The Homeopathic Treatment of Corticosteroid-Dependent Asthma

A double-blind, placebo-controlled study

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Introduction

Asthma is a chronic inflammatory disorder of the airways in which many different cell types play a role, including neutrophils, basophils, eosinophils, macrophages, and lymphocytes.

The neutrophils possess a well-developed oxidoreductive system based on H_20_2, Cl-, and mycloperoxidase. From 8 to 15 percent of neutrophils in healthy subjects have the ability to reduce nitroblue tetrazolium (NBT) to black formazon granules.[1] The striking increase in the oxidoreductive potential of neutrophils in patients with bronchial asthma may be responsible for tissue destruction and prolongation of asthmatic manifestations, among other conditions. Our earlier studies showed that the granulocytes of patients with bronchial asthma had a defect of migration.[2] These disturbances may also be responsible for more frequent recurrences of viral and bacterial infections, as compared to healthy persons.

Activated eosinophils release a number of mediators which are directly involved in the pathogenesis of asthma, such as major basic protein (MBP), eosinophilic cationic protein (ECP), and eosinophil protein X.[3] ECP secreted during allergic inflammatory processes, however, is capable of inducing the release of histamine from mast cells and mediating the destruction of tissues.[4]

Bronchial asthmatic individuals produce increased amounts of immunoglobulin E (IgE), a type of antibody with a high affinity for mast cells. These cells are located throughout the body and release histamine and other inflammatory agents when triggered by the allergen.[5]

Mucosal membranes of the respiratory tract are protected against excessive stimulation by environmental antigens via humoral and cellular mechanisms. Mucosal antibodies, represented primarily by secretory IgA and IgA in serum, appear to play an essential role in cases studied, suggesting that perturbations of IgA-mediated mucosal immunity enhance the incidence of allergic respiratory diseases.[6]

Airway inflammation and immune activation are thought to play a critical role in the pathogenesis of asthma. As a result, recent guidelines for the treatment of asthma has focused on the use of anti-inflammatory therapy, particularly glucocorticoids.[7] However, these drugs, when taken over long time periods in high doses, lead to many dangerous complications.[8]

In view of this, the aim of our current study was to analyze the effects of Traumeel® S on the clinical condition and certain spirometric and immunological indices in patients with corticosteroid-dependent asthma. Traumeel® S is an anti-inflammatory, analgesic homeopathic combination formulation of twelve botanical substances and two mineral substances.

Materials and methods

The study involved 103 patients with corticosteroid-dependent asthma, aged 20-74 years (mean age 48 years). Sixty-two of the patients were female, aged 20-74 years (mean age 42 years). The control group was composed of 20 healthy subjects, aged 24-60 years (mean age 38 years).

The trial was begun in January 1995 and was completed in December 1995. This report shows results taken only from January through May 1995.

Corticosteroid-dependent asthma was diagnosed after history-taking physical examination, spirometric tests, and long-lasting treatment with corticosteroids. All the patients had been taking, for at least five years, triamcinolone (under the brand name of Polcorton®, by the largest Polish pharmaceutical manufacturer, Polfa) at a dosage of 4-8 mg daily. All the patients experienced numerous complications with this treatment including osteoporosis, muscle atrophy, spontaneous bruising, and weakness.

Spirometric determination of FVC and FEV_1 were done with the Eutest-2 spirometer and PEFR was determined with a Mini-Wright unit. PEFR determinations were performed daily upon rising from bed with results recorded by the patients on special diary cards. In addition, the patients noted their daily doses of corticosteroids.

Seventy-one of the patients received Traumeel® S by the double-blind method, 1 ampule subcutaneously at intervals of 5-7 days. The remaining 32 patients received placebo. Besides corticosteroids, Traumeel® S, or placebo, the patients were given methyloxanthine preparations for liquefaction of mucus. Tetracycline was given in cases of exacerbation of infection.

