

Pandemics of Sexually Transmitted Infections (STIs): Clinical Use of Ezrin Peptide Therapy in Russia to Treat and Prevent Candida, Chlamydia, Trichomonas vaginalis, Syphilis, HPV and Herpes (HSV-1 & 2)

Rupert D Holms*

Newal R&D Ltd, London.

*Correspondence:

Rupert D Holms, Newal R&D Ltd, London, E-mail: dr RupertHolms@gmail.com.

Received: 26 May 2023; Accepted: 06 Jul 2023; Published: 12 Jul 2023

Citation: Holms RD. Pandemics of Sexually Transmitted Infections (STIs): Clinical Use of Ezrin Peptide Therapy in Russia to Treat and Prevent Candida, Chlamydia, Trichomonas vaginalis, Syphilis, HPV and Herpes (HSV-1 & 2). *Microbiol Infect Dis*. 2023; 7(3): 1-21.

ABSTRACT

There is a global problem of increasing incidence and prevalence of sexually transmitted infection (affecting more than ten percent of the world population), and there is a growing problem of drug and vaccine resistant infections: human ezrin peptide therapy presents a novel solution. This review summarizes the results of 17 clinical trials on the use of human ezrin peptide one (HEP-1 “Gepon”), a 14 amino acid adaptive immunity amplifying peptide registered as a pharmaceutical, which has been in use in the Russian Federation since 2001, for the treatment of a broad spectrum of sexually transmitted diseases caused by infections of bacteria, viruses, fungi and protozoans. HEP-1 and RepG3 (a derivative of HEP-1) have also been successfully used to treat SARS-CoV-2 infection. The high prevalence of chlamydia, candida, Trichomonas vaginalis, Herpes (HSV-1 & HSV-2), Human Papilloma Virus (HPV) are the result of pandemics of sexually transmitted infections (STIs) that are generally increasing world-wide, particularly in women. Although treatments or vaccines are available for the various infections, the current medical interventions have not significantly reduced the growing problem. Multi-drug resistant bacterial & viral strains, and increasing sexual promiscuity are adding to the problem, so new solutions are required. In the Russian Federation, human ezrin peptide therapy with HEP-1 (brand name “Gepon”) is used to treat candida, chlamydia, Trichomonas vaginalis, herpes, and HPV infection. In addition HEP-1 (Gepon) has been shown to be effective in combination with antibiotics, for the treatment of Syphilis. Ezrin peptides induce biological responses in patients to achieve the same or better treatment results than anti-biotic, anti-fungal, anti-viral and anti-protozoan pharmaceuticals, as well as enhancing adaptive protective immune responses like a vaccine. Ezrin peptides can be used as a post-infection vaccination strategy against re-infection. Human Ezrin Peptides can also overcome the rapidly growing problem of drug resistant strains of bacteria, protozoa and viruses. In addition, ezrin peptides amplify adaptive immune responses while simultaneously inhibiting expression of IL-1b, IL-6, IL-8 and TNFa, quickly suppressing mucosal inflammation. Human Ezrin Peptides also stimulate fibroblasts to repair damaged tissues.

Keywords

Ezrin Peptide Therapy, Sexually Transmitted Infections, STIs, HEP-1.

Introduction

Short alpha helical synthetic peptides mimicking the Alpha domain of human ezrin, activate adaptive immune responses while inhibiting pro-inflammatory cytokine expression (down

regulation of IL-1b, IL-6, IL-8 and TNFa). Ezrin peptides also stimulate fibroblasts to repair tissues. Ezrin peptides were reverse-engineered from HIV, after the discovery that the c-terminus of HIV gp120 mimics the Alpha domain of human ezrin and this mimicry is mutation-stable, indicating functionality. Part of the human immune system is hacked by HIV to control immune functions beneficial to its life-cycle. After more than 17 clinical trials in Russia, ezrin peptides have been found to be a safe one-

stop solution for treating any Sexually Transmitted Infection (whether of viral, bacterial, fungal or protozoan origin), which also induce some immune protection from relapse and re-infection. Intravaginal, intrarectal and oral administrations of ezrin peptides, as short 5 day courses of treatment, can stop *all* STIs, by amplification of adaptive immunity of the mucosa (while inhibiting inflammation). Ezrin peptides cure common urogenital problems such as chronic candida and chlamydia (cystitis), as well as serious infections such as HPV (the cause of cervical cancer) and syphilis.

There is a pandemic of sexual infection developing due to changes in social behaviour (women are having more sex partners in a lifetime) and mutant infections are evolving drug & vaccine resistance. World-wide, approximately 1.4 billion people have a sexual infection. In 2021 there were four million people diagnosed with an STI symptom in the UK, about a quarter of the sexually active population. NewalR&D is developing RepG3, the modified & improved peptide developed from Human Ezrin Peptide One (HEP-1 brand name "GEPON") for the treatment of sexually transmitted infections (STIs) of viral, bacterial, fungal and protozoan origin. RepG3 & HEP-1 are both anti-inflammatory adaptive immune amplifying ezrin peptides but RepG3 has better bio-availability and twice the activity.

Ezrin Peptide Therapy

Ezrin peptide therapy was invented in the UK as an HIV /AIDS therapy by Dr Rupert Holms in 1993 [1]. However, with British investment funds, HEP-1 was first developed in Moscow as a general therapy for STIs [2-4]. HEP-1 (Gepon) is an alternative treatment and prevention strategy to STIs, which over-comes the drug resistance problems of antibiotics & antivirals and can amplify immunological protection to STIs, like a vaccine [5]. Human Ezrin Peptide One, HEP-1 was registered as a pharmaceutical called "Gepon" in the Russian Federation in 2001. Gepon is produced by Immapharma Ltd located on the territory of the Gamaleya Institute, Moscow, which is now a subsidiary of Avexima (www.avexima.ru) [6].

