Immunotherapy of Fibromyalgia and Chronic Fatigue Syndrome by a Staphylococcus Toxoid Vaccine

Carl-Gerhard Gottfries* MD, PhD¹, Ove Häger RN¹, Johan Gottfries PhD², Olof Zachrisson MD, PhD¹

¹ Institute of Neuroscience and Physiology at The Sahlgrenska Academy, University of Gothenburg, Sweden. Gottfries Clinic, Krokslätts Torg 5, SE-431 37 Mölndal, Sweden. Tel.: +46 31 343 23 97 Fax.:+46 31 209938 E-Mail cgg@gottfries.se oz@gottfries.se
² Umeå University, SE 90187 Umeå Sweden. Phone +46 736 266 508 E-Mail johan.gottfries@chem.umu.se

Address for correspondence: Carl-Gerhard Gottfries professor emeritus Gottfries Clinic, Krokslätts Torg 5, SE-431 37 Mölndal, Sweden.

Keywords:
Biologic agents; Chronic fatigue syndrome; Fibromyalgia;
Immunotherapy; Staphylococcus vaccine
ABSTRACT

Background
In previous clinical double blind investigations a significant effect is recorded in patients with fibromyalgia and/or chronic fatigue syndrome when treated with a staphylococcus vaccine. The aim of this study is to report long-term efficacy and safety of this immunotherapy.

Methods
One hundred and sixty patients with fibromyalgia and chronic fatigue syndrome who had previously participated in vaccine treatment studies were continuously observed during one year in a follow up study. At inclusion mean age was 53±11 years and mean treatment time 22±10 months. In a subgroup of 97 younger patients (48±10 years) with a mean treatment time of 50.4±17.8 months a Principal Components Analysis (PCA) was performed.

The patients were on immunotherapy by a staphylococcus vaccine administered subcutaneously in a dose of 1 mL every 3rd to 4th week. Medically educated and trained staff using the rating scale CPRS-15 evaluated efficacy. Safety was evaluated continuously.

Results
Ratings showed improvement from start of treatment and further improvement was recorded during the follow-up period. The total mean rating CPRS-15 score was reduced by more than 50 %. Five items (Concentration difficulties, Failing memory, Irritability, Sadness and Autonomic disturbances) had mean levels below one at the time of the last rating, indicating that these symptoms on a group level were within the range of normality. The PCA also indicated improvement in the subgroup of 97 middle-aged patients. Adverse events were few and the adherence to the treatment was surprisingly fine. During the observation period of one year 14% withdrew from treatment.

Conclusions
The result was considered impressive and in view of the lack of effective treatment in fibromyalgia and chronic fatigue syndrome the results are of interest but need to be confirmed.
BACKGROUND

Although the terms fibromyalgia (FM) and chronic fatigue syndrome (CFS) are of relatively new origins, clinical conditions of chronic pain and fatigue have been described in the medical literature for centuries. In 1990 for FM and 1994 for CFS new concepts were defined by internationally established criteria, which enable any interested physician to evaluate the patient and make a diagnosis (1, 2). Complex multi-organic chronic signs and symptoms, including muscle pain, joint pain, chronic fatigue, sleeping problems, neuro-cognitive and gastrointestinal complaints, characterize both syndromes. In FM the emphasis is on widespread pain and in CFS on chronic fatigue. FM and CFS overlap to a considerable degree. Seventy percent of FM cases may also meet the case definition for CFS and 35-70 % of CFS patients meet the case definition for FM. Thus many patients fulfill the criteria for both syndromes at the same time (3, 4, 5, 6, 7). Their prevalence is substantial for FM 2-4 % (8, 9) and for CFS 0.2-2.6 % (10, 11, 12, 13).

