

Long-Term Treatment with a *Staphylococcus* Toxoid Vaccine in Patients with Fibromyalgia and Chronic Fatigue Syndrome

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ABSTRACT. One hundred and sixty patients with fibromyalgia and chronic fatigue syndrome, who were on a continuous treatment with a *Staphylococcus* vaccine, were followed during one year with repeated consultation visits. The patients had participated in controlled studies and been on continuous treatment with the vaccine for 22 ± 10 months before inclusion into this follow-up study. They were treated with 1 mL of the vaccine subcutaneously every third to fourth week. Adverse events were few. The adherence to the treatment was very good. Over a period of one year, 8% withdrew, and in only 5%, the withdrawal was due to insufficient clinical effect. Only in two cases where the patients were allergic to the preservative of the vaccine, the side effects caused the withdrawal of the treatment. Ratings with scales (CPRS-15 and FibroFatigue) showed improvement from start of treatment and also

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Journal of Chronic Fatigue Syndrome, Vol. 13(4) 2006

Available online at <http://jcfs.haworthpress.com>

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doi:10.1300/J092v13n04_04

further improvement during the follow-up year. In view of the natural history for these disorders the result is of interest. doi:10.1300/J092v13n04_04 [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2006 by The Haworth Press, Inc. All rights reserved.]

KEYWORDS. Fibromyalgia, chronic fatigue syndrome, *Staphylococcus* vaccine, long-term treatment

BACKGROUND

Although the terms “fibromyalgia” (FM) and “chronic fatigue syndrome” (CFS) are of relatively new origin, clinical conditions of chronic pain and fatigue have been described in the medical literature for centuries. In 1990 (Wolfe et al.), 1988 (Holmes et al.), and 1994 (Fukuda et al.), these new concepts were defined by internationally established criteria, which enable any interested physician to easily evaluate the patient and make a diagnosis. Both syndromes are characterized by complex multi-organic chronic signs and symptoms, including muscle pain, joint pain, chronic fatigue, sleeping problems, neuro-cognitive and gastrointestinal complaints, among others. 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 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 (Aaron et al., 2000, 2001; Buchwald, 1996; Buchwald and Garrity, 1994; White et al., 2000). Their prevalence is substantial for FM (2-4%) (White et al., 1999; Wolfe et al., 1995) and for CFS (0.2-2.6%; Jason et al., 1999; Kawakami et al., 1998; Steele et al., 1998; Wessely et al., 1997).

There are nonpharmacological treatments, some with promising result, for example, cognitive behavioral therapy (Whiting et al., 2001). In a randomized 12-week study by Arnold et al. (2004) duloxetine was an effective and safe treatment for symptoms seen in FM. Therapy with amplitgen, assumed to downregulate the 2-5A oligoadenylate synthetase/Rnase L pathway, has also been associated with clinical improvement (Suhadolnik et al., 1994; Strayer et al., 1994).

Although the immunological studies in CFS have met with controversial results (De Becker et al., 2002), we have applied the concept of a disrupted immune function as proposed by Patarca et al. (2000) and Kennedy et al. (2004).

In order to modulate the immune system, we have since 1995 performed clinical trials using a *Staphylococcus* toxoid vaccine (Staphypan) (Gottfries, 1999). The results of two double-blind placebo-controlled trials have been published (Andersson et al., 1998; Zachrisson et al., 2002a). The patients receive subcutaneous injections in increasing dosages during the initial eight-week period, and thereafter once a month. A positive clinical effect was recorded in 65% of the patients. After withdrawal, most responders deteriorate within two months, which explains why the treatment was continued.

In a group of patients treated with Staphypan for six months, blood samples before and after treatment showed an increase of serum antibody titres, especially against alpha-toxin, that was significantly correlated with the clinical improvement as assessed by rating scales (Zachrisson et al., 2004).

Staphypan is a mixture of *Staphylococcus* strains and a toxoid, and is manufactured by Berna Biotech Ltd., Switzerland. Extracts of *Staphylococcus aureus* and epidermidis are included. Staphypan also contains the well-known preservative thiomersal, which is a double salt including component of both salicylate and ethyl mercury.

Objectives

The aim of this investigation is to record adverse events in long-term treatment with Staphypan in patients with FM/CFS. Rating scales assessed the clinical effect in this open study.

