SUMMARY REPORT

STUDY on the EFFECTS of FIBROM-X CREAM in LOCOMOTOR DISORDERS

Protocol: FIBRO II/1 SU

2003, Budapest

Semmelweis University, Budapest

At the Semmelweis University a clinical trial was conducted with FIBROM-X cream (manufacturer: In Vitro Kft., Hungary) between February, 2002 – May, 2003 with the sponsorship of In Vitro Kft, in patients suffering from rheumatoid disorders. The study was performed according to protocol FIBRO II/1 SE.

I. Aim of the study

Evaluation of the efficacy of FIBROM-X cream in patients suffering from rheumatoid disorders in order to evaluate whether FIBROM-X cream can be beneficial for relief of the symptoms.

II. Type and duration of the study

This was a controlled, double-blind, 2-week trial in 100 patients.

III. Selection of patients

In this trial patients of both sexes between 20 – 80 years of age could be included after their prior written consent on participation. Every participant received the necessary information on the trial before deciding to sign the letter of consent.

In order to create homogeneous group of patients, we selected participants with periarthritis humeroscapular syndrome (bursitis, tendinitis), whose shoulders could be moved passively.

Inclusion criteria

- Pain at rest: medium level (waking up because of pain once at night)
- Pain at motion: medium level (pain is increasing at the half of the orbit of movement)
- Pain at passive movement: medium level (pain is increasing from the second half of the manageable orbit of movement)
- Sensitivity to pressure: reacting with grimace to pain sensation

Exclusion criteria

- „Frozen" shoulder
- Symptoms suggesting cervical root compression
- Signs of stimulation of cervical sympathetic fibers
- TOS hand-shoulder syndrome
- Inflammatory shoulder joint processes (RA, SPA, polymyalgia rheumatica)
- Bacterial infection
- Aseptic bone necrosis
- Signs and symptoms of a serious disease of parenchyma organs, hematopoietic system or central nervous system
- Therapeutical X-ray irradiation of the shoulder within the last 3 months
- Known allergy to beesting
- Skin disorders (psoriasis, dermatitis, etc.)

IV. Treatment

Patients used FIBROM-X cream 3-4 times a day locally as a wet pack on the diseased joint for 30-40 minutes.

V. Other therapies

Systematic and local use (on the treated shoulder) of concomitant analgesics, nonsteroidal anti-inflammatory agents (NSAIDs), steroids or physiotherapy was forbidden.

VI. Control examinations

There were 3 control examinations as follows:

- at baseline (day 0.)
- in the middle of the trial (7^{th} day $\pm$ 1 day)
- at the end of the trial (14^{th} day $\pm$ 2 days)

VII. Evaluation

Evaluation was performed as follows:

VII/1.1. Evaluation of therapeutical efficacy

Pain at rest:
0 = no pain
1 = mild pain (pain emerges only occasionally and the night rest is not disturbed by pain)
2 = medium level pain (pain is usually not permanent and the patient wakes up because of pain at night only once)
3 = severe pain (pain is usually permanent and the patient wakes up because of pain frequently at night)

Pain at motion
0 = no pain
1 = mild pain (only extreme movements are painful)
2 = medium level pain (pain is felt already at the half of the active orbit of motion)
3 = severe pain (even the slightest movement is painful)

Pain at passive movement
0 = no pain
1 = mild pain (only at the endpoint of the normal movability)
2 = medium level pain (increasing pain at the half of the orbit of movement)
3 = severe pain (even a small passive movement increases the pain)

Sensitivity to pressure
0 = no pain
1 = mild pain (the patient indicates his/her pain to the doctor verbally)

2 = medium level pain (the patient indicates his/her pain verbally but at the same time he/she grimaces
3 = severe pain (the patient makes a defensive reflex movement with his/her shoulder)

VII/1.2. General evaluation of the doctor on the efficacy of the study medicine at the end of the study period or at withdrawal, on a four-grade scale:

0 = excellent
1 = good
2 = satisfactory
3 = ineffective

VII/1.3.Opinion of the patient on the efficacy at the end of the trial or at pre-term withdrawal (drop-out):

0 = satisfactory
1 = ineffective

VII/2 Tolerability

VII/2.1. Side effects were investigated by indirect questions:

a./ did you felt such symptom that had not yet been experienced in association with your disease? If yes, describe this symptom.
b./ if skin symptoms appeared on the treated skin surface, time of development (which day) and characteristics were documented

VII.2.2. General evaluation of the doctor on tolerability at the end of the trial, at the end of the 2nd week and at necessary suspension of the treatment

0 = satisfactory
1 = not satisfactory

VIII. Results

The study was conducted between 14. 01. 2002. – 11. 04. 2003. From the 112 enlisted patients 100 persons finished the study.
After breaking the randomization code it turned out that from these 100 patients 50 individuals (50%) were administered placebo preparation and 50 patients (50%) were treated with active study preparation.
In the placebo group (24 men and 26 women) the mean age was 54,6 years (29-72 years), whereas in the active treatment group (23 men and 27 women) the mean age was 53,2 years (28-76 years).
Results are summarized in Tables 1-4.