HEP-1 (Gepon) Sequence, Structure and Drug Delivery

Ezrin Peptide HEP-1 (Gepon) is an alpha-helical synthetic peptide mimic of amino acid 325 to amino acid 338 of the Alpha domain of human ezrin protein [7]. The primary sequence of 14 amino acid HEP-1 is: Thr-Glu-Lys-Lys-Arg-Arg-Glu-Thr-Val-Glu-Arg-Glu-Lys-Glu (TEKKRRETVEREKE). Generally, HEP-1 (Gepon) is used as a 0.2 mg to 2 mg per mL aqueous solution taken orally, or applied topically to the mucus membranes (orally, vaginally or anally), or as an aerosol spray to the upper airways. Ezrin Peptide HEP-1 (Gepon) is also used topically in the form of ointment: 2mg HEP-1 (Gepon) blended with 6g of ointment base (2mL distilled water: 2g lanolin: 2g olive oil). A standard dose of HEP-1 (Gepon) is 2mg for a 70 -100 Kg adult, once a day for 3 to 5 days, although prolonged courses of oral 2mg HEP-1 (Gepon) once per day treatment, have been used safely for more than 12 months. In addition, intra-muscular or sub-cutaneous injections of 0.2 mL of a 1mg /mL solution of HEP-1 (Gepon) in 0.85% NaCl, have

been safely used to control herpes virus outbreaks, particularly in painful outbreaks of shingles, caused by the reactivation of the varicella-zoster virus (VZV), also known as herpes zoster.

Biological Activity of HEP-1

HEP-1 (Gepon) is easily absorbed through the epithelium of mucous membranes to activate local immunity and tissue regeneration. HEP-1 (Gepon) induces an effective immunological defence against bacterial, viral, fungal and protozoan infection by amplifying T-Cell and B-Cell responses of the adaptive immune system. HEP-1 is also an inhibitor of inflammation triggered by the innate immune system. In cell culture and animal models, HEP1 was demonstrated to inhibit the expression of the pro-inflammatory cytokines IL-1b, IL-6, IL-8 and TNFa. Due to the profound anti-inflammatory effect of HEP-1, 24 hours after the use of HEP-1 (Gepon), symptoms of inflammation are significantly reduced, in particular, the redness & swelling, as well as the feeling of soreness, burning & itching in the area of inflamed mucous membranes. HEP-1 (Gepon) also changes the expression pattern of many cytokines [8].

HEP-1 was also demonstrated to increase the activity and number of CD4+ T cells, increasing the content of activated CD4+ CD45RA+ T Helper-cells and CD4+ CD45RO+ Memory-cells. HEP-1 (Gepon) stimulates B-Cell and Plasma Cell production of antibodies to infectious microorganisms. HEP-1 increases the number of both CD16+ CD56+ NK cells & CD16+ CD56- NK cells and increases the expression of HLA-DR on the NK cells, a marker of NK-activation. HEP-1 (Gepon) mobilizes and activates macrophages. HEP-1 (Gepon) normalises the activity of neutrophils and CD8+ T-cells. HEP-1 (Gepon) stimulates production of alpha and beta interferons. HEP-1 (Gepon) has antiviral activity in cell culture suppressing the replication of HIV, HCV and other viruses [9]. In addition, HEP-1 has been shown to activate fibroblasts and accelerate tissue repair [10].

HEP-1 (Gepon) is effective in the treatment of recurrent infections of the mucous membranes and skin of the vagina caused by fungi of the genus *Candida*, gram-negative bacterium *Chlamydia*, the protozoan parasite *Trichomonas vaginalis*, Herpes Simplex Viruses type 1 and type 2, as well as in the complex treatment of chronic urethritis and cystitis. HEP-1 is also effective in reducing or eliminating "sero-resistant" syphilis. HEP-1 (Gepon) is effective in controlling HPV infection as a monotherapy. Other applications for HEP-1 (Gepon) include the treatment of acute viral respiratory infections with inflammatory complications [11]. In addition, HEP-1 (Gepon) is effective therapy for the treatment of hepatitis (HepA, HepB and HCV) and in the treatment of ulcers & inflammatory diseases of the gut (including ulcerative colitis).

Summary of Clinical Results of HEP-1 (Gepon) treatment of STIs

The following clinical trials in the Russian Federation were ethically reviewed, planned and conducted according to the regulations and standards of the Russian Federation and published in the Russian language in respected peer-reviewed Russian medical journals and text books.

Ezrin Peptide HEP-1 (Gepon) treatment of Candida

HEP-1 (Gepon) is a very effective treatment for both acute and chronic recurrent candidiasis of the vaginal and cervical mucosa. The standard protocol is syringe-irrigation (no needle) of the mucous membranes of the vagina with 5mL of 0.4mg HEP-1 / mL 0.85% NaCl solution, on Day-1, Day-3 and Day-5 of treatment, while the patient is lying flat on her back or supporting herself on elbows & knees, for up to ten minutes (some gynaecologists recommend the insertion of a tampon to retain the HEP-1 solution). For the treatment of external skin candidiasis, a gauze napkin moistened with 5mL of 0.4mg HEP-1 / mL 0.85% NaCl solution, can be applied to the affected areas.

Generally, a significant anti-inflammatory effect is observed in all patients over the first few days of HEP-1 (Gepon) treatment, with the visible reduction of redness & swelling and pain & itching of the mucosa. Ninety per cent of women suffering candidiasis respond rapidly to HEP-1 (Gepon) treatment by eliminating candida, while the remaining ten per cent experience a significant decrease in the intensity of the symptoms of infection. Inflammatory candidiasis disappears in the first few days of HEP-1 (Gepon) treatment, but it takes a further four weeks from start of treatment for about ninety per cent of women to clear candida fungal spores and mycelia.

Gepon is unique in that it not only effectively treats acute urogenital candidiasis, but also amplifies adaptive mucosal immune responses to prevent relapses in women suffering recurrent candidiasis. However, there is evidence that the immunological protection conferred by HEP-1 (Gepon) treatment, is candida-strain specific and a new strain of candida introduced as a new sexually transmitted infection, can cause another acute candidiasis episode. HEP-1 (Gepon) is also effective therapy in combination with anti-fungal suppressive therapy such as fluconazole or itraconazole [12-14].

Clinical Trial No. 1

HEP-1 (Gepon) treatment of Candida (and Syphilis) in 25 women

In 2000-2001, the first clinical trial of HEP-1 (Gepon) treatment of urogenital candida infection was performed at the Medical Faculty of the Dermatology & Venerology department, at the Russian University of Druzbi Narodov (Friendship of Peoples) in Moscow. The principle investigator of the clinical trial was Professor A.L.Tischenko, MD. The clinical trial was authorised by the Decision of the Committee on Ethics (Minute 6 of 06 December 2000), Decision of the Pharmacology Committee (Minute 14 of 21 December 2000), Permission to conduct clinical trials issued by the Department of the State control of quality, efficacy and safety of medical preparations and equipment (Minute 183 of 31 January 2001). The clinical report was approved by Professor O.A. Sheveliov, Dean of The Medical Faculty of The Russian 'Druzbi Narodov' University (19 March 2001) [15].