MATERIALS AND METHODS

The patients included in the study are cared for at our outpatient unit and have completed previous clinical trials. These include 200 patients who were involved in pilot studies (not published), which started already 1995 with the aim of testing the administration and dosing of the vaccine and the methodology for the evaluation of effects. One double-blind placebo-controlled study was finalized in 1998 and included 28 patients (Andersson et al., 1998). Another double-blind placebo-controlled study was finalized in 2001 and included 100 patients (Zachrisson et al., 2002a). After the study, patients treated with placebo were offered treatment with active vaccine. In the double-blind studies all patients fulfilled the criteria for both FM and CFS. The data were not analysed for the two diagnosis kept apart due to the great overlap.

Around two-thirds of the patients improved in the above-mentioned studies and these patients wanted to continue the treatment with monthly vaccine injections. They all had to make a withdrawal trial before being included in the present long-term study.

On October 1, 2003, we had 160 patients in continuous treatment with the vaccine, and as we at that time also started to use a new rating scale for evaluating the clinical status of patients, we decided to carefully follow these patients during one year. Thus the patient material in this follow-up study was heterogeneous. All patients suffered from FM and/or CFS; most of them had both diagnoses. The subgroups were not kept apart. The only selection criterion is that they have reacted favourably to treatment with the *Staphylococcus* vaccine Staphypan. The most important aim was to evaluate safety with this thiomersal containing vaccine, which was given repeatedly over a long time.

The 160 patients consisted of 9 men and 151 women. The mean age was 53 ± 11 (SD) years. At the start of the follow-up, the patients had been on continuous treatment with the vaccine for 22 ± 10 (SD) months.

A research nurse, or a supervised district nurse, gave the patients subcutaneous injections of 1 mL Staphypan every third to fourth week. Berna Biotech Ltd. generously supplied us with Staphypan.

The patients visited our unit every third month for reporting adverse effects. Blood samples for routine laboratory investigations were taken before and after the observation year.

Before the study, the patients had been rated only with the CPRS-15 scale (Andersson et al., 1998), a subscale to the comprehensive psychopathological rating scale (CPRS). This subscale includes 15 variables. Each variable is rated according to a 7-step scale in which the scale steps 0, 2, 4, and 6 are defined. The scale is sensitive to changes over time. The reliability and validity of the CPRS is well tested (Asberg et al., 1978).

The new scale was named the Fibro-Fatigue scale (FF-scale) (Zachrisson et al., 2002b) and it is a slight modification of the CPRS-15 scale adapted for measuring symptoms in FM/CFS. It has nine items in common with CPRS-15. In the FF-scale six items from the CPRS-15 scale were omitted ("Inner tension," "Worrying over trifles," "Pessimistic thoughts," "Suicidal thoughts," "Hypochondria," and "Phobias") as the patients did not score on these items. Three new items named "Irritable bowel," "Headache," and "Subjective experience of infection" are added. The reliability and validity of the scale is well tested (Zachrisson et al., 2002b).

During the one year of follow-up, the patients were rated every third month with both the CPRS-15 and the FF-scales. Ratings were performed independently of previous ratings.

Statistics

Group differences before and at the end of observation year were analysed with Students t-test (dependent samples). Whenever a value was missing, the last rated value was carried forward. One hundred fifty-nine subjects were included with the intention to treat sample. If a patient discontinued the treatment for more than two months, the patient was excluded from further statistical analysis, even if the treatment was restarted later on.

Ethics

The Ethical Committee of Gothenburg University has approved a pilot study, two double-blind studies (Andersson et al., 1998, Zachrisson et al., 2002a) and this long-term study in which the *Staphylococcus* vaccine Staphypan was used.

RESULTS

Withdrawal from the Study

Of the 160 patients 18 withdrew from the treatment with the *Staphylococcus* vaccine during the observation year. The reasons for withdrawal were insufficient effect in eight patients, adverse events in nine, and one patient did not come to control visits.

Adverse Events

In two patients there was a strong local reaction, which was due to allergy to the salicylate salt of the preservative. Two patients stopped treatment due to surgery not related to the treatment. Two patients suffered from depressive illness and one of them committed suicide during treatment. She had contact with a psychologist and was on pharmacological antidepressive treatment. Last injection with Staphypan had been given four weeks before the patient committed suicide. No connection between suicide and Staphypan treatment was considered. One patient had a neurological illness (tremor) and one patient gastritis. One patient became pregnant and therefore stopped treatment. Later, she gave birth to a normal child.