Immunological studies in CFS have not yielded consistent findings (14). Our concept of disrupted immune function in patients with FM and CFS is based on findings presented in the literature (15, 16), as well as clinical findings that (virus) infections often trigger CFS and that infections are common in the medical history of these patients. In order to modulate the immune system, we have performed clinical trials using a staphylococcus toxoid vaccine (Staphypan) (17). The results from two double-blind placebo-controlled trials, where the patients fulfilled the criteria for FM and CFS have been published (18, 19). The patients received weekly subcutaneous injections in increasing dosages of the vaccine during the initial 8-10 week period, and thereafter once a month. A positive clinical effect was recorded in 65 % of patients on active treatment according to global ratings. The items fatigability, reduced sleep, failing memory, concentration difficulties, hostile feelings and sadness improved significantly more in the active group compared to the placebo group. During a two-month controlled and blind withdrawal period, however, most responders relapsed and they were therefore offered maintenance treatment.

The vaccine used, Staphypan, is composed of a mixture of staphylococcus strains and
a toxoid. The preparation includes extracts of Staphylococcus aureus and Staphylococcus epidermidis. Staphypan also contains the preservative thiomersal, which is a double-salt including salicylate and ethyl-mercury. Staphypan was developed by Berna Biotech Ltd., Switzerland in the 1950s, but has since 2005 been withdrawn from the market. The withdrawal was not due to any problems with the use of the vaccine but was explained by costly need of modernizing the manufacturing processes and of low sale.
OBJECTIVES

The aim of this investigation was to assess the maintenance of effect and long-term safety of staphylococcus vaccine immunotherapy in patients with FM and CFS during one year. The clinical effect was assessed by the use of a medical observer rating scale and adverse events were recorded.

METHODS

Participants
Enrollment beginning in Oct 2003 included 160 patients, 9 men and 151 women of whom 80 had the diagnosis of FM, 18 of CFS and 62 fulfilled the criteria for both diagnoses. All patients were cared for at our outpatient unit. The mean age at study entry was 53±11 (SD) years. The patients were recruited from previous controlled studies, as follows:

a) a pilot study (non published), which started in 1993 with the aim of testing the administration and dosing of the vaccine;
b) the first double blind placebo controlled study which was completed in 1998 (n=28) (18);
c) the second double blind study completed in 2001 (n=100) (19).

In the pilot study and in the two double blind studies around 65 % of the patients improved significantly. After a withdrawal period patients were offered maintenance treatment. Some data from this study is already reported on (20).

The mean treatment time with vaccine before inclusion in this long-term study was 22 ± 10 months.

Instrument: Comprehensive Psychopathological Rating Scale (CPRS) (21)

CPRS comprises 65 items covering a broad range of psychiatric symptoms. The CPRS-15 sub scale includes fifteen items assumed to be of interest for rating symptoms in patients with FM and CFS (see table 2). Each item is rated according to a 7-step scale in which the scale steps 0, 2, 4 and 6 are defined. The maximum score is 90 and the
scale is assumed to be sensitive to change over time. The patients were rated with CPRS-15 before any vaccine treatment and every third month during the one year duration of this long-term study.

**Procedure**

Patients had started up the vaccine treatment with an 8-10 week titration phase during which the vaccine dose was increased weekly from a start dose of 0.1 mL to a maximum dose of 1.0 mL. During continued treatment the patients received a dose of 1 mL vaccine every 3rd or 4th week. A research nurse, or a supervised district nurse, administered the subcutaneous injections of vaccine. Berna Biotech Ltd. has generously supplied us with Staphypan.

The patients visited a doctor every third month for clinical evaluation and recording of adverse events. Blood samples for routine laboratory investigations were taken once a year. During 2005 the treatment had to be stopped, as the vaccine was withdrawn from the market.

In January 2005, 97 patients (mean age 48±10) of 132 remaining in the study were invited to a special investigation, as they had not reached retirement age. They had made regularly ratings with the CPRS-15 subscale before any treatment as well as during the follow up period. The mean treatment time of this group was 50.4 ± 17.8 months when their treatment data was analyzed with a Principal Components Analysis (PCA), which is reported on here.