The selective criteria for inclusion of women volunteers into the trial were as follows: age 18 and older; clinical manifestation of fungal infections of the skin and mucosa caused by candida

albicans; failure of anti-fungal preparations at treating these infectious inflammations; confirmation of candida fungal infection by laboratory microscopic microbiological assessment of swabbed material from the focus of the inflammatory infection. The selective criteria for exclusion from the trial were as follows: women who were pregnant or breast-feeding, women with any intolerance towards peptides, women suffering from alcohol and substance abuse, and women with psychiatric disorders.

All patients were given information on the known safety and efficacy of Gepon, and the aims of the clinical trial to determine if Gepon was an effective treatment of chronic recurrent skin and mucosal candidiasis. All women volunteers provided their written consent to join the study. The 25 female patients (between 18 and 51 years old), who were suffering from inflammatory-infectious diseases of the urogenital tract, had already been admitted for treatment to the Department of Skin and Venereal Diseases of the Medical Faculty of the Russian University 'Druzbi Narodov', when they volunteered to enter into this clinical trial.

Each patient was examined by a gynaecologist prior to her inclusion in the trials, then three times: during treatment, immediately after treatment, and one-month following treatment. During the clinical examination, the location and intensity of any pathologies were assessed.

On admission to the clinical trial, 25 of 25 of the women volunteers complained about severe itching of the vagina, 16 of 25 experienced a burning sensation in the genital labia or in the vaginal entrance, 9 of 25 suffered pain in the lower abdomen or in the perineum and 3 of 25 suffered sharp pain during urination. Vulval-vaginal candidiasis was diagnosed in all 25 tested patients, and 15 of 25 also had cervicitis / endo-cervicitis. 22 of 25 patients were suffering from chronic urogenital candidiasis with duration of disease varying between 1 and 8 years with an average longevity of 3.1 years. The frequency of exacerbation of the chronic candidiasis varied between 2 and 12 recurrences per year (with an average of 4.6 per year). 3 of 25 women had only recently been diagnosed 1 to 3 months prior to the commencement of the trial, with chronic anti-fungal resistant candidiasis.

All 25 of 25 patients displayed obvious inflammatory processes in the vagina, with redness of the vaginal mucosa at the vaginal entrance and in the interior of the vestibule. 11 of 25 patients also had inflammation of the genital skin, 16 of 25 had inflammation in the cervix and 13 of 25 patients in the uterine adnexa. Oedema and swelling of the vaginal mucosa was observed in 18 of 25 patients, a whitish deposit on the surface of the vaginal mucosa in 10 of 25 patients, evidence of cervicitis in 13 of 25 patients, abnormal dryness (xerosis) of the vaginal mucosa in 3 of 25 patients, erosion and ulceration on the vaginal mucosa-in 2 of 25 patients, and in 1 of 25 patients, skin damage on the large genital labia.

All 25 patients had a variety of vaginal discharges, in most cases abundant. The discharge was 'curd-cheese'-like in 23 of 25 patients;

slimy mucous in 6 of 25 patients, milky mucous in 3 of 25 patients, milky in 3 of 25 patients, purulent (pus-like) in 5 of 25 patients and muco-purulent in 9 of 25 patients. During vaginoscopy of each patient, the material from the vagina and cervix was collected on swabs and used for microscopic slide preparations that were fixed and coloured with Gram's methyl violet. During the microscopy of the Gram's coloured swabs, the presence of candida was analysed by quantifying the pseudo-mycelia and the budding fungal forms. The results of candida infestation was quantified in categories from zero to 4+. All 25 of 25 women in the clinical trial displayed urogenital infection with abundant pseudo-mycelia and budding fungal forms of candida. 15 of 25 women had maximum 4+ infection, 8 of 25 women had 3+ infection and 2 of 25 women had 2+ infection (no women had zero infection).

Microscope analysis of swabs, also revealed evidence of epithelial destruction due to inflammation associated with candidiasis. Swabs from 25 of 25 women contained large numbers of activated leucocytes and large numbers of epithelial cells lost from the damaged mucosa. 20 of 25 patients had between 30 to 70 active leukocytes in the visual field (at 900X magnification). There was evidence of serious leukocytosis in vaginal secretions and in the cervical canal, which is typical of infectious inflammation caused by bacteria and fungi.

Co-infections in 14 of 25 woman volunteers

Following admission all patients were tested for syphilis (Wassermann's reaction with cardiolipin antigen) and HIV infection (ELISA analysis for HIV antigens) and other bacterial infections, in addition to *Candida albicans*. Further microbiological analysis revealed co-infections in 14 of 25 patients. Bacterial vulva-vaginitis was detected in 4 of 25 patients and 10 of 25 patients were infected with syphilis of which: 8 of 25 had primary syphilis, 1 of 25 had secondary syphilis and 1 of 25 had tertiary neuro-syphilis. All of the 10 syphilis co-infection patients were given penicillin anti-syphilis therapy (either Procaine-penicillin or Benzil-penicillin 1 million Units).

The swabs examined under a microscope at 900X magnification revealed co-infections with bacterial cocci, diplococci, and bacilli. 6 of 25 patients had moderate intracellular cocci bacterial infection and 15 of 25 had severe intracellular cocci bacterial infection. 4 of 25 patients had severe diplococci extracellular infection. 9 of 25 had moderate bacilli bacterial infection. However, neither gonococci of *Neisseria gonorrhoeae* nor the protozoan cells of *trichomonas vaginalis* were detected.

HEP-1 (Gepon) treatment

Twenty patients were randomly assigned to Standard Treatment using HEP-1 (Gepon): Sterile vials of 2mg lyophilized HEP-1 (Gepon) produced by Immapharma Ltd (Moscow) were dissolved in 5 ml of sterile physiological solution of 0.85% NaCl (a 0.4mg / mL solution) and applied with a syringe (no needle) into the vagina of the women, to irrigate the mucosa of the vaginal walls and vaults. During and following the irrigation, the women remained in a horizontal position for 10 minutes. The procedure was repeated 3

times during approximately one week (generally on Day-1, Day-3 and Day-5 of treatment), a total dose of 6mg HEP-1 (Gepon).

