Keywords

Immunomax®

Human papilloma virus

Prostatitis

Prostate carcinoma

Infections of the urogenital tract

Immunomax® therapy to obtain relief in papilloma virus infections, prostatitis, and prostate carcinoma

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Abstract

Background: Immunomax® is a novel immunostimulant manufactured from potato sprouts. It consists of acidic peptidoglycans with a molecular mass of 1,000–40,000 kDa. In order to demonstrate its therapeutic effectiveness and safety, we here present data on the treatment of papilloma virus infections, and two pilot studies on prostatitis and prostate carcinoma treatment.

Methods: Immunomax® was investigated using *in vitro* murine macrophage activation studies and by efficacy studies in human patients suffering from either recurrent anogenital warts caused by papilloma virus, or from chronic prostatitis type IIIa, as determined by the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), or from prostate carcinoma.

Results: Immunomax® stimulated nitric oxide (NO) production in murine bone marrow derived macrophages. In human patients, Immunomax® was effective for treating recurrent anogenital warts caused by papilloma virus. Immunomax® therapy also showed, in two pilot studies, a pronounced therapeutic benefit in chronic prostatitis and prostate carcinoma. Patients with chronic prostatitis responded with a significant reduction of leukocytes in exprimate urine, and an increase in quality-of-life as determined by the NIH-CPSI. In case reports on prostate carcinoma, patients responded well to the treatment with a long lasting reduction in prostate-specific antigen. All patients tolerated Immunomax® treatment well without any allergic or undesirable reactions.

Conclusions: Immunomax® has been shown to be a novel useful therapeutic agent for the treatment of disorders of the urogenital tract.

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Introduction

Immunomax®, a potent immunostimulant obtained from potato sprouts, has been registered for medical use by the Ministry of Health of the Russian Federation for protection against infections caused by viruses (e.g. human papilloma virus, herpes simplex virus, parvovirus, carnivore plague virus) or bacteria (e.g. *Escherichia coli*, *Salmonella*, *Staphylococcus*, *Chlamydia*, *Mycoplasma*, and *Ureaplasma*). In particular, Immunomax® is applied as therapy for bacterial infections of the urogenital tract, and also for the treatment of purulent surgical processes. The therapeutic benefit of Immunomax® therapy has been clinically investigated in numerous studies, and no toxicity or adverse reactions have been detected [1–4].

The human papillomavirus (HPV) causes infections in the stratified epithelium of the skin or mucous membranes. Many types of HPV are sexually transmitted and infect the anogenital region. Some HPV types cause genital warts, while persistent infections with

other HPV types can lead to precancerous lesions and invasive cancer [5–9]. Prostatitis and urethritis are widespread diseases. Patients with chronic bacterial prostatitis (category II according to the National Institutes of Health (NIH) consensus classification) experience recurrent episodes of bacterial urinary tract infection, usually caused by *E. coli*, *Enterococcus* or other Gram-negative bacteria. Typical treatment is based on antibiotics and the results often seem successful during the initial weeks after treatment. However, the infection reoccurs in a substantial percentage of patients, and chronic urethritis and prostatitis are rather resistant to further treatment. More than 90% of symptomatic patients suffer from chronic abacterial prostatitis/chronic pelvic pain syndrome (CPPS) (category III according to the NIH consensus classification: IIIa inflammatory, IIIb non-inflammatory). Patients with the inflammatory subtype have leukocytes in their expressed prostatic secretions, in postprostate massage urine, or in semen [10,11]. Here, we demonstrate the therapeutic benefit of Immunomax® for treating recurrent anogenital warts caused by papilloma virus, chronic prostatitis IIIa and prostate carcinoma.

Subjects, materials and methods

Clinical study on the treatment of anogenital warts

Patients

The trial was performed at the Department of Skin Diseases and Sexually Transmitted Diseases of the Russian University of Peoples' Friendship, Moscow. Thirty patients (14 women and 16 men) being treated for recurrent anogenital warts caused by HPV took part in the trial. The ages of the patients varied from 18 to 46 years. Anogenital warts were detected in all 30 patients, and 'recurrent anogenital warts caused by HPV' was the main diagnosis in all of them. The patients were informed about Immunomax®, the purposes of the clinical trial, the possible therapeutic effect of the drug, and the possible side effects of the treatment. After receiving this information, patients were included in the trial provided that they gave their written consent.