As data in Table 1. show, the **total score of the symptoms** at baseline is nearly the same in both patient groups: 7,02 scores in the placebo group and 7,38 scores in the active treatment group.
During the study, in the 7th day the above parameter was 6,64 scores and in the 14th day 6,38 scores in the placebo group.
The active treatment group achieved at the above points of time 4,86 scores and 2,22 scores.

Table 2. shows the mean score of each symptom in the **active treatment group** before and after the study.

The score of **pain at rest** was at baseline 1,90, which changed to 1,18 at the 7th day and to 0,36 at the 14th day.
The score of **pain at motion** was at baseline 2,20, which changed to 1,52 at the 7th day and to 0,90 at the 14th day.
The score of **pain at passive movement** was at baseline 1,76, which changed to 1,20 at the 7th day and to 0,58 at the 14th day.
The score of **sensitivity to pressure** was at baseline 1,58, which changed to 0,96 at the 7th day and to 0,38 at the 14th day.

The mean scores of the placebo group for each symptom are presented in Table 3.

As the data of Table 3. show, in this patient group:
The score of **pain at rest** was at baseline, in the first physical examination 1,62, which changed to 1,38 at the 7th day and to 1,28 at the 14th day.
The score of **pain at motion** was at baseline, in the first physical examination 2,16, which changed to 2,08 at the 7th day and to 2,02 at the 14th day.
The score of **pain at passive movement** was at baseline, in the first physical examination 1,82, which changed to 1,84 at the 7th day and to 1,82 at the 14th day.
The score of **sensitivity to pressure** was at baseline, in the first physical examination 1,42, which changed to 1,34 at the 7th day and to 1,26 at the 14th day.

The doctor's (study investigator's) opinion about the study preparation at the end of the study

The doctor's opinion about the study preparation is presented in Table 4. The doctor (study investigator) evaluated the preparation in a four-grade scale (0 = excellent, 1 = good, 2 = medium, 3 = ineffective).

According to the doctor's opinion, in the active treatment group the study preparation proved to be of excellent efficacy in 32% of the patients, whereas in 47% the efficacy was rated as good and in 22% as of medium level.
In the case of the placebo group, according to the doctor's opinion, the placebo proved to be ineffective in 72% of the patients while in 28% it had medium level efficacy.

We presented the patients' opinion about the preparation in the same Table.
According to the patients' evaluation, the placebo preparation was ineffective in 82% and appropriate in 18% of the users.
The active study preparation was of appropriate efficacy in 90% of the patients of the active treatment group while 10% said that it was ineffective.

During the whole study period there were no reports on any side effects in both patient groups.

IX. Evaluation

We treated 100 patients with FIBROM-X cream manufactured by IN VITRO Kft.
One half of the patients received a placebo preparation and the other half of the participants received active treatment.

Patient group treated with FIBROM-X cream

According the data in Table 1, the total scores of symptoms decreased from the 7,38 mean baseline value until the 7th day of treatment to 4,68. There was an even bigger change at the 14th day, when the mean score indicating the severity of the symptoms decreased to 2,22.
The above score reductions are significant at both points of time. The condition of each patient markedly improved as a consequence of the treatment. 20% of the patients become completely free of symptoms and in case of 36% only 1 or 2 of the 4 parameters were slightly detectable at the end of the study, so, the majority of the patients become free of symptoms.
Table 2 shows the treatment's effect on the changes of symptoms.
As it can be seen from the Table, the severity of the symptoms decreased already at the 7th day of the study in the case of all the 4 studied parameters and later, at the 14th day this reduction was even larger.
If we consider the severity of symptoms at baseline 100%, then

The severity of **pain at rest** decreased at the 7th day to 64,1% and at the 14th day to 19,6%.
The **pain at motion** decreased at the 7th day to 69,1% and at the 14th day to 40,1%.
The **pain at passive movement** decreased at the 7th day to 68,2% and at the 14th day to 32,9%.
The **sensitivity to pressure** decreased at the 7th day to 60,8% and at the 14th day to 24,0%.

Changes of each symptom (pain at rest, pain at active motion, pain at passive movement and sensitivity to pressure) were statistically significant compared to the baseline values on the one hand and to the placebo group's result on the other hand.

Patient group treated with placebo preparation

According to data in Table 1., the total scores of symptoms changed from the 7,02 mean baseline value until the 7th day of treatment to 6,64 and at the 14th day to 6,38. The above score reductions are non-significant at both points of time. In the case of 12% of patients increasing severity of some of the symptoms were observed during the study period.
As it can be seen, in general, the symptoms somewhat decreased, however these reductions were not significant. This can be interpreted as "placebo effect", well known from the literature. We emphasize, however, that 12% of the patients reported some symptoms of increased severity.

Table 3. shows the changes of each symptom as a consequence of treatment.
If we consider the severity of symptoms at baseline 100%, then

The severity of **pain at rest** changed at the 7th day to 85,2% and at the 14th day to 79%.
The **pain at motion** changed at the 7th day to 96,3% and at the 14th day to 93,5%.
The **pain at passive movement** changed at the 7th day to 101,1% and at the 14th day remained at 100%.
The **sensitivity to pressure** changed at the 7th day to 94,4% and at the 14th day to 88,7%.