Five patients were randomly assigned to Low Dose Treatment using HEP-1 (Gepon). With these patients sterile vials of 2mg lyophilized HEP-1 (Gepon) were dissolved in 10 ml of sterile physiological solution of 0.85% NaCl (a 0.2mg /mL solution) and this half-concentration solution was applied with a syringe (no needle) into the vagina of these women, to irrigate the mucosa of the vaginal walls and vaults. The procedure was repeated 3 times during approximately one week (generally on Day-1, Day-3 and Day-5 of treatment), a total dose of 3mg HEP-1 (Gepon).

Results

Safety: no local nor general allergic irritations nor toxic reactions were detected with HEP-1 (Gepon) treatment. Neither the patients, nor the doctors that conducted the trials, detected any reactions that could have been referred to as a side effect or adverse event. Of the 25 patients that received HEP-1 (Gepon) therapy, not one registered an increase in body temperature, nor ailment, nor dizziness, nor palpitation, nor physiological dysfunction of any kind. Two of the patients who had previously suffered allergy and intolerance to various medical preparations, easily tolerated the HEP-1 (Gepon) therapy with neither allergic nor other side effects.

Efficacy: all 25 candidiasis patients in the clinical study had already failed to respond to anti-fungal therapy. However, soon after the application of HEP-1 (Gepon), all of the patients felt reductions of itching, pain and redness of the skin and mucosa. The symptoms of inflammation were significantly reduced in the first 24 hours of treatment. Early in treatment the burning sensation disappeared in all patients, itching disappeared in 92% of patients and all pains disappeared in 88% of patients. By Day-2 of therapy, doctors observed a noticeable reduction of hyperaemia and oedema of the vaginal mucosa, cervix and large genital labia. Vaginoscopy confirmed the termination of vaginal inflammation in the majority of the patients. Mucosal hyperaemia disappeared in 84% (21 out of 25) patients, cervicitis disappeared in 84% (11 out of 13) patients whilst oedema, whitish deposits and macerations disappeared in all patients that received HEP-1 (Gepon) therapy. The efficacy of HEP-1 (Gepon) treatment was assessed by microbiological analysis of the amount of mycelia & budding forms of candida, present in material collected from vaginal, cervical and uterine secretions; before treatment, 7 days after treatment and 30 days after treatment (Figure 1 & Figure 2).

Prior to treatment the patient group displayed the following spectrum of mycelia & budding candida abundance in swabs: 4+ abundance in 15 of 25 patients, 3+ abundance in 8 of 25 patients, 2+ abundance in 2 of 25 patients. In contrast, 7 days after HEP-1 (Gepon) treatment, the patient group displayed the following spectrum of mycelia & budding candida abundance in swabs: zero 4+ and zero 3+ levels of candida abundance, 2+ abundance in only 1 of 25 patients, 1+ abundance in 19 of 25 patients, and 5 of 25 patients had already cleared the candida infection.

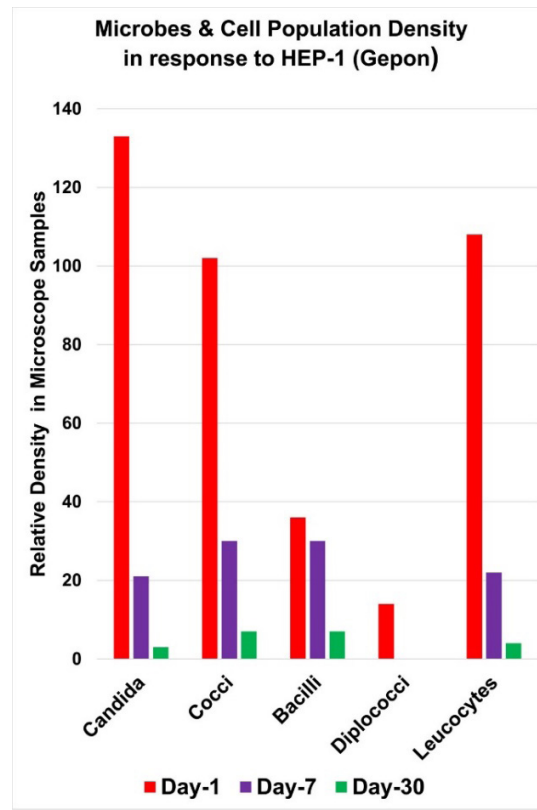
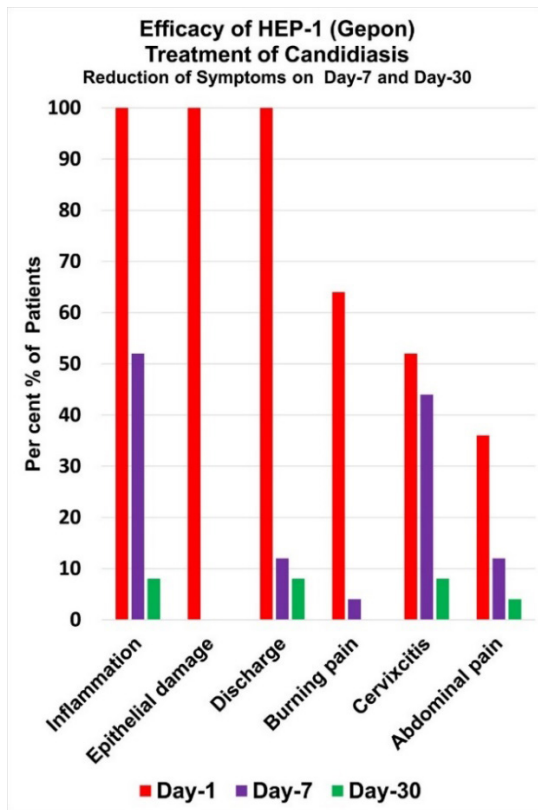


Figure 1: Efficacy of HEP-1 (Gepon) treatment of candida infection measured by the reduction in the per cent of 25 patients presenting symptoms of candidiasis. Clinical trial of HEP-1 (Gepon) treatment of urogenital candida infection in 25 women with chronic recurrent anti-fungal resistant candidiasis, performed at the Medical Faculty of the Dermatology & Venerology department, at the Russian University of Druzbi Narodov (Friendship of Peoples) in Moscow.