Ethical approval

The clinical trial was approved by the resolution of the Committee for Ethics (Record no. 20 of November 28, 2001), by the resolution of the Pharmacological Committee (Record no. 17 of November 29, 2001), and a permission for Clinical Trial issued by the Department of State Supervision over the Quality, Effectiveness, and Safety of Drugs and Medical Equipment (Permission no. 440 of December 7, 2001).

Inclusion criteria

The following criteria were used when selecting volunteers: an age of 18 years or older, the presence of anogenital warts caused by HPV, a history of recurring anogenital warts after their removal, and an informed written consent. Pregnant or breast-feeding women, persons with alcoholism, drug/toxicant takers, and persons with mental disorders were excluded.

Immunomax treatment

An Immunomax® 200 U (40 μg) lyophilized preparation (vials; series 1112001) was used. The content of a vial (200 U) was dissolved immediately before use in 2 ml of sterile water for injections, and the resultant solution was injected intramuscularly (i.m.) on days 1, 2, 3, 8, 9, and 10. This treatment regimen was used in 20 out of the 30 patients. In 10 patients, an Immunomax® dose of 100 U was used. Large warts were surgically removed at the same time as the Immunomax® treatment.

Clinical laboratory examination

At the beginning of the trial, all patients were examined for syphilis and HIV infection. Blood serum samples were tested using the Wassermann test and immunoenzyme analysis in the presence of HIV antigens, respectively. A dermatologist/venereologist examined each patient before the trial, three times during the treatment, immediately after the treatment course, and 3 months after the end of the treatment. The examination included clinical assessment of lesion foci, their location, and the intensity and depth of pathological changes in the affected tissue. Samples of material were taken from the vagina, cervix uteri, and urethra of female patients, and epithelium was sampled from the urethra of male patients. The material was immediately placed on specially prepared mounts to obtain

smears for subsequent microscopic examination. The smears were fixed, Gram-stained with methylene blue, and examined under a microscope in transmitted light at a magnification of ×900. Epithelial cells, leukocytes, and bacteria (*cocci* and *bacilli*) were counted. The following infectious agents were monitored by direct immunofluorescence: *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Candida albicans*, and herpes simplex virus.

Polymerase chain reaction

Polymerase chain reaction (PCR) was used to estimate the amount of HPV in the material sampled from the pathological foci. The type of the virus and whether it was high-oncogenic (types 16, 18, 31, 33, 35, 45, and 56) or low-oncogenic (types 6, 1, 42, 43, and 44) was determined simultaneously.

Pilot studies on the treatment of chronic prostatitis/prostate carcinoma

Two pilot studies were performed in cooperation with the Urology Clinic of the Sechenov Moscow Medical Academy, Moscow, Russia. No formal permission by the Ministry of Health was required since the medical use of Immunomax® had been approved by the Pharmacological Committee, Ministry of Health of the Russian Federation, July 11, 2002, and authorized on December 9, 2002 by the Department of State Supervision over Drugs and Medical Equipment, Ministry of Health of Russia with the Registration Number P No.001919/02-2002, for the following indications: correcting impaired immunity, treating pathological states (condylomata, warts, dysplasia, etc.) caused by HPV, and treating infections caused by herpes simplex virus, *Chlamydia*, *Mycoplasma*, *Ureaplasma*, and other bacteria and viruses.

Animals, drugs and methods

Animals

Balb/c mice (female, 6–8 weeks of age) were obtained from the animal facilities of the University Hospital, Freiburg, Germany.

Drugs

Immunomax® 200 U (40 μg) lyophilised preparations were obtained from Immapharma, Moscow, Russian Federation. Lipopeptide adjuvant was obtained from ECHAZ microcollections, Tuebingen, Germany.