Before and after 20 weeks of treatment by Traumeel® S or placebo, spirometric tests were carried out and levels of the serum immunoglobulins IgE, IgG, IgA,

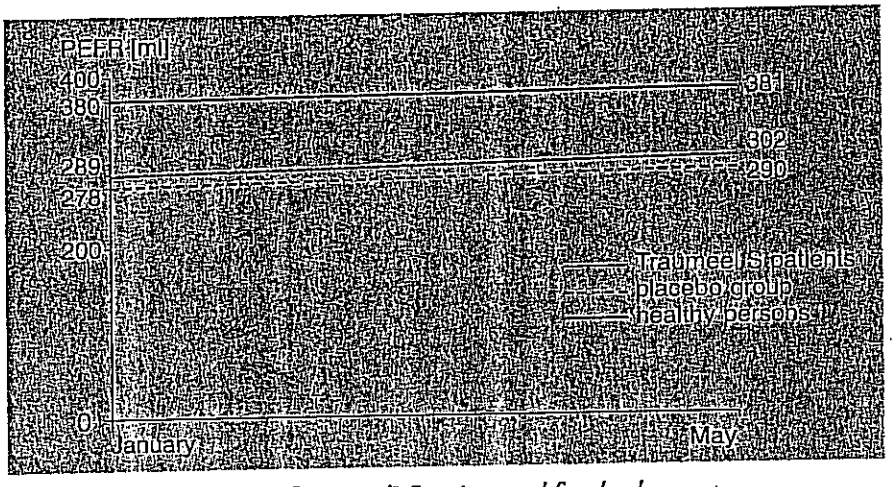

Fig. 1: Mean PEFR values of Traumeel® S patients and for placebo group.

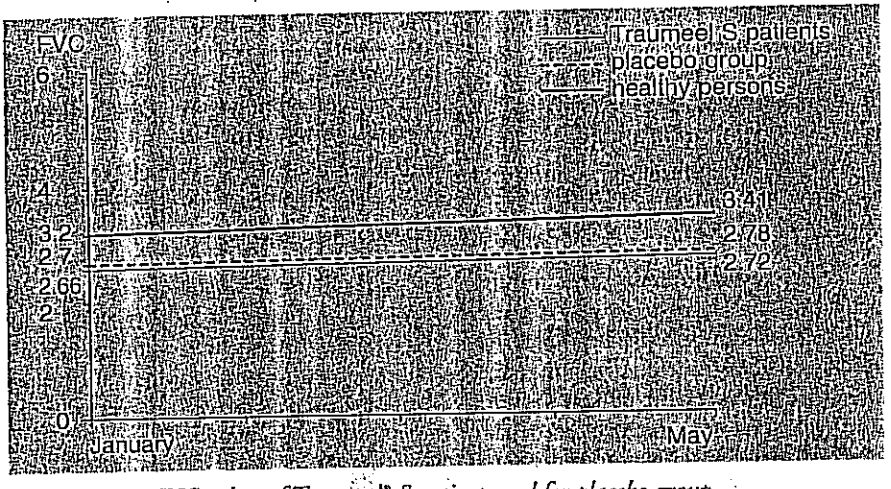

Fig. 2: Mean FVC values of Traumeel® S patients and for placebo group.

and IgM were measured.

The test of granulocyte migration in vitro was done by the Clausen test,[9] the ability of granulocytes to reduce nitroblue tetrazolium by the Park test,[1] quantitative assessment of superoxide radical O_2 generation by peripheral blood granulocytes by the test of Bellavite,[10] and eosinophilic cationic protein (ECP) in serum by the radioimmunoassay method provided by Pharmacia Belgium.[11] IgE was measured by the enzymatic method of 3M, while IgA, IgM, and IgG were measured by the immuno-turbidmetric method, in which an investigated antigen reacts with a specific antibody. In addition, the following analyses were carried out: morphotic element of blood, urine, serum creatine, urea, potassium, sodium, calcium, magnesium, glucose, AlaT, AspAT, cholesterol, and lipids.

The Clausen test

The medium with Parker's solution was supplemented with antibiotics and a 1% $NaHCO_3$ solution was added to obtain a pH value of 7.3. The medium was mixed with an equal amount of properly prepared agarose, and equine serum from the Warsaw Sera and Vaccine Laboratory was added. The dissolved medium at 48°C was placed on Petri dishes and kept for 30 minutes in a refrigerator at +4°C. Four wells, each 2.3 mm in diameter, were cut in the solidified medium and filled with appropriately prepared peripheral blood leukocytes of the studied patients.