Figure 2: Relative density of candida infection and bacterial co-infections (cocci, bacilli & diplococci) and active leucocyte numbers on Day-7 and Day-30 after commencement of HEP-1 (Gepon) therapy. Clinical trial of HEP-1 (Gepon) treatment of urogenital candida infection in 25 women with chronic recurrent anti-fungal resistant candidiasis, performed at the Medical Faculty of the Dermatology & Venerology department, at the Russian University of Druzbi Narodov' (Friendship of Peoples) in Moscow.

One month after the start of HEP-1 (Gepon) treatment, the patient group displayed the following spectrum of mycelia & budding candida abundance in swabs: zero level 4+ & zero level 3+ of candida abundance, 2+ abundance in only 1 of 25 patients, 1+ abundance in only 1 of 25 patients, and 23 of 25 patients had cleared the candida infection. Etiological cure was achieved in 92% of the patients. The termination of pathological vaginal discharge occurred in almost all patients (22 of 25) and it was replaced by healthy natural vaginal lubricating mucus. Only one patient maintained 'curd-cheese'-like discharge, and low volumes of milky discharge were noted in 2 other patients. HEP-1 (Gepon) therapy proved to be completely effective in curing vagina mucosal ulceration and dry-vagina syndrome (xerosis).

swabs from any of the patients.

In addition, the effect of HEP-1 (Gepon) treatment on the numbers of epithelial cells and leukocytes in the swabs before and after treatment confirmed the anti-inflammatory and tissue regeneration properties of HEP-1 (Gepon). Before HEP-1 (Gepon) treatment 25 of 25 patients had an abundance of epithelial cells in the swabs revealing serious epithelial tissue damage. However, only seven days after start of treatment, there were no epithelial cells in the

The profound fall in leukocyte numbers in the swabs revealed the progressive restoration of health. Prior to treatment the patient group displayed 25 of 25 patients had ten to seventy leukocytes per microscope view field. Seven days after treatment only 5 of 25 patients had ten to seventy leukocytes and 20 of 25 patients had less than ten leukocytes per microscope view field. One month after treatment only 1 of 25 patients had ten to twenty leukocytes, only 2 of 25 patients had five to ten leukocytes and 22 of 25 patients had a healthy number less than five leukocytes per microscope view field, an indication that all chronic infections had been eliminated. At the same time polymorphous cells that resembled macrophages appeared on Day-7 and became more abundant by Day-30.

This positive conclusion was confirmed by the unexpected bonus of the therapeutic benefit of HEP-1 (Gepon) treatment in reducing cocci, diplococci and bacilli bacterial infections. Prior to treatment, 21 of 25 patients had intracellular cocci bacterial infection, but in the one month follow-up after the start of HEP-1 (Gepon) treatment, these 21 of 25 patients were free of all intracellular

cocci bacterial infection. Prior to treatment, 4 of 25 patients had extracellular diplococci bacterial infection, but in the one month follow-up after the start of HEP-1 (Gepon) treatment, no patient had any intracellular diplococci bacterial infection. 15 of 25 patients had bacilli bacterial infection but in the one month follow-up after the start of HEP-1 (Gepon) treatment, eleven patients had cleared the infection and only 4 of 25 patients had low level bacilli infection. Muco-purulent and purulent (pus-like) vaginal discharge reflecting the presence of active bacterial infection, was present in 14 of 25 patients before therapy. Following the HEP-1 (Gepon) therapy, muco-purulent and purulent discharge was eliminated.

10 out of 25 patients that participated in the clinical trials were suffering from syphilis and were given courses of antibiotic treatment, including procaine-penicillin (course dose 24 million Units for 20 days) and penicillin (course dose 80 million Units for 20 days). No complications with aggravation of candidiasis occurred during antibiotic therapy for syphilis in combination with HEP-1 (Gepon) therapy. This was a surprise because generally antibiotic therapy aggravates candidiasis.

In the patients co-infected with candida and syphilis, 9 of 10 patients cleared candida infection with antibiotic plus HEP-1 (Gepon) therapy. The therapeutic effect of HEP-1 (Gepon) on syphilis was not investigated in this study, but the unexpected greater than usual success of the penicillin therapy in the study, led to further clinical trials to assess the benefits of HEP-1 Gepon as monotherapy or antibiotic combination therapy for syphilis. HEP-1 (Gepon) was later shown to be an effective treatment for 'sero-resistant syphilis' where antibodies to *Treponema pallidum* were detected due to hidden reservoirs of infection, in the absence of direct evidence of the microbe. No significant differences in treatment efficacy were detected when comparing low dose (1mg) and standard dose (2mg) HEP-1 (Gepon) treatment per day.

Clinical Trial No. 2

HEP-1 (Gepon) treatment of Candida in 70 women

A second clinical trial of HEP-1 (Gepon) treatment of urogenital candida infection was performed in 2001 at the Medical Faculty of the Department of Dermatology & Venerology, at the Russian University of Druzbi Narodov' (Friendship of Peoples) in Moscow. The principle investigator of the clinical trial was Professor A.L. Tischenko, MD.

70 women with chronic recurrent vulvo-vaginitis caused by *Candida*, who had not responded to treatment with anti-fungal drugs, were intra-vaginally treated with 2mg HEP-1 (Gepon) in 5 ml of 0.85% NaCl saline, once a day, on Day-1 Day-3 and Day-5 of the study. This 70 patient study confirmed the results of the previous 25 patients study. No side effects nor adverse events were detected with HEP-1 (Gepon) therapy. Generally, there was a rapid decline of intensity of inflammation of the vulvo-vaginal mucosa before Day-3 of treatment. At the one month follow up after Day-1 of HEP-1 (Gepon) treatment, elimination of *Candida* was confirmed in 93% of the patients. HEP-1 (Gepon) treatment

also eliminated bacterial cocci co-infections in 81% of patients [16,17].

Clinical Trial No. 3

HEP-1 (Gepon) treatment of Candida in 15 women and 10 men

In 2001, a third clinical study of HEP-1 (Gepon) treatment of *Candida* in 15 women and 10 men, was performed at the Department of Dermo-Venerology, Moscow State Medical Stomatological University in collaboration with Dermo-Venerological Dispenser No.8, Moscow. The principle investigators were Professor V.N. Grebenyuk, MD and Professor Yu.N. Perlamutrov, MD, (the STI specialist of Dermo-Venerological Dispenser No.8, Moscow), in collaboration with Dr A.M. Soloviev [18].