**STATISTICS**

Differences between results of ratings before and during treatment were analyzed with Student T-test dependent samples. Subanayes of stratified CFS, FM, CFS/FM groups were performed and no group differences were found, though the group size of the CFS alone group was small. Missing data due to withdrawal were supplemented with the corresponding last rated scoring by a carry-forward technique.

In the subsample of 97 patients nine core-items from CPRS-15 were selected for a Principal Components Analysis (PCA), which is a projection tool for multivariate data
analyses (22). By use of bilinearization of the patient data matrix, scores for the objects (i.e. patients) and loadings for the variables (i.e. clinical ratings) were calculated as vectors. The number of principal components (PC) was guided by inspection of cross-validation (CV) and Eigen vector size (23). Data were mean centered and unit variance scaled before initiating PCA, and all calculations were performed using the SIMCA software package (Umetrics, Sweden v. 11.5).

ETHICS

The study was conducted in accordance with the Declaration of Helsinki after approval by the medical research Ethics Committee of Gothenburg, Sweden.

RESULT

_CPRS-15 ratings_

Patients were rated with the CPRS-15 scale before start of vaccine treatment and achieved a mean score of 33±7.5. At the inclusion in this one-year follow up study the patients had been on the immunotherapy for a mean of 22 ±10 months. Reassessment with CPRS-15 then showed improvement compared to baseline; the mean score was 20.7 ± 8.5 points (p<0.02). A further significant reduction of the mean score to 14.6±7.4 (p<0.05) was seen during the 12 months continued vaccine treatment indicating improvement more than two years after start of treatment (Table 1).

According to the definition of the items, a rating level below one is considered normality. Five items (Concentration difficulties, Failing memory, Irritability, Sadness and Autonomic disturbances) had mean levels below one at the time of the last rating, indicating that these symptoms on a group level were within the range of normality. Three items, aches and pain, fatigue and sleep disturbances, were significantly reduced, however, not to mean levels below one. The item muscular tension did not improve significantly (Table 2).

At the CPRS-15 ratings it was found that the items Inner tension, Worrying over trifles, Pessimistic thoughts, Suicidal thoughts, Hypochondriasis and Phobias had a baseline
incidence below 70 % indicating low clinical relevance. For this reason they were excluded from further statistical analyses. The other nine items of CPRS-15 were analyzed with PCA. The first PC comprised a R2 (explained variance by regression) of 0.51 with a confidence interval (CV) of 0.35, the second and third PCs had negative CVs, but further explained 12 % and 9 % respectively and the Eigen vectors were larger than noise vectors. Thus a PCA model using 3 PCs was chosen, which in total explained 72% of data (R2 cumulative after 3 PC = 0.723). The first PC explained the difference between the assumed healthy profile (hypothetical objects given combinations of 0 and 1 ratings for the clinical ratings, according to experimental design) and the patient objects, i.e. all clinical ratings showed loading towards the same and positive direction indicating severity of disease. The second PC indicated positive loading for Mood and negative loading for Autonomic disturbances, while Irritability and Sleep disturbances loaded positively and negatively respectively in PC3. All other ratings revealed close to zero loadings in PCs 2 and 3. The model was created using the clinical rating data at patient inclusion together with the assumed healthy profiles. The patient profiles after start of treatment were predicted by the PCA model and overlaid for comparison. The distribution after treatment with vaccine (black triangles Fig 1) showed a shift of patient scores in PC1 towards symptom relief.

SAFETY

Laboratory data
During the study blood samples were taken for routine laboratory investigation once a year. No change that was judged related to the treatment was recorded.

Serious (SAE) and Adverse events (AE)
During the observation year a total of six SAEs were recorded. Two patients were hospitalized due to chest pain. In none of the cases there were signs of heart disease. One woman became pregnant during treatment and withdrew when the pregnancy was diagnosed. She gave birth to a normal child. One patient committed suicide. She had contact with a psychologist and was on pharmacological antidepressive treatment. The last injection with Staphypan was given five weeks ahead of the time of suicide. One patient had an epileptic seizure, suspected to be due to abuse of analgesics. One
patient had a uterus operation made during treatment. None of these SAEs were considered related to the treatment with the staphylococcus vaccine.

