the LV intake may explain some of the clinical improvements seen. Furthermore, the CIC concentration decreased in parallel with an increase in the IgM concentration, indicating that IgM in particular may form part of the CIC in patients with SS. Complement proteins from be part of the CIC; they are important for maintaining immune complexes in a soluble state, and can induce mast cell and basophil degranulation (17). This could explain the decrease in the number of basophils in both groups while on LV. On the other hand, the decreased peripheral levels of CIC and the number of basophils induced by LV could also be due to an increased deposition in the tissues/vessel walls. If so, this could explain the skin reactions experienced by three patients while on LV.

The total and pancreatic fraction of α-amylase in the serum increased significantly during the 4 months on LV in Group B, and during the 4 months after the LV intake in Group A. Amylase is an important digestive enzyme which may be a marker of pancreatic function. Maury et al. (19) reported diminished pancreatic secretion in patients with SS, and based on the increase in pancreas α-amylase seen in the present study, it may be hypothesized that LV could impair the functioning of the pancreas. In addition to the recommended daily dosages of vitamins, LV contains a whole range of trace elements. Significant inadequacies of nutritional intake have formerly been reported in patients with SS (20). The benefit of LV in patients with SS is therefore not surprising. In conclusion, the results of the present study indicate that some patients with SS may benefit from a regular intake of LV. However, further studies with LV in the treatment of SS are needed in order to confirm or disprove the results of the present study, and should be performed on groups of primary and secondary SS patients separately.

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