The dishes were then placed in a thermostat with in-flow of air and CO_2. The size of the granulocyte migration area was calculated using the ηr^2 formula after 18 hours, after removing the agarose with methanol and fixation with 40% formalin.

The Park test

The blood obtained in volumes of 1 ml from the antecubital vein was mixed in a plastic disk with 0.1 ml Heparin (50 µg/l.) One ml of this prepared blood was then transferred into another plastic disk to which 0.1 ml of a mixture containing equal quantities of phosphate buffered saline at pH 7.2 and 0.1 ml of a 0.2% solution of nitroblue tetrazolium NBT (2 mg/ml) was added. After drying, the material was incubated for 15 minutes at 37°C and for another 15 minutes at room temperature. Smears were made on microscopic slides, air-dried and stained with the May-Grünwald-Giemsa method. Two hundred granulocytes containing formazon deposits were counted. Reduction indexes were calculated by counting the number of cells which had formazon deposits per 100 granulocytes present in the specimen.

The Bellavite test

This method is based on the assessment of the degree of cytochrome C reduction by superoxide anion radicals generated by granulocytes from whole peripheral blood. For each sample three determinations were performed. The first tube served as a control test. In the second tube the production of superoxide anion radicals by resting granulocytes was determined, and in the third tube the generation of superoxide anion radicals was measured in granulocytes activated with opsonized zymosan.

Aliquots of 0.3 ml of cytochrome C from bovine hearts (Sigma) were added to the tubes; 0.2 ml of 0.9% NaCl solution buffered to pH 7.2-7.4 (PBS) was added to the first and second test tube, and 0.1 ml of opsonized zymosan was added to the third tube.

After incubation during 5 minutes at 37°C, 2 ml of SOD-I (3000 U/ml solution) (Sigma) was added to the first tube with 0.1 ml of the tested blood. The tube was left standing at +4°C. After ten

minutes, 2 ml of SOD-I (3000 U/ml) was added to the second and third tubes. Then all three tubes were spun in a Janetzki K-70 centrifuge at 2000 r.p.m. at +4°C.

The absorption of the supernatant was measured in a Specol II spectrophotometer at 550 nm wavelength. The results were expressed in mmols of O^2 released during one minute by one cell.

The results were statistically analyzed with the Student t-test.

Results

As seen in Figure 1, mean PEFR values in asthmatic patients treated by Traumeel® S are not significantly different from values among patients treated by placebo (302 ml vs. 290 ml), p>0.01.

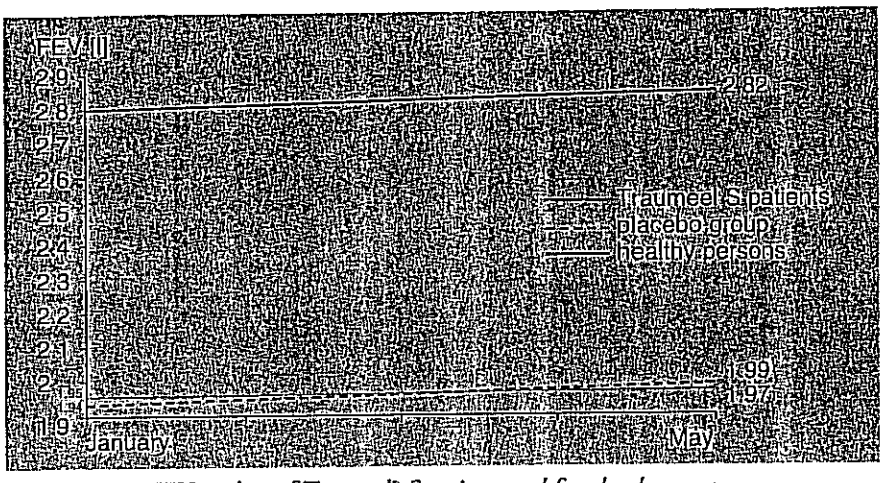

Fig. 3: Mean FEV_1 values of Traumeel® S patients and for placebo group.