The most common AEs were different forms of infections. Cold, sinusitis or tonsillitis was reported by 47 patients (29 %), urinary tract infections by 10 and eye inflammation by three. Four patients reported muscle inflammation; two patients reported pneumonia, two herpes and two carbuncles. In single cases erysipelas, ear inflammation, prostate inflammation and lichen ruber was reported. Gastritis was reported in eight cases, diarrhea in two and bleeding from anus in one. Of neuropsychiatric AEs one reported dizziness, one herpes zoster, one partial loss of sight and one sciatic pain. Four patients reported depressed mood. In six cases minor surgery was made. None of the above mentioned AEs were considered related to the vaccine treatment.

All patients had a local reaction at the site of the injection. In the beginning of the treatment the local reaction was normally around 10-15 cm in diameter. After about one year the local reaction became rather small (2-5 cm in diameter) and of no discomfort. In one patient the local reaction was severe (allergic) and caused withdrawal of the treatment. Two patients reported local itching. One patient reported dysphoria, one loss of appetite and one tiredness symptoms present for a few days after injections. Some patients reported headache but as this symptom is common and fluctuating in this group of patients it was not recorded as an AE. Twenty-two patients (14 %) stopped treatment before scheduled. Six did not show up for appointments, four considered the effect insufficient, two had a high sedimentation rate and in single cases the reason for withdrawal was allergy, dryness of mouth, gastritis, tremor, fever reaction, repeated urinary tract infections and varicose ulcer. One patient stopped due to planned pregnancy, one for travelling abroad and one for amalgam sanitation. One patient improved and therefore stopped treatment.

**DISCUSSION**

In two controlled investigations, we have shown that immunotherapy by a staphylococcus toxoid vaccine (Staphypan) is of benefit for patients with FM/CFS. However, it is obvious that after up-titration the effect of a single booster dose of the
vaccine only lasts for 3-4 weeks. Repeated injections during long-term treatment are necessary to maintain the effect.

At our out patient unit we have had 160 patients in long-term treatment. FM was the primary diagnosis for 80, CFS for 18 and 62 for both diagnoses. Due to the great overlap of symptoms in the two disorders and the small number of primary CFS subjects, the groups were combined. In 2005 the delivery of vaccine was stopped as the producer of the vaccine Biotech Berna decided that the vaccine should be withdrawn from the market.

As a result of the treatment the mean rating score on the CPRS-15 measure was reduced by more than 50% and the improvement continued during a consecutive year of follow-up. According to the definition of the items in CPRS, a rating level below one is considered normal. The items Concentration difficulties, Failing memory, Irritability, Sadness and Autonomic disturbances had mean levels below one at the time of the last rating, indicating that these symptoms on a group level were normalized (Table 2).

In the somewhat younger subgroup of 97 patients (age 48±10) with a mean treatment time of 50.4±17.8 months (variance 30-120), nine CPRS-15 core items rated before as well as during treatment with the vaccine were analyzed with PCA. A model was created using the clinical rating data at patient inclusion together with the assumed healthy profiles. The patient profiles after start of treatment were predicted by the PCA model and overlaid for comparison. The predicted values show loadings (black triangles Figure 1), which have changed clearly in direction towards the normal group indicating improvement. The data show that this subgroup of middle-aged women after four to five years’ treatment still has an impressive beneficial effect.