25 volunteers with candidiasis (15 women and 10 men) aged between 18 and 42 years old, were recruited between January and March 2001. Longevity of chronic recurrent candidiasis was up to 10 years. The selection criteria for inclusion in the clinical trial was the clinical manifestation of fungal infections of skin and mucosa, caused by candida-type fungi, unsuccessful attempts at treatment with anti-fungal therapy, and microbiological microscopic confirmation of the presence of the fungal infection caused by candida. The selective criteria for exclusion from the trial was patients who were below the age of 18, who were pregnant or breast-feeding, who had intolerance towards peptides, who had diagnosed psychiatric disorders, alcoholism or substance addiction. Termination of participation in the study were subject to the independent opinion of the patient's GP regarding any clinical and laboratory test results which indicated any progressive deterioration of the patient's condition during treatment. Prior to starting the trials, patients were given verbal information on the known safety and efficacy of HEP-1 (Gepon) treatment, the aims and purposes of the trial, followed by written agreement by a patient confirming their willingness to participate in the trial.

Fifteen women (n=15) all with vulvo-vaginitis caused by candida were entered into the clinical program. The main complaints of the candida infected women were itching vagina (pruritus) and discharges. Clinical examination revealed most female patients showed hyperaemia and oedema of the genital tract mucosa as well as the presence of abundant milky and 'curd-cheese'-like vaginal discharges.

Ten men (n=10): 3 with candida balanoposthitis (inflamed & infected glans of the penis), 3 with candida balanoposthitis combined with candida urethritis, 2 with candida balanoposthitis combined with candida lesions in the oral cavity mucosa, 1 with candida urethritis, and 1 with candida paronychia (infection of the nails of the fingers and toes), were entered into the clinical program. The main complaints of the candida infected men were itching, burning and discomfort on the glans of the penis and in the urethra.

Clinical examination of male patients revealed a redness of the

penis glans mucosa (7 patients) and the presence of a whitish deposit (6 patients), a redness of urethral labia and the presence of mucous discharge (5 patients), hyperaemia, oedema of mucosa and presence of a 'curd-cheese'-like deposit on the tongue and in the sides of the mouth (2 patients), presence of redness, erosion and scaling of the nail crease skin on the fingers (1 person).

Previous anti-fungal therapy had been administered to all 25 patients but had failed to effectively treat the infection. The previous treatment had included both local (nistatin, clotrimazol, nizoral, pimafutsin, pevarilorungal, lamizil) and general therapy (nistatin, nizoral, pimafutsin, orungal, lamizil).

HEP-1 (Gepon) treatment was prepared by dissolving 2mg sterile lyophilized peptide in 5mL 0.85% NaCl saline to produce a 0.4mg / mL solution. In female patients, the HEP-1 (Gepon) solution was squirted into the vagina with a 5ml syringe (no needle) to irrigate the vaginal mucosa and vulva. With male patients the 0.4mg / mL solution of HEP-1 (Gepon) in 5mL 0.85% NaCl saline was used to soak a napkin that was applied to damaged areas of the glans-penis mucosa, a syringe was used to wash the urethra of male patients suffering urethritis and in male patients with oral candidiasis, the solution was held in the mouth then swallowed. HEP-1 (Gepon) treatments were performed once in 24 hours with 1-3 day breaks per course of therapy. Generally, treatment was on Day-1, Day-3 and Day-5 of therapy.

Results

Disappearance of signs of inflammation was visible after Day-1 of treatment in 88% of patients. Only in 2 men and 1 woman who had previously displayed signs of severe inflammation prior to therapy, did a light hyperaemia of the mucosa persist. The obvious clinical anti-inflammatory effect, correlated with the reduction of infection, which was confirmed by microbiological microscopic tests.

By Day 7 after start of treatment, swabs from 11 women and 9 men revealed the disappearance of spores and mycelia of candida fungi from the glans and urethra of men; and vagina and cervical canal mucosa of women, an 88% cure rate. Of the remaining one male patient there was only an insignificant amount of fungi spores from his glans and urethra. Of the remaining 4 female patients, there was also only an insignificant amount of fungal spores and mycelia.

The one month follow-up after therapy, showed only one female patient with recurrence of candidiasis. In another two female patients, who enjoyed effective clinical cure on Day-7 examination, but who still had residual fungal spores and mycelia, they had cleared the candida completely by the Day-30 follow up, which was confirmed by the microbiological microscopic tests. Therefore, the final indicator of clinical and etiological efficiency for HEP-1 (Gepon) therapy was 84% in this patient group. None of the patients demonstrated any side effects from HEP-1 (Gepon) therapy.

Clinical Trial No. 4

HEP-1 (Gepon) treatment of Candida in 40 women and 10 men

Another clinical trial of HEP-1 (Gepon) treatment of urogenital candida infection was later performed at the Department of Dermo-Venerology, Moscow State Medical Stomatological University (MSMSU) in collaboration with Dermo-Venerological Dispenser No.8, Moscow. The principle investigators were Professor V.N Grebenyuk, MD and Professor Yu.N Perlamutrov, MD, (the STI specialist of Dermato-Venerological Dispenser No.8, Moscow), in collaboration with Dr. A.M Soloviev [19,20]. 50 patients who had all failed to clear candidiasis using anti-fungal drug therapy (age range 18 to 42 years old), volunteered for the study. In this larger study there were 40 women with recurrent vulvo-vaginitis caused by candida, and 10 men with recurrent balanopostitis (infection & inflammation of the glans of the penis caused by candida).

Treatment

As before, in the 40 women, the HEP-1 Gepon treatment involved vaginal irrigation of 2mg HEP-1 (Gepon) in 5ml 0.85% NaCl saline using a syringe (no needle). In the 10 men 2mg HEP-1 (Gepon) in 5ml 0.85% NaCl saline solution was washed up into the urethra using a syringe (no needle) for treatment of urethritis, and also the glans of the penis was treated by the application of an HEP-1 (Gepon) soaked gauze. Treatment was performed on Day-1 Day-3 and Day-5 of the trial.