Stimulation of nitric oxide production

Murine bone marrow derived macrophages (BMDM) were differentiated *in vitro* from Balb/c murine bone marrow precursor cells, as previously described (one mouse/experiment) [12]. Cells were suspended in RPMI 1640 medium (Gibco) supplemented with 10% FCS, 1% non-essential amino acids, 100 U/ml penicillin, and 100 μg/ml streptomycin. Next, 1 x 10^5 cells were seeded per well into 96-well flat bottom microtiter plates (Falcon, Becton Dickinson, Heidelberg, Germany) and stimulated with various concentrations of the agents in a total volume of 200 μl. Culture supernatants were harvested after 40 h. Production of nitric oxide (NO) was determined by measuring nitrite, a stable metabolite of NO, in culture supernatants using the Griess reagent (1% sulfanilamide and 0.1% N-(1-naphthyl) ethylene diamine in 2.5% phosphoric acid) [13]. Finally, 100 μl culture supernatant was mixed with 100 μl Griess reagent, and the absorbance at 570 nm was measured using a Dynatec MRX ELISA plate reader (Denkendorf, Germany).

Results

Immunostimulation by Immunomax® in vitro

The immunostimulatory activity of Immunomax® was first investigated by *in vitro* studies in mice. In a typical experiment (out of 3), it was demonstrated that the drug stimulated a concentration-dependent NO production in murine BMDM (Figure 1); NO production was detected at concentrations >0.3 μg/ml and grew in a dose dependant manner up to the highest concentration of 10 μg/ml. For comparison, the effectiveness of the bacterial immunostimulant lipopeptide was tested. Maximum macrophage activation was observed at lipopeptide concentrations of around 50 μg/ml.

Treatment of recurrent anogenital warts caused by papilloma virus

Safety

Intramuscular (i.m.) injections of the solution containing 100 or 200 U of Immunomax® did not cause any general or local toxic reactions.

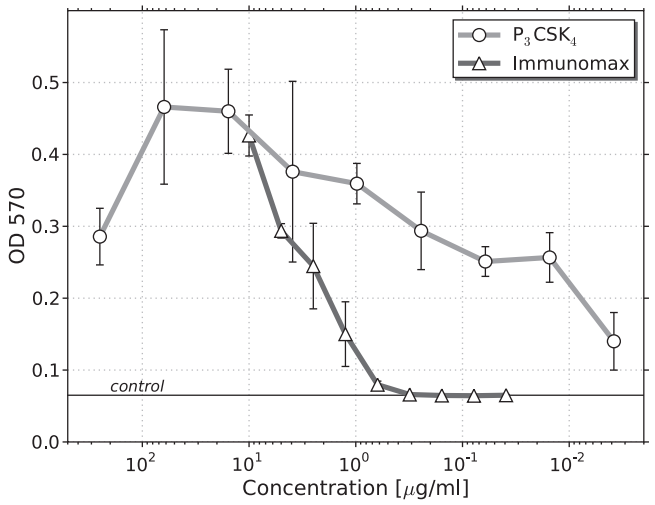

Figure 1 Induction of nitric oxide (NO) release in murine bone marrow derived macrophages (BMDM) by Immunomax® and by lipopeptide adjuvant. Dose–response for NO release of 1 x 10^5 BMDM/well for 40 h. Results are shown from 1 representative experiment out of 3. Values represent means ± standard deviation (SD) of triplicate cultures for each agent concentration.

On the contrary, the itching, burning sensation, and redness of the affected tissues considerably decreased within 1–2 days after the start of treatment. The patients tolerated treatment well: no rise in temperature or arterial pressure, and no ailing, dizziness, tachycardia, or disturbance in physiological functions was observed in any of the 30 patients.

Effectiveness

The effectiveness of the treatment was estimated by the amount of HPV in the material sampled from affected foci before and after therapy. At the same time as determining the amount of virus, any changes in the number of warts was estimated, as well as their localisation, the intensity and depth of pathological changes in the affected tissues, and the duration of remission. As can be seen in Table 1, the material from pathological foci from 12 of the patients (12/30: 40%) contained large amounts (+++ or ++) of oncogenic HPV types before treatment, and the amount was moderate (+) in 2 patients (7%). Non-oncogenic HPV types were abundant (+++ or ++) in the affected tissues of 14/30 patients (47%), and moderate (+) in 14 patients (47%). Immediately after the Immunomax® treatment, large amounts (+++ or ++) of oncogenic HPV types were found in the material from pathological foci from 8/30 patients (27%), with moderate amounts (+) in the material from 2 patients (7%). Large

Table 1 HPV infection in 30 patients before and after Immunomax® treatment.