In a previously published study (24) 14 patients receiving active treatment with the staphylococcus vaccine and 14 receiving placebo, anti-body status against extracellular toxins/enzymes, cell-wall components, and enterotoxins was evaluated in serum at baseline and after six months treatment. Significant changes were recorded in the group with active treatment while no change was seen in the controls. Treatment led to increased capacity of serum to neutralize alpha-toxin (p< 0.001) and a significant increase in serum IgG to alpha-toxin (p< 0.01) and lipase (p< 0.01). Furthermore, the
increase in the serum parameters paralleled the improvement in clinical out-come. Thus, the greater the serological response, the greater was the clinical effect. This relationship may indicate a working mechanism of the vaccine.

There was a dropout of 22 patients (14 %) during the observation year. Only four withdrew treatment due to insufficient effect. Six patients did not show up for control visits and in 12 the reason for dropout was not considered related to the vaccine treatment. In one patient the treatment was stopped due to a severe local reaction at the injection site. In two patients in previous investigations similar reactions have been seen and were considered an allergy to the salicylate in the preservative (confirmed by in vitro MELISA-testing). No patients appeared to be sensitive to mercury.

Very few side effects were seen in relation to the treatment. So far, no severe complications have been recorded. According to the manufacturer, the vaccine has been used in more than 10 million dosages over the years, and no severe complications have been reported.

Our clinical impression is that a majority of patients with FM/CFS are prone to infections. During the treatment the clinical impression was that the frequency of infections and symptoms of irritable bowel was reduced. Our patients found the increased resistance to infections of great value.

Limitations

The long-term study presented here was not blinded, however, it was preceded by two controlled studies performed according to the double blind technique. Further controlled studies with a staphylococcus vaccine are important to prove the effect.

Berna Biotech informed us at 2005 that Staphypan would be withdrawn from the market. Staphypan was an old product where the manufacturing process had to be developed to cope with modern GMP rules in EU and US. The present owner of Berna Biotech, the company Crucell in the Nederlands will not take any economic or medical responsibility for developing a modern Staphypan. We have tried to find a vaccine that could replace Staphypan but there is no such product at least in the western world. At present we make efforts to develop a Staphypan-like product for use in further clinical
investigations. We assume that a vaccine treatment of the kind presented here eventually due to a super-antigen effect, can be of use for patients with CFS, FM and possibly other immune deficiency syndromes.

CONCLUSIONS

FM and CFS are disorders of unknown etiology. In controlled investigations we have shown that an immunotherapy, as conveyed by repeated injections of a staphylococcus vaccine preparation, is of clinical importance for a significant number of patients with FM and/or CFS. The effect is seen after 24 months treatment when the dose of Staphypan has been increased to 1 mL, the maximum dose used in our studies. The treatment should be continued long-term with booster injections of vaccine every 3rd to 4th week in order to maintain the effect. The treatment is safe and the adherence to the treatment is impressive.
REFERENCES


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Table 1
Clinical rating scores in FM and CFS patients before and during treatment with a staphylococcus vaccine. P-values from Students t-test. ITT data n= 160. CPRS-15 is a subscale to the Comprehensive Psychopathological Rating Scale (21).

Table 1

<table>
<thead>
<tr>
<th>Rating occasion</th>
<th>Before start of treatment</th>
<th>Treated 25.2±10 months (Study entry)</th>
<th>+ 3 months</th>
<th>+ 6 months</th>
<th>+ 9 months</th>
<th>+ 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPRS-15 mean ± SD</td>
<td>33.0±7.5</td>
<td>20.7±8.5</td>
<td>17.9±6.9</td>
<td>16.5±7.1</td>
<td>16.0±7.6</td>
<td>14.6±7.4</td>
</tr>
<tr>
<td>Students t-test</td>
<td></td>
<td>p&lt;0.01, (1/2)</td>
<td>p=0.01, (1/3, 2/3)</td>
<td></td>
<td></td>
<td>p&lt;0.05, (2/6)</td>
</tr>
</tbody>
</table>

Table 2
Patients with FM/CFS on long-term treatment with a staphylococcus vaccine (n=160). Rating scores before treatment, after 2210 months treatment and during 12 months of follow up. Values are given as mean SD. Range of score is 0 (no symptom) to 6 (severe symptom) on individual items. Statistical within-group differences test for dependent samples.