Side effects during the first six months of treatment with a *Staphylococcus* vaccine were reported in detail by Zachrisson et al. (2002a; Table 1).

As is evident from the Table 1, headaches were reported more often in the group treated with vaccine compared to placebo. During this one-year follow-up study, side effects were few and transient. Less than 5% reported headache and being slightly unwell for a day or two after an injection.

All patients had a local reaction at the site of injection. In the beginning of the injective treatment the local reaction was normally around 10-15 cm in diameter. At the time of this follow-up study, when patients had been treated for two to four years, the local reaction was small (2-5 cm in diameter), and gave no discomfort.

Laboratory Data

Before and after the observation year blood samples were taken for routine laboratory investigation. No changes were recorded that could be related to the treatment.

Adherence to the Treatment

At start of follow-up, the number of patients was 160, after 3 months 153, after 6 months 151, and after 12 months came down to 142. Al-

TABLE 1. Most frequent adverse events and clinical global impression of side effects at endpoint (week 26).

	Placebo <i>n</i> = 50	Active Drug <i>n</i> = 50
Headache/migraine	3	12
Infections	11	5
Skin disorders	5	4
Gastro-intestinal problems	2	2
Nausea/vomiting	1	3
Depression	2	1
Cardiovascular problems, palpitations	2	1
Global assessment of side effects at endpoint		
No side effects	43	37
Do not significantly interfere with functioning	2	5
Significantly interfere with functioning	0	2
Outweigh therapeutic effect	5	6

Adverse events were listed irrespective of a causal relationship with the study drug applied. Clinical trial of *Staphylococcus* toxoid in fibromyalgia/chronic fatigue syndrome patients (*n* = 100). (Adapted from Zachrisson et al., 2002a).

though 18 patients withdrew during the one-year follow-up period, five patients did restart the treatment after two to four months thus the actual dropout was 13 patients (8%).

Result of Ratings

As is evident from Table 2 and Figure 1, the mean score of CPRS-15 before any treatment was 33.0 ± 7.5 . At the time for the start of this open follow-up study, the CPRS-15 mean score was reduced to 20.8 ± 8.6 points. During the observation year there was a further reduction of the mean CPRS-15 score to 14.5 ± 7.3 points. When mean values before and after the observation year were compared the difference was significant ($t = 7.9$, $p < 0.001$, Table 2).

The results of the ratings by the FF-scale are in agreement with the CPRS-15 scale. As is evident from Table 2 the ratings with the FF-scale showed a significant improvement during the observation year for all items but “muscular tension.” When mean values before and after the observation year were compared the difference was significant ($t = 11.1$, $p < 0.001$). Also the new items in the FF-scale were reduced; “Irritable bowel” from 1.5 ± 1.46 (mean \pm SD) to 0.8 ± 1.12 ($p < 0.001$), “Headache” from 1.8 ± 1.65 to 0.8 ± 1.15 ($p < 0.001$) and “Subjective experience of infection” from 0.7 ± 1.23 to 0.5 ± 0.88 ($p < 0.05$).

According to the definition of the items, a rating level below one is considered normality. Eight items according to the FF-scale had mean levels below one at the time of the last rating (“Concentration difficulties,” “Failing memory,” “Irritability,” “Sadness,” “Autonomic disturbances,” “Irritable bowel,” “Headache,” and “Subjective experience of infection”) which indicate that on a group level these symptoms had vanished (Table 2).

Four items were not reduced to mean levels below one: “Aches and Pain,” “Muscular tension,” “Fatigue,” and “Sleep disturbances.” Although there was significant improvement in three of these core items, they were still bothering patients to some degree, in spite of several years of treatment.

DISCUSSION

In two previous controlled investigations, we have shown that treatment with a *Staphylococcus* toxoid vaccine (Staphypan) is of benefit for 65% of patients with FM/CFS. However, it is obvious that the effect of an injection of the vaccine lasts for only 3-4 weeks. Therefore, repeated injections are necessary to maintain the effect. In this investigation, we report the safety and the clinical effect of long-term treatment with Staphypan.