	Before treatment		Immediately after treatment		3 months after treatment	
	Hr	Lr	Hr	Lr	Hr	Lr
abs	16	2	20	26	26	28
+	2	14	2	0	1	0
++	0	2	2	0	0	0
+++	12	12	6	4	3	2

Polymerase chain reaction (PCR) was used to estimate semi-quantitatively the amount of human papilloma virus (HPV) in the material sampled from the pathological foci. Simultaneously, the type of the virus, and whether it was high-oncogenic (types 16, 18, 31, 33, 35, 45, and 56) or low-oncogenic (types 6, 1, 42, 43, and 44) was determined. The results of PCR are represented as the amount of HPV expressed as scores from + to +++. Absence of HPV in the samples was denoted as abs. The Table shows the distribution of the patients with respect to the amount and type of HPV. abs, the virus is absent; Hr, high-oncogenic virus; Lr, low-oncogenic virus.

amounts (+++ or ++) of non-oncogenic HPV types were detected in 4/30 patients (13%), but in none of the patients was a moderate amount (+) of these types of HPV found. Three months after the Immunomax® treatment, the material from pathological foci from only 3/30 patients (10%) contained large amounts of oncogenic HPV types (+++ or ++), and material from just 1 patient (3%) contained moderate amounts of the virus (+). Non-oncogenic HPV types were abundant (+++ or ++) in 2/30 patients (7%), but in none of the patients was a moderate amount (+) of non-oncogenic types of HPV found. In 2 patients, the follow-up examination 3 months after treatment showed the presence of both oncogenic and non-oncogenic types of HPV. The subjective sensations (itching, burning sensation, etc.) connected with inflammation disappeared in all patients. In 6/30 patients, a slight feeling of discomfort was retained. As a rule, small warts (0.1–0.3 cm) disappeared within 2–4 days after the first injection of Immunomax®. The changes in large warts were not monitored, as they were removed simultaneously with Immunomax® treatment. Three months after treatment, anogenital warts re-appeared in only 4/30 patients (13%). It is noteworthy that the number of warts in those 4 patients was drastically decreased (from 10–17 to 2–3), and the remission increased by a factor of 2–3. Finally, 26/30 patients (87%) were completely cured as judged by clinical etiological characteristics.

Single doses of 200 U and 100 U were used in the course of treatment in 20 and 10 patients, respectively. The results of treatment using different single doses were practically the same. Eight out of ten patients (80%) that received the course of treatment using single Immunomax® doses of 100 U (6 i.m. injections over 10 days) were clinically and etiologically cured of recurrent anogenital warts. These results did not differ much from the results of the course of treatment using single doses of 200 U (6 i.m. injections over 10 days). Therefore, the data on the results of treatment for all 30 patients reported were pooled, irrespective of the single dose used.

Associated infections

The results of serologic tests for syphilis and HIV infection were negative in all patients. Also, in smear specimens, the presence and number of epithelial cells, leukocytes, and bacteria (*cocci* and *bacilli*) were estimated, and the effect of the drug on associated infections was analyzed: monotherapy using Immunomax® led to the disappearance of some associated infections. Herpes simplex type 2 virus disappeared in 6 out of 7 patients; *Ureaplasma urealyticum* in 5 out of 7 patients, *Mycoplasma hominis* in all of the 6 infected patients; *Trichomonas vaginalis* in the only infected patient; and *Candida albicans* in 2 of the 8 infected patients.