Similarly, significant differences were not found in mean values of FVC (Figure 2: 2.78 l vs. 2.72 l), p>0.01. Statistically significant differences were also not shown between mean FEV_1 values of asthmatic patients treated with Traumeel® S and patients treated with placebo: p>0.01 (Figure 3).

Table 1 shows that in patients with corticosteroid-dependent asthma, the ability of peripheral granulocytes to reduce NBT increased significantly in the Traumeel® S group, from 10.34% to 6.50%, comparable to the levels in healthy persons, (6.10%), p<0.01.

The Clausen test showed that the ability of the granulocytes to migration *in vitro* from patients with corticosteroid-dependent asthma following treatment by Traumeel® S increased significantly, from 27.04 mm^2 to 34.25mm^2, compared with the placebo patients, 26.99 mm^2 to 24.14 mm^2 (Table 2).

Similarly, as shown in Table 3, the ability of peripheral blood granulocytes to generate superoxide radical O^2 was much lower in the group treated with Traumeel® S (9.4 and 18.7) than in the placebo group (16.4 and 25.8), p<0.01.

In patients with bronchial asthma from both groups the ability of the eosinophils to release ECP was significantly higher (70.9 and 42.9) compared with the healthy group (12.04) p>0.01. After treatment with Traumeel® S the ability of eosinophils to release ECP decreased significantly to 25.6, p<0.01 (Table 4).

As illustrated in Table 5, serum IgE

Traumeel® S (p<0.01)		before treatment	10.34% granulocytes
		after treatment	6.50% granulocytes
Placebo (p<0.01)		before treatment	10.50% granulocytes
		after treatment	9.60% granulocytes
Healthy persons			6.10% granulocytes

Tab. 1: Ability of peripheral granulocytes to reduce NBT in patients with corticosteroid-dependent asthma: results for Traumeel® S patients, placebo patients, and healthy persons.

Traumeel® S (p<0.01)		before treatment	27.04 mm^2 ± 7.22
		after treatment	34.25 mm^2 ± 10.07
Placebo (p>0.01)		before treatment	26.99 mm^2 ± 7.50
		after treatment	24.14 mm^2 ± 4.27
Healthy persons			42.13 mm^2 ± 10.03

Tab. 2: In vitro migration ability of granulocytes in patients with corticosteroid-dependent asthma: results for Traumeel® S patients, placebo patients, and healthy persons.

Traumeel® S (p<0.01)	before investigation	before treatment	16.6
		after treatment	9.4
	after investigation	before treatment	29.3
	after treatment		18.7
Placebo (p>0.01)	before investigation	before treatment	15.5
		after treatment	16.4
	after investigation	before treatment	24.4
		after treatment	25.8
Healthy persons	before investigation		7.13 ± 2.03
	after investigation		18.04 ± 8.14

Tab. 3: Ability of peripheral blood granulocytes to generate superoxide radical O^2 (mmol/cell/min) in patients with corticosteroid-dependent asthma: results for Traumeel® S patients, placebo patients, and healthy persons.

levels in patients with corticosteroid-dependent asthma who were treated with Traumeel® S decreased significantly (from 132.0 µg/l to 40.1 µg/l), $p<0.01$. Statistically significant differences were not confirmed regarding levels of IgA, IgG and IgM, among patients treated with Traumeel® S and placebo patients.

Figure 4 shows a reduction of corticosteroid doses (4.6 mg/day to 2.6 mg/day) among patients treated with Traumeel® S compared with placebo patients (4.0 mg/day to 5.8 mg/day.)

Discussion

This study has shown that the dosage of corticosteroids taken by patients with corticosteroid-dependent bronchial asthma treated for 20 weeks with Traumeel® S could be reduced from 4.6 mg to 2.6 mg daily. This is highly important for patients who must take corticosteroids on a chronic basis, possibly even throughout their whole life.

Our observations suggest that long-term treatment with corticosteroids in doses below 2 mg daily is not connected with serious complications.[5] Additionally, however, among patients treated with Traumeel® S, the general clinical condition improved significantly. Complications of corticosteroid therapy became less evident, muscle power increased, and, based on our observations, the patients' sense of well-being improved. The frequency of recurrent infections decreased from 3-4 before Traumeel® S treatment to 0-1 during Traumeel® S treatment. The clinical improvement of the patients during Traumeel® S treatment was not reflected, however, in the values of spirometric indices.