Table 2

<table>
<thead>
<tr>
<th>Single items in CPRS-15</th>
<th>Ratings before start of vaccine treatment</th>
<th>Ratings after 25.2±10 months of treatment (Study entry)</th>
<th>+ 3 months</th>
<th>+ 6 months</th>
<th>+ 9 months</th>
<th>+ 12 months</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aches and pain</td>
<td>4.6 [0.98]</td>
<td>3.0 [1.50]</td>
<td>3.0 [1.46]</td>
<td>2.7 [1.44]</td>
<td>2.7 [1.46]</td>
<td>2.5 [1.33]</td>
<td>T=4.7 p&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.8 [0.80]</td>
<td>3.3 [1.49]</td>
<td>3.2 [1.31]</td>
<td>3.0 [1.29]</td>
<td>2.9 [1.40]</td>
<td>2.6 [1.41]</td>
<td>T=3.7 p&lt;0.001</td>
</tr>
<tr>
<td>Concentration difficulties</td>
<td>2.8 [1.19]</td>
<td>2.0 [1.45]</td>
<td>1.4 [1.16]</td>
<td>1.1 [0.97]</td>
<td>1.1 [1.05]</td>
<td>0.8 [0.95]</td>
<td>T=10.8 p&lt;0.001</td>
</tr>
<tr>
<td>Failing memory</td>
<td>2.8 [1.19]</td>
<td>1.3 [1.18]</td>
<td>0.8 [0.83]</td>
<td>0.7 [0.70]</td>
<td>0.7 [0.77]</td>
<td>0.7 [0.73]</td>
<td>T=7.4 p&lt;0.001</td>
</tr>
<tr>
<td>Irritability</td>
<td>2.2 [1.29]</td>
<td>1.5 [1.32]</td>
<td>1.2 [1.17]</td>
<td>1.6 [1.00]</td>
<td>1.0 [1.10]</td>
<td>0.9 [1.10]</td>
<td>T=4.1 p&lt;0.001</td>
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<tr>
<td>Sadness</td>
<td>1.3 [1.13]</td>
<td>0.8 [0.93]</td>
<td>0.6 [0.82]</td>
<td>0.6 [0.84]</td>
<td>0.5 [0.79]</td>
<td>0.5 [0.76]</td>
<td>T=4.0 p&lt;0.001</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>3.8 [1.24]</td>
<td>2.3 [1.51]</td>
<td>1.7 [1.20]</td>
<td>1.7 [1.41]</td>
<td>1.8 [1.57]</td>
<td>1.6 [1.46]</td>
<td>T=5.2 p&lt;0.001</td>
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<tr>
<td>Autonomic disturbances</td>
<td>2.5 [1.32]</td>
<td>1.6 [1.12]</td>
<td>0.9 [0.57]</td>
<td>0.8 [0.72]</td>
<td>0.7 [0.75]</td>
<td>0.8 [0.77]</td>
<td>T=8.8 p&lt;0.001</td>
</tr>
<tr>
<td>Hostile feelings</td>
<td>2.2 [1.35]</td>
<td>2.2 [1.46]</td>
<td>2.0 [1.39]</td>
<td>1.7 [1.45]</td>
<td>1.6 [1.21]</td>
<td>1.6 [1.31]</td>
<td></td>
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</table>
Figure 1

Scatter plot indicating PCA scores for the model as indicated under statistics.
- Red boxes indicate assumed healthy objects (in total 16 objects)
- Blue points for untreated patients as rated at inclusion.
- Black triangles for treated patients. Each patient was re-assessed with last rating 50.4 17.8 months (variance 30-120) after study start (n=97) and his or her individual ratings predicted by the PCA model.
The distribution after treatment with vaccine (black triangles) showed a shift of patient scores in PC1 towards symptom relief.