Treatment of chronic prostatitis

Immunomax® was used in a pilot study for the treatment of chronic prostatitis IIIa (NIH-CPSI) [11]. The study was performed in 8 patients, aged 45.6±8 years. Their time since diagnosis was >6 years. Severeness of the disease as estimated by the NIH Chronic Prostatitis Symptom Index (CPSI) was 25–30 (mean = 27). Patients were treated i.m. with doses of 200 U (40 μg) of Immunomax® (3 injections/week for 8 weeks). During Immunomax® treatment, no other medication was given. Figure 2 demonstrates that treatment markedly reduced the leukocyte count in exprimate urine, as measured 8 weeks after the start of therapy. The decrease was significant (P=0.02) from 230±129 to 76±37 leukocytes/μl. Also, Immunomax® treatment tended to decrease the volume of residual urine, however, that decrease was not significant (before treatment 47.1±26.4 cm^3, after treatment 38.9±18.6 cm^3, P = 0.1; see Figure 3). During treatment, the prostate volume was not altered (before treatment, mean volume was 14±7.7 cm^3, after treatment, 14.1±5.8 cm^3, P = 0.9; see Figure 4). Overall, treatment drastically reduced the NIH-CPSI score, as determined 8, 12 and 16 weeks after starting treatment. The individual initial values were 30, 28, 27, 33, 24, 25, 23 and 26; after the 8 week treatment, corresponding values were: 18, 17, 16, 19, 15, 14, 12, and 19; at 12 weeks, i.e. 4 weeks after the end of treatment, scores were: 20, 17, 18, 19, 16, 14, 18, 22; and at 16 weeks (8 weeks after the end of treatment), scores were: 24, 19, 17, 19, 22, 20, 19 and 20 (Figure 5).

Treatment of prostate carcinoma

Initial studies were also performed for the treatment of prostate carcinomas by Immuno-

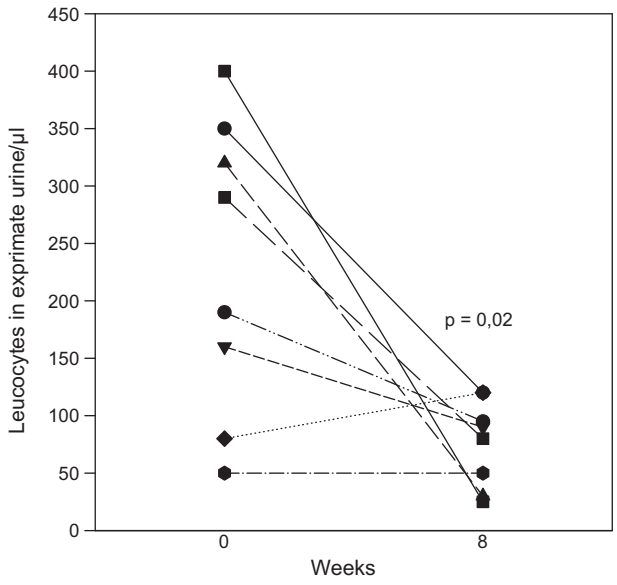

Figure 2 Treatment of chronic prostatitis IIIa (NIH-CPSI). Patients were treated i.m. with doses of 200 U Immunomax® (3 injections/week for 8 weeks). Immunomax® reduced leukocytes in exprimate urine from 230 ± 129 to 76 ± 37, $P = 0.02$ (paired Student's *t*-test).

max®. Two treatment case reports are included here, where Immunomax® was administered in combination with androgen blockade. Androgen blockade alone resulted in a further increase of prostate specific antigen (PSA), which was normalized by Immunomax®. The patients responded well to treatment with a long lasting slight reduction in PSA (see Figures 6a, b). No adverse reactions or side effects were detected.

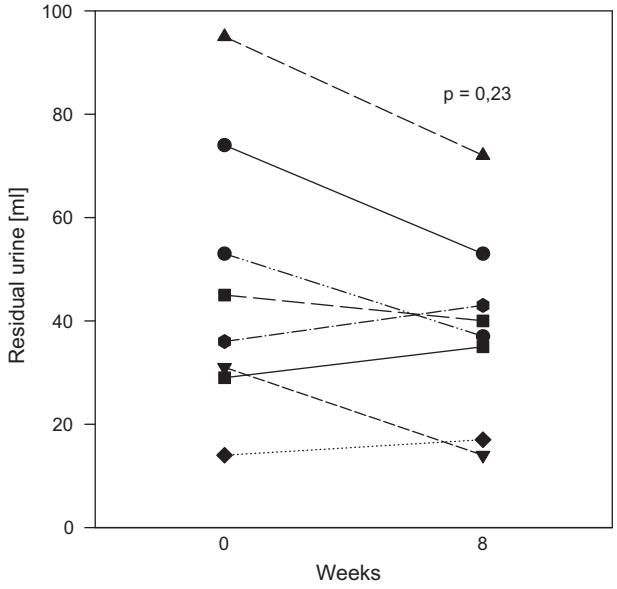

Figure 3 Treatment of chronic prostatitis IIIa (NIH-CPSI). Patients were treated i.m. with doses of 200 U Immunomax® (3 injections/week for 8 weeks). Immunomax® treatment tended to decrease the volume of residual urine. Before treatment, mean volume = 47.1±26.4 cm^3, after treatment, volume = 38.9±18.6 cm^3, $P = 0.1$ (paired Student's *t*-test).