Results

In response to HEP-1 (Gepon) therapy, there was a very rapid reduction of inflammation: clinical signs of inflammation of the vaginal mucosa and skin of the foreskin and the glans (redness, swelling, soreness and itching), was terminated on Day-1 and Day-2 of the application of HEP-1, (Gepon), but the total elimination of candida infection was slower. During the first week after the start of HEP-1 (Gepon) treatment, microscopy of swab-smears revealed that the number of candida pseudo-mycelia obtained from the mucous membranes and skin of patients, declined over the following 30 days. One month after start of treatment, in 84% of patients no candida pseudo-mycelia nor spores were detected. In the remaining 16% of patients only a low level of candida infection persisted. The result of treatment was the disappearance of signs of inflammation of the mucosa & skin, and clearance of Candida spores & mycelia in 84% of patients.

Generally, further clinical work on the treatment with HEP-1 (Gepon), of chronic recurrent candidiasis that was resistant to anti-fungal therapy, confirmed that in approximately ninety per cent of patients, inflammation of the mucosa was rapidly eliminated before Day-5 of treatment (usually in less than three days), but complete elimination of candida infection was observed on Day-30 after the end of treatment. This revealed that the full anti-candida effect of HEP-1 (Gepon) was due to the induction of an effective anti-candida immunological defence.

Clinical Trial No. 5

HEP-1 (Gepon) treatment of 16 men with Candida + Trichomonas sexually transmitted co-infection.

In 2002-2003, a clinical trial was performed at the Clinic of the Department of Dermatology and Venerology, Russian Medical Academy of Postgraduate Study, Moscow, by Professor E.A Batkaev, MD, in collaboration with Dr. D.V Ryumin MD and Dr. I.M Shakov MD, in 16 male patients with chronic candida and Trichomonas vaginalis co-infections of the urogenital tract, to assess the benefits of oral HEP-1 (Gepon) solution monotherapy. The study documented a breakthrough in the treatment of Trichomonas vaginalis [21,22].

Patients were screened by serum antibody tests and PCR for a range of STIs: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Mycoplasma hominis, Mycoplasma genitalium, Neisseria gonorrhoeae, Ureaplasma urealyticum, HSV-1, HSV-2, CMV, HPV and HIV. Patients were only included in the study if they had candida and trichomonas co-infection only. Other patients were excluded from the study after they were determined to be infected with multiple sexually transmitted diseases.

The 16 male patients (from 18 to 50 years old) who were recruited to the clinical study, all presented mixed candida and trichomonas vaginalis infection of the uro-genital tract (with durations of 2 months to 6 years). Analysis of the state of the microflora of the urogenital tract by swabbing, microscopy and micro-organism culturing, confirmed all patients had combined candida albicans and trichomonas vaginalis infection. Prior to HEP-1 (Gepon), patients had received treatment with 5-nitro-imidazols, but they had failed to clear the trichomonas vaginalis infections. Eight of the patients had been on repeated courses of antifungal therapy, which failed to clear candida infection.

2mg HEP-1 (Gepon) was dissolved in 5mL of water for each oral dose, which was held sublingually for about 4 minutes to aid mucosal absorption, after which the solution was swallowed. Patients received this oral HEP-1 (Gepon) solution treatment on Day-1, Day-2 and Day-3 of therapy (a total course of treatment of 6mg HEP-1 (Gepon)).

All patients noted the absence of side-effects or adverse reactions to HEP-1 (Gepon). On Day-2 or Day-3 of therapy, patients and physicians noted there was a significant decrease of inflammatory manifestations on the glans of the penis (balanopostitis) and a significant decrease or complete disappearance of itching in the urethra and pains during urination.

Microscopic analysis of the state of the microflora of the urogenital tract, was repeated at the end of therapy on Day-4. It revealed that no urogenital Trichomonas vaginalis could be found in the urethra of 5 patients, and there was evidence of massive lysis and death of trichomonas in 10 patients. Only one patient did not respond to HEP-1 (Gepon) treatment, there was no change in his microbial flora, and living Trichomonas vaginalis were still observed in his

urethra. In addition, candida albicans could not be detected in 5 patients, and the ruptured debris of mycelia from the death of candida were observed in 9 patients, while some viable spores and mycelia still survived in 2 patients.

Microbiological culture analysis of swabs from the urogenital tract, for the viability of the microflora was also done on Day-10 after start of therapy. Trichomonas vaginalis could not be cultured in 9 patients but were still viable in 7 patients. Candida albicans could not be cultured from 10 patients and were still present in 6 patients. In 11 of 16 patients, elimination of the candida-trichomonas double infection was achieved after 10 days.

The 5 other patients who still had viable candida-trichomonas double infection, were patients who had been chronically infected with candida & trichomonas for 4 to 5 years. In these patients, oral HEP-1 (Gepon) solution treatment was repeated and combined with anti-fungal and 5-nitro-imidazol treatment. In 4 of these 5 patients, the total elimination of the candida-trichomonas double infection of the urogenital tract was achieved. Only in one patient was the result unknown, because the patient stopped attending the clinic after moving from Moscow.

Clinical Trial No. 6

HEP-1 (Gepon) treatment of Trichomonas vaginalis & Candida co-infection in 12 men

A further clinical analysis was done to confirm the efficacy of HEP-1 (Gepon) monotherapy as an effective treatment for mixed Trichomonas vaginalis and Candida infection, in another 12 men. The study was performed at the Department of Dermatology and Venerology of Russian Medical Academy of Postgraduate Study, Moscow. The principal investigator was Professor E.A Batkaev, MD and assisted by Dr. D.V Ryumin, MD [23].

12 male patients (19 to 48 years old) were selected because they were diagnosed with candida-trichomonas co-infection of the urogenital tract. The duration of infection in this group was from 3 months to 5 years and was confirmed by PCR and microbiology. Prior to recruitment into the study, all patients were screened by PCR and serum antibody tests to eliminate other co-infections. In the group of 12 male patients there was no evidence of Chlamydia trachomatis, nor Mycoplasma hominis, nor Mycoplasma genitalium, nor Neisseria gonorrhoeae, nor Ureaplasma urealyticum, nor Herpes simplex virus, nor Cytomegalovirus.