TABLE 2. Patients with FM/CFS on long-term treatment with a *Staphylococcus* vaccine.

Single Item Score	CPRS-15 Scores		FF Rating Scores (Every Third Month During One-Year of Close Follow-Up)					t-Test
	0 [Before Any Treatment]		1	2	3	4	5	
Aches and pain	4.6 [0.98]		3.0 [1.50]	3.0 [1.46]	2.7 [1.44]	2.7 [1.46]	2.5 [1.33]	4.7*
Muscular tension	3.1 [1.13]		2.5 [1.51]	2.6 [1.30]	2.6 [1.27]	2.6 [1.26]	2.3 [1.24]	1.3, ns
Fatigue	4.8 [0.80]		3.3 [1.46]	3.2 [1.31]	3.0 [1.29]	2.9 [1.40]	2.6 [1.41]	5.7*
Concentration difficulties	2.8 [1.19]		2.0 [1.45]	1.4 [1.16]	1.1 [0.97]	1.1 [1.05]	0.8 [0.95]	10.8*
Failing memory	2.8 [1.19]		1.3 [1.18]	0.8 [0.83]	0.7 [0.70]	0.7 [0.77]	0.7 [0.73]	7.4*
Irritability	2.2 [1.29]		1.3 [1.32]	1.2 [1.17]	1.0 [1.00]	1.0 [1.10]	0.9 [1.10]	4.1*
Sadness	1.3 [1.13]		0.8 [0.93]	0.6 [0.82]	0.6 [0.84]	0.5 [0.79]	0.5 [0.76]	4.0*
Sleep disturbances	3.8 [1.24]		2.3 [1.51]	1.7 [1.20]	1.7 [1.41]	1.8 [1.57]	1.6 [1.46]	5.2*
Autonomic disturbances	2.5 [1.32]		1.6 [1.12]	0.9 [0.57]	0.8 [0.72]	0.7 [0.75]	0.8 [0.77]	8.8*
Irritable bowel	not rated		1.5 [1.46]	0.9 [1.07]	0.8 [1.06]	0.9 [1.24]	0.8 [1.12]	7.2*
Headache	not rated		1.8 [1.65]	1.2 [1.38]	1.2 [1.32]	1.0 [1.29]	0.8 [1.15]	9.2*
Subjective experience of infection	not rated		0.7 [1.23]	0.4 [0.67]	0.3 [0.71]	0.5 [1.01]	0.5 [0.88]	2.3**
Total score								
FF scale	not rated		22.2 [9.12]	18.0 [6.91]	16.6 [6.82]	16.4 [7.75]	14.7 [7.24]	11.1*
CPRS-15	33.0 [7.52]		20.8 [8.60]	17.8 [6.85]	16.5 [7.08]	15.8 [7.58]	14.5 [7.32]	7.9*

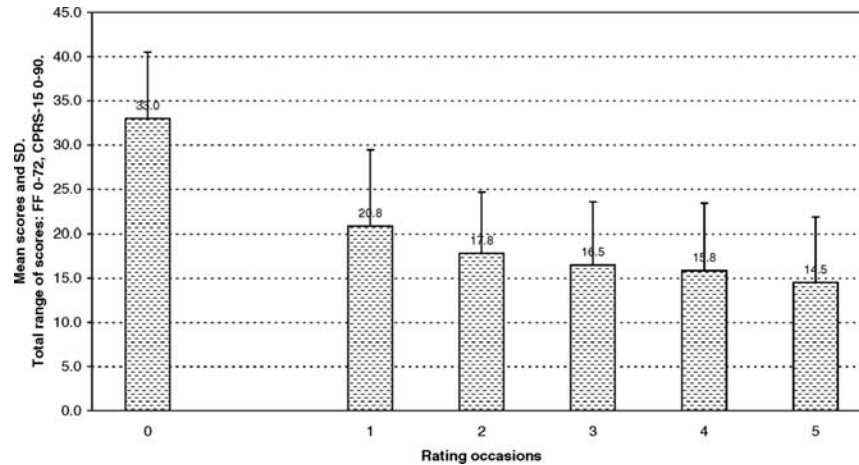
Values are given as mean [SD]. Range of score is 0 (No symptom) to 6 (Severe symptoms) on individual items. Statistical within-group differences, between time points 1 and 5, using t-test for dependent samples.