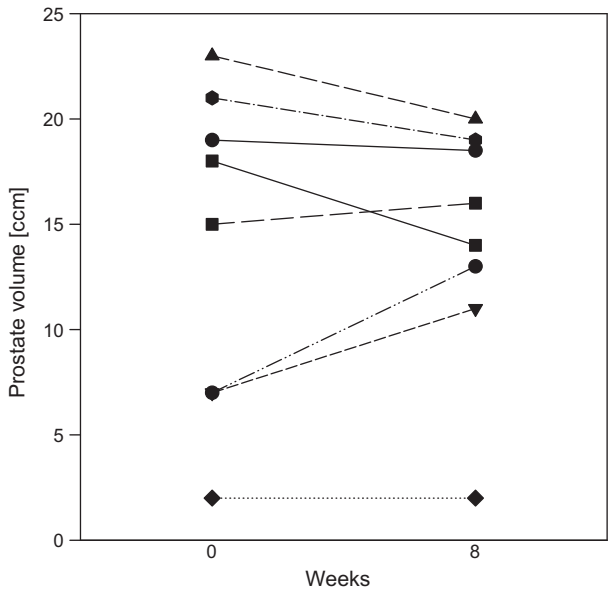

Figure 4 Treatment of chronic prostatitis IIIa (NIH-CPSI). Patients were treated i.m. with doses of 200 U Immunomax® (3 injections/week for 8 weeks). Immunomax® treatment did not alter the prostate volume. Before treatment, volume = 14±7.7 cm^3, after treatment, volume = 14.1±5.8 cm^3, P = 0.9 (paired Student's t-test).

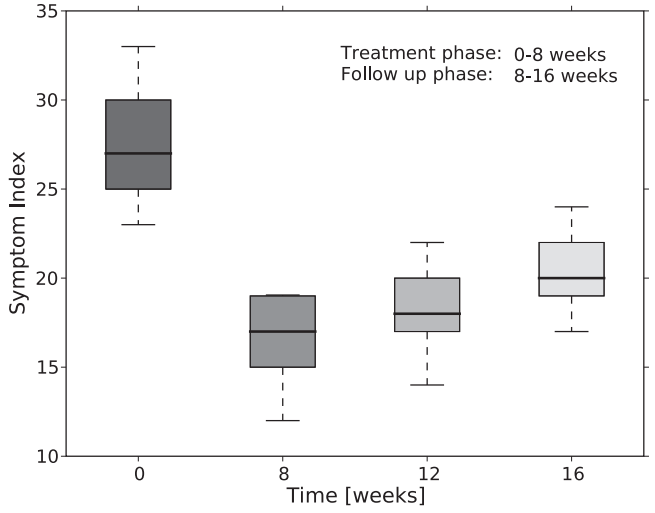

Figure 5 Treatment of chronic prostatitis IIIa (NIH-CPSI). Immunomax® treatment reduces the Chronic Prostate Symptom Index (NIH-GPSI) score. Patients were treated i.m. with doses of 200 U Immunomax® (3 injections/week for 8 weeks), and the GPSI score was determined after 8, 12 and 16 weeks. At all three time points after treatment, the symptom index was significantly lower than before treatment (Mann-Whitney U-test, critical U for one-tailed analysis = 15; actual U values at 8, 12 and 16 weeks = 0, 0 and 1.5, respectively).