The indices FVC, FEV_1, and PEFR determined before Traumeel® S treatment (2.66, 1.95, and 289, respectively) were not significantly different from those measured after 20 weeks of this treatment (2.72, 1.92, and 302.) This can be explained by the fact that the patients chose for themselves the doses of corticosteroids which relieved their subjective feeling of dyspnea. Therefore the daily doses of these drugs were decreased without changing breathing conditions.

Traumeel® S ($p<0.01$)	before treatment	170.90 ± 52.4	
	after treatment	25.60 ± 19.3	
Placebo ($p>0.01$)	before treatment	42.90 ± 50.2	
	after treatment	57.20 ± 48.9	
Healthy persons		12.04 ± 1.80	

Tab. 4: Ability of the eosinophils to release ECP in patients with corticosteroid-dependent asthma: results for Traumeel® S patients, placebo patients, and healthy persons.

	Traumeel® S			Placebo			Healthy persons
	before treatment	after treatment	p	before treatment	after treatment	p	
IgE µg/l	132.0 ± 67.0	40.1 ± 32.0	<0.01	84.0 ±	79.2 ±	<0.01	38.4 ± 12.0
IgA µg/l	218.8 ± 117.8	261.8 ± 59.1	<0.01	240.0 ± 65.8	237.0 ± 54.5	<0.01	280.0 ± 34.0
IgM µg/l	165.0 ± 88.01	274.8 ± 54.6	<0.05	260.5 ± 94.3	248.0 ± 78.9	<0.01	235.5 ± 25.0
IgG µg/l	1115.2 ± 262.0	1234.5 ± 174.9	<0.01	1292.6 ± 271.0	1994.2 ± 231.0	<0.01	1100.0 ± 30.0

Tab. 5: Serum immunoglobulin levels in patients with corticosteroid-dependent asthma: results for Traumeel® S patients, placebo patients, and healthy persons.

The clinical improvement of patients after Traumeel® S can be explained in many ways. Only a few of the possible causes of improvement were studied in this trial. Traumeel® S probably modulates the humoral response of the organism as evidenced by changes of serum IgE levels during treatment with Traumeel® S, as compared to patients receiving placebo. Before treatment with Traumeel® S the mean IgE level in the serum was 132 µg/l and following the treatment it fell to 40.1 µg/l. In the placebo group, the mean IgE value before the study was 84.0 µg/l and was not significantly changed after 20 weeks of treatment, 79.2 µg/l.

Immunoglobulin E plays a key role in the humoral response of the organism. Mounted on mast cells, after binding with a specific antigen, it releases a num-

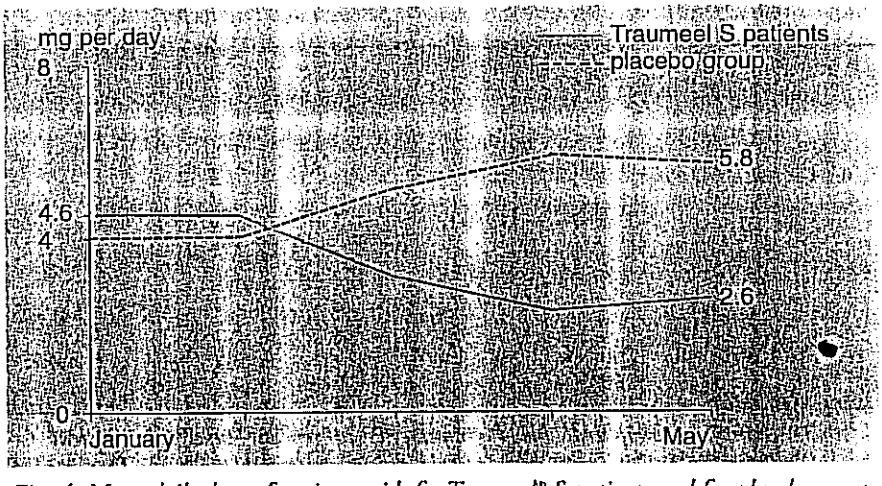

Fig. 4: Mean daily doses of corticosteroids for Traumeel® S patients and for placebo group.