Changes of each symptom (pain at rest, pain at active motion, pain at passive movement and sensitivity to pressure) were statistically non-significant.

At the end of the study both the doctor (study investigator), both the patients evaluated the efficacy of the study. These evaluations are summarized in Table 4.

According to the doctor's opinion, in the active treatment group the study preparation proved to be effective. Excellent efficacy was observed in 32% of the patients, whereas in 47% the efficacy was rated as good and in 22% as of medium level.
In the case of the placebo group, the placebo proved to be ineffective in 72% of the patients while in 28% it had medium level efficacy.

Interestingly, according to the patients opinion, the active study preparation was of appropriate efficacy in 90% of the patients of the active treatment group while 10% said that it was ineffective.
The placebo preparation was rated by the patient as ineffective in 82% and effective in 18%.

It is important to note, that during the study period no skin irritations, allergic skin reactions or any other side effects were observed with both (the active and the placebo) preparation.

X. Summary

We conducted a clinical trial with FIBROM-X cream in patients with humeroscapular syndrome. Based on our observations and experiences with this preparation, we

found it effective, having beneficial effects on the symptoms. Compared to the control group, in patients treated with the active study preparation each studied symptoms' severity significantly decreased. We found no significant change in patients treated with the placebo preparation. Doctors (study investigators) rated the active preparation (FIBROM-X cream) as very good from efficacy and tolerability points of view. According to the patient's opinion, the active preparation was effective in the studied conditions and decreased their symptoms.
According to our evaluation, FIBROM-X cream can be used alone or as an adjuvant treatment in the above described conditions or in other rheumatoid disorders for symptomatic relief.

Budapest, 16 June, 2003. July 1.

Prof. Béla Büki, MD

Placebo group (n=50)						**Active treatment group (n=50)**						**Statistical evaluation**	
Points of time/total score of the symptoms						Points of time (day)/total score of the symptoms						7th day	14th day
0. day		7th day		14th day		0. day		7th day		14th day		**P value**	
Score	%	Score	%	Score	%	Score	%	Score	%	Score	%		
7,02	100	6,64	94,6	6,38	79,0	7,38	100	4,86	65,8	2,22	30,1	p<0,05	p<0,001

n = number of patients
0 score = no symptom; 1 score = mild symptom; 2 scores = medium level symptoms; 3 scores = severe symptoms

Table 1.

Total scores of parameters of patients participating in the clinical trial with FIBROM-X cream and their changes in percent (%).

	Points of time/mean scores of the symptoms			P value	
Studied parameter	0 day	7th day	14th day	7th day	14th day
Pain at rest	1,90 (100%)	1,18 (64,1%)	0,36 (19,6%)	**p**<0,001	**p**<0,001
Pain at motion	2,2 (100%)	1,52 (69,1)	0,90 (40,1%)	**p**<0,05	**p**<0,001
Pain at passive movement	1,76 (100%)	1,20 (68,2%)	0,58 (32,9%)	**p**<0,05	**p**<0,001
Sensitivity to pressure	1,58 (100%)	0,96 (60,8%)	0,38 (24,0%)	**p**<0,05	**p**<0,001

Table 2.

Mean scores of symptoms of patients participating in the clinical trial with FIBROM-X cream, at baseline, at 7th day and at 14th day of treatment.
(**0** score = no symptom; **1** score = mild symptom; **2** scores = medium level symptoms; **3** scores = severe symptoms)

	Points of time/mean scores of the symptoms			P value	
Studied parameter	0 day	7th day	14th day	7th day	14th day
Pain at rest	1,62 (100%)	1,38 (85,2%)	1,28 (79,0%)	**ns**	**ns**
Pain at motion	2,16 (100%)	2,08 (96,3%)	2,02 (93,5%)	**ns**	**ns**
Pain at passive movement	1,82 (100%)	1,84 (101,1%)	1,82 (100%)	**ns**	**ns**
Sensitivity to pressure	1,42 (100%)	1,34 (94,4%)	1,26 (88,7%)	**ns**	**ns**

ns = non-significant

Table 3.

Mean scores of symptoms of **placebo-treated** patients participating in the clinical trial with FIBROM-X cream, at baseline, at 7th day and at 14th day of treatment.
(**0** score = no symptom; **1** score = mild symptom; **2** scores = medium level symptoms; **3** scores = severe symptoms)

Evaluation	**The doctor's opinion on the efficacy of the preparation at the end of the study**			
	Placebo group (n =5 0)		Active treatment group (n = 50)	
	Number of patients	%	Number of patients	%
Excellent	0	0	16	32
Good	0	0	23	46
Medium level	14	28	11	22
Ineffective	36	72	0	0

Evaluation	**The patients' opinion on the efficacy of the preparation at the end of the study**			
	Placebo group (n =5 0)		Active treatment group (n = 50)	
	Number of patients	%	Number of patients	%
Appropriate	9	18	45	90
Ineffective	41	82	5	10

n = number of patients

Table 4.

Opinion of the doctor's and patients' on the efficacy following a 14-day treatment with FIBROM-X cream or placebo