Discussion

The novel immunostimulant Immunomax® is useful in human patients for the treatment of infections caused by viruses (e.g. papilloma virus, herpes simplex virus) or bacteria (e.g. *Escherichia coli*, *Salmonella*, *Staphylococcus*, *Chlamydia*, *Mycoplasma*, *Ureaplasma*). The immunological mechanisms underlying the effect of the drug are the activation of several components of the immune system: 2–3 h after Immunomax® administration natural killer (NK) cells

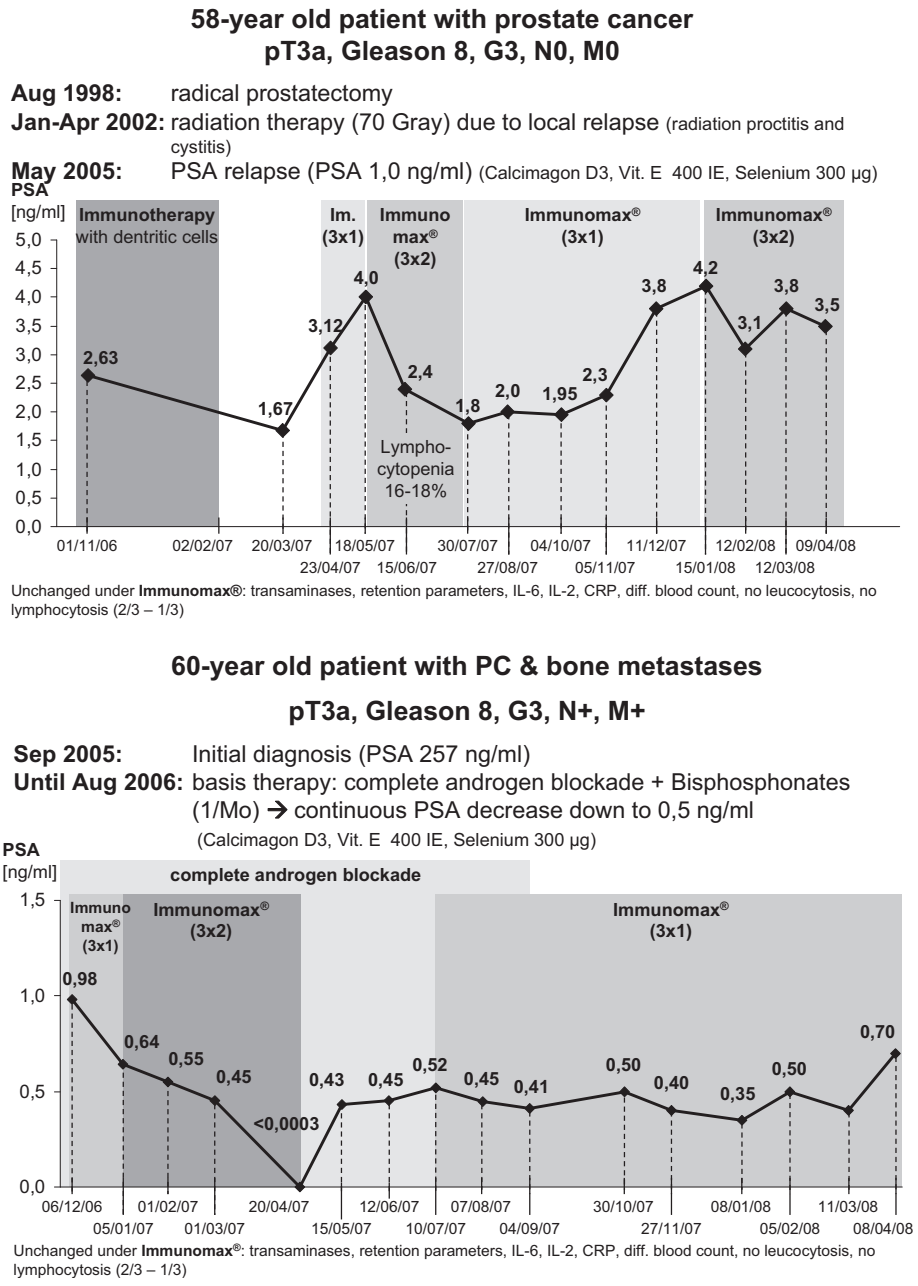

Figure 6 Treatment of prostate carcinoma with Immunomax®. Two case reports. Immunomax® was administered in combination with androgen blockade (supplementary details are indicated in the Figures).

show an enhanced expression of CD69, intracellular cytolytic granules with perforin and cytolytic capacity against K562 tumor target cells. Circulating monocytes began secreting cytokines, including interleukin (IL)-8, IL-1β, and tumor necrosis factor (TNF)-α, 2–4 h after Immunomax® application. IL-8 secreted by monocytes resulted in the activation of neutrophilic granulocytes, which became manifest 24 h after Immunomax® administration. In tissue macrophages, the production of bactericidal substances is enhanced [1]. The macrophage activating properties of Immunomax® were demonstrated in this study.