ber of immune mediators such as histamine, platelet activating factor (PAF), leukotrienes, serotonin, and other kinins.[12] The released mediators of the allergic reaction cause the development of inflammatory foci which, as well as the mediators, are powerful chemotactic factors for neutrophils, eosinophils, basophils, tissue macrophages, platelets, and lymphocytes. Chemotaxis is one of the most important functions of granulocytes. In our earlier studies we found defective migration of granulocytes in patients with bronchial asthma.[2]

Among patients treated with Traumeel® S, the migration ability of granulocytes increased from 27.04 mm² to 34.25 mm² following the treatment. It is possible that this increase was the reason for the reduced frequency of recurrent infections. Granulocytes are activated by various factors in inflammatory foci as evidenced by the ability of reduction of nitroblue tetrazolium (NBT) in the Park test.[1] As observed in our earlier studies, in patients with bronchial asthma, approximately 15 to 20% of granulocytes reduced NBT to black formazon granules.[13] In patients with corticosteroid-dependent asthma treated with Traumeel® S, the ability of granulocytes to reduce NBT was decreased. This could be evidence of an incipient extinction of the chronic inflammatory process resulting from this treatment. Further evidence of this benefit could be the reduced release of peroxide radicals during Traumeel® S therapy as compared with patients receiving placebo. After Traumeel® S treatment, the amount of amino radicals released by granulocytes decreased from 16.6 and 29.3 to 9.4 and 18.7

An important role in the allergic process is played by eosinophils and by toxic proteins which they release: eosinophil cationic protein (ECP), major base protein (MBP), and eosinophil protein X.[3] ECP is released from eosinophilic granules and has in the organism a defensive function of killing bacteria and of inducing histamine with consequent damage to surrounding tissue.[14] Raised serum ECP levels have been observed in bronchial asthma and in atopic dermatitis patients.[15] In patients treated with Traumeel® S, serum ECP levels decreased while in the placebo group it remained unchanged. Traumeel® S may stabilize the lyosomal membranes of basophil granulocytes, thus reducing ECP release. A similar action of stabilizing lyosomal membranes in neutrophil granulocytes could decrease the release of perioxide radicals.

Immunoglobulin A, in particular the secretory IgA (S-IgA) has an important place in the humoral immunity of the lungs. S-IgA present on the mucosa is a specific hapten for foreign proteins with which it binds, preventing their absorption into the organism.[16]

In contrast to other immunoglobulins, the antigen-IgA-complex is not an activating complement. In fact, it even inhibits activation by IgM or IgG.[17] IgA inhibits the Prausnitz-Kustner reaction mediated by IgE.[18] Thus it is not unexpected that its deficit in the lungs can enhance the already present inflammatory process.

In our study the mean serum IgA levels in bronchial asthma patients were within normal range, but in the group treated with Traumeel® S they had an increasing tendency, from 218.8 to 261.8. No such tendency was noted in the placebo group. However the difference was not statistically significant and no greater importance need be ascribed to this observation.

IgG and IgM levels studied in this clinical experiment showed no significant differences between the study group and the placebo group.

We believe that some attention should be given to the observation that among patients with corticosteroid-dependent bronchial asthma and chronic hepatitis (5 cases in the Traumeel® S group) the transaminase levels fell statistically significantly (AlaT from 104.01 to 49.05 and AspAT from 269.0 to 68.0) No such decrease was observed in two patients receiving placebo. Of course, no reliable conclusion can be based on the observation of seven cases, but further, more detailed, study of a greater number of cases seems worthwhile.

In summary, it can be stated that Traumeel® S is a drug deserving attention in the treatment of corticosteroid-dependent bronchial asthma. It is worth stressing that only two patients withdrew from this treatment because of increased dyspnea and development of allergic rash. We add that all patients qualified for this clinical trial had intradermal tests with this drug and only cases with negative results were recruited for the trial. In 13 cases the test was positive and those patients were not accepted in the study group.

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