CPRS-15 = Subscale of Comprehensive psychopathological rating scale FF = FibroFatigue scale.

*p < .001; **p < .05.

Intention-to-treat population, n = 159. Rating scores before any treatment (at time point 0), after 22 ± 10 months (at time point 1), and during one year of close follow-up (at time points 2-5).

FIGURE 1. Rating scores on CPRS-15 scale in FM/CFS patients on long-term treatment with a *Staphylococcus* vaccine. Ratings before treatment (time point 0), after 22 ± 10 months (time point 1), and during one year of close follow up (time-points 2-5). Intention-to-treat population, n = 159.



The patient material is heterogeneous. It consists of patients with FM and CFS; most of them fulfill the criteria for both disorders. The patients have participated in previous pilot and controlled studies and have had benefit of the treatment with the *Staphylococcus* vaccine Staphypan. The study is open and therefore the data about adherence and toxicology are the most valid but ratings of clinical symptoms are also performed.

Of the 160 patients, there was a dropout of 18 during the observation year. Five patients, however, decided to restart the treatment after a few months withdrawal. The actual number of dropouts, therefore, was 13. Only 8 patients withdrew treatment due to insufficient effect. Nine patients withdrew due to adverse effects none of which was serious. The preservative, thiomersal, contains salicylate to which two patients were allergic. A dropout frequency of 8% during one year is a low frequency, in relation to the rather complicated procedure in which the patients have to participate; seeing a nurse for monthly injections, repeated ratings, and repeated laboratory check-ups.

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 adverse events have been reported.

In the 160 patients, there was a reduced CPRS-15 mean rating score before any treatment started to the end of this follow-up study with more than 50%. As is evident from Figure 1, the improvement continued during the year of follow-up. Although the study was open it can be assumed that the effect of the vaccine treatment most probably remains over 3-5 years or even longer.

The working mechanism of the vaccine treatment is unclear. Some data indicate a relationship between the clinical improvement and the serological response especially in the form of increased antibodies to alpha-toxin (Zachrisson et al., 2004). It is, however, surprising that the effect lasts only for 3-4 weeks, given the traditional opinion about the memory capacity of the immune system. The short-lasting effect might indicate an effect of the adjuvant (merthiolate) rather than that of an antigen. Further studies are needed.

A clinical impression is that a majority of patients with FM/CFS have infections in the respiratory and/or the urogenital tract. During the treatment with the *Staphylococcus* toxoid vaccine, the frequency of infections was reduced (Table 2), which the patients found to be of very great value.

According to our findings (Zachrisson et al., 1999), and those of others (Gomborone et al., 1996; Sivri et al., 1996), about 60% of patients with FM/CFS also suffer from Irritable Bowel Syndrome (IBS). The FF-scale also rates the IBS symptoms, which were significantly improved during the open follow-up study (Table 2).

The Medical Product Agency of Sweden has informed us that Staphypan, in its present form, may not be approved for continuous treatment of FM/CFS patients owing to its preservative (thiomersal). Thiomersal, when injected into the body, is dissociated into compounds of salicylate and ethyl mercury in extremely small quantities. During the trials with Staphypan a few patients were sensitive to salicylate. However, no patients appeared to be sensitive to mercury (confirmed by *in vitro* MELISA-testing). Ongoing pharmacokinetic studies indicate that ethyl mercury in our patients is eliminated within 1-2 weeks (not published). The Berna Biotech Ltd. is prepared to manufacture a newer preparation of Staphypan without thiomersal, if economically supported.

CONCLUSIONS

FM/CFS are disorders of unknown etiology. In controlled investigations it has been shown that an immune-modulating therapy as conveyed by repeated injections of a *Staphylococcus* toxoid preparation, is of clinical

importance for a significant number of patients with FM/CFS. The effect is usually seen when the dose of Staphypan has been increased to 1 mL. The treatment must, however, be continued with 1 mL injection of vaccine every 3-4 weeks, and the treatment appears to be safe. After continuous treatment for three to five years, there were no severe adverse events and the adherence to the treatment was impressive. The clinical effect remained over time according to ratings.

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RECEIVED: 11/11/04

ACCEPTED: 20/10/05

doi:10.1300/J092v13n04_04