In this paper, we have demonstrated the use of Immunomax® for the treatment of anogenital warts caused by HPV, as has also been previously shown [14]. For treatment, the drug was administered by i.m. injections at a single dose of 100 or 200 U (a course of 6 injections). Treatment led to clinical recovery in 87% of the patients. Interestingly, Immunomax® was simultaneously effective for the improvement of herpes, *Chlamydia, Mycoplasma, Ureaplasma*, or

Trichomonas infections. We also demonstrated that the drug was well tolerated, causing neither local nor general adverse reactions. The effects of Immunomax® on the biochemical parameters in blood and urine were monitored in all patients before, immediately after, and 3 months after treatment and all values remained within their normal ranges. It should also be emphasized that patients with bronchial asthma or atopic dermatitis tolerated treatment without any allergic or other undesirable reactions.

Prostatitis and prostate carcinoma are very common, especially in elderly patients. This report shows the therapeutic benefit of Immunomax® therapy in abacterial prostatitis IIIa. In a pilot study, 8 patients responded well to an 8 week treatment regimen: they showed a significant reduction of leukocytes in exprimate urine, a slight reduction in PSA levels (data not shown), and a reduction in the volume of residual urine. Moreover, we found an impressive reduction in the NIH-CPSI score. The beneficial effect of treatment was still seen about 4 weeks after the termination of treatment. The results of a pilot treatment study of prostate carcinoma by Immunomax® have also been reported here in the form of two case reports (2 other case reports were not shown here), as communicated previously in abstract form [3]. Immunomax® had a mitigating effect; patients responded well to the treatment with a long-lasting slight reduction in PSA level. No adverse reactions or side effects were detected. Following these two pilot studies, which had very small sample sizes of $n = 8$ (prostatitis) and $n = 4$ (prostate carcinoma), randomized controlled trials are planned to prove the effectiveness of the drug as well as the lack of adverse effects.

Immunomax® has been shown before to be useful in the therapy of microbial infections. Batkaev *et al.* demonstrated an effect of Immunomax® for the treatment of *Chlamydia* infections in combination with antibiotic therapy. No adverse reactions or side effects were detected and the therapy had no negative impact on the immunological status of the patients [2]. Tishchenko *et al.* performed therapy studies on urogenital *Trichomonas* infections. They treated patients with Immunomax® (200 U i.m. daily for 6 days) in combination with conventional treatment using metronidazol. Treatment induced healing and elimination of *Trichomonas* in all patients and also showed a beneficial effect on accompanying infections of e.g. *Mycoplasma, Ureaplasma, Candida*, Herpes, or bacterial vaginitis [15]. Budanov [16] described the therapeutic effect of Immunomax® treatment for *Herpes genitalis* infections. After treatment, herpes outbreaks occured less frequently and showed enhanced healing with minimal clinical symptoms. The time of remission was extended by a factor of 5–7. Immunomax® treatment was effective for herpes simplex virus-1 (HSV-1) and HSV-2 infections, and for the therapy of *Herpes perinealis* and *Herpes glutaealis* infections. Immunomax® therapy after the failure of Aciclovir treatment reduced relapses by a factor of 2.8 [16]. Finally, Immunomax® can be used for the treatment of purulent surgical processes. The administration of 200 U Immunomax® as daily injections for 3–6 days caused speedy wound healing, decreased the need for anti-bacterial therapies, and prevented the formation of rough scars [4].

In summary, the therapeutic benefit of Immunomax® in the therapy of recurrent anogenital warts, prostatitis and prostate cancer has been shown, and no toxicity or adverse reactions caused by the treatment have been detected.

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