Microbiological analysis of the microflora of the urogenital tract was performed prior to therapy, which confirmed candida-trichomonas vaginalis co-infection in all 12 patients. On Day-1 Day-3 and Day-5 of the treatment period, 2mg HEP-1 (Gepon) in 5mL water solution was administered orally, held in the mouth for a few minutes for mucosal absorption, then swallowed. On Day-2 or Day-3 patients noted a significant decrease or complete disappearance of painful urination, itching in the urethra and a significant decrease in inflammation of the glans of the penis.

On Day-7, after the end of therapy, as a result of HEP-1 (Gepon) treatment: four patients no longer had trichomonas in their urethra, and samples from seven other patients revealed ruptured dead trichomonas. Microbiological culture confirmed that Trichomonas had been eliminated in eight patients. In addition, in three patients candida could no longer be detected, and in seven patients only numerous small fragments of mycelia from the ruptured fungus were present, while in two patients there were still some viable candida cells and mycelia. Microbiological culture confirmed that Candida had been eliminated in nine patients. One of the twelve patients did not respond to HEP-1 (Gepon) therapy. At the end of the HEP-1 (Gepon) treatment period, regardless of the results of clinical and laboratory assessment, all patients were given standard therapy according to generally accepted treatment schemes.

A one month follow up using microscopic, culture and PCR diagnostic methods showed that 10 of 12 patients had cleared both candida infection and trichomonas infection. There were no side effects nor adverse events as a result of the HEP-1 (Gepon) therapy (Figure 3).

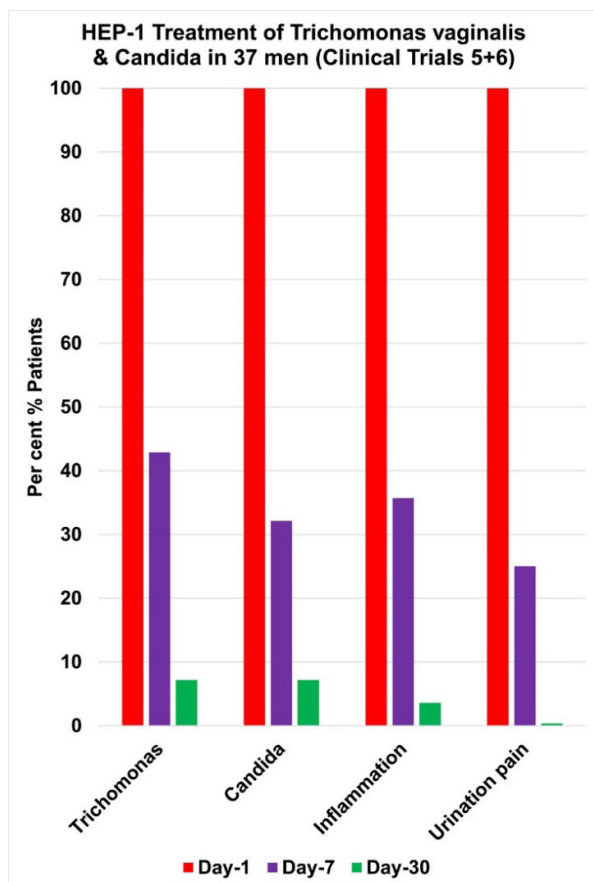


Figure 3: Combined results of Clinical Trial 5 (16 men) and Clinical Trial 6 (12 men), a total 37 men after one drop-out, treated by HEP-1 (Gepon) for mixed Trichomonas vaginalis and Candida infection revealing the efficacy on Day-1 and Day-30 after commencement of treatment, expressed as the per cent of 37 patients positive for Trichomonas and candida, and the main symptoms of inflammation and urination pain.

Clinical Trial No. 7

HEP-1 (Gepon) treatment of Chlamydia trachomatis in 68 women

Chlamydia infection is particularly dangerous in pregnant women and can cause pregnancy complications such as placental insufficiency, intra-uterine hypoxia, foetal malnutrition and premature birth. Chlamydia Trachomatis plays a significant role in fallopian tube sterility. New-borns from infected mothers have a greater risk of developing congenital pneumonia and conjunctivitis. Effective pre-treatment of urogenital chlamydia infection, should be performed before conception & pregnancy for optimal prevention of these complications.

Despite the use of antibiotics like azithromycin and doxycycline for Chlamydia trachomatis infection, which both have significant side-effect problems, anti-microbial treatment only temporarily suppresses intracellular chlamydial infection, which can still persists and periodically re-surface. There is a growing problem with drug-resistant strains of Chlamydia trachomatis. Effective adaptive T-cell immunity with active CD4+ T-cells is essential to clear this infection. HEP-1 (Gepon) acts locally on mucous membranes and also systemically via secondary signalling, to induce amplification of B-cell and T-cell adaptive immunity, while inhibiting innate immunity mediated inflammation [24,25].

In late 2003 and 2004, 68 women with chronic chlamydia infection were recruited at the Siberian State Medical University in Tomsk, by the Principal Investigator Prof A A Radionchenko and his colleagues, for a new treatment protocol using HEP-1 (Gepon) intra-vaginal therapy in combination with standard oral azithromycin antibiotic therapy. The HEP-1 (Gepon) plus azithromycin treatment was compared with Polyoxidonium (a cheap Russian synthetic immune-stimulating polymer administered as a rectal suppository) plus azithromycin [26].

The initial inclusion criteria for the clinical study were women between 18 and 50 years old with chronic urogenital chlamydia infection with disease duration of at least two months. The exclusion criteria from this clinical study were any patients suffering severe somatic and venereal diseases, acute respiratory viral infection or narcotic drug use.

Diagnosis of urogenital chlamydia was established by three methods: direct immunofluorescent microscopy with monoclonal antibodies to Chlamydia trachomatis, using “Chlamyslide” (NPF “Labdiagnostika” Moscow); an enzyme immunoassay using the “ChlamyBest C trachomatis IgG” test system (CJSC Vector Best, Koltsovo, Novosibirsk region); and by using the Polymerase Chain Reaction (PCR) Amplisense Chlamydia trachomatis Kits (Research Institute of Epidemiology of the Ministry of Health of the Russian Federation, Moscow)”.

A large patient group of 214 women (n=214) between 19 and 47 years old, were recruited and randomly allocated to three different treatment groups: 68 women to HEP-1 (Gepon) plus azithromycin

treatment (the HEP-1 Group), and 146 women to the rectal suppository Polyoxidonium plus oral azithromycin treatment (The Polyoxidonium Group).

The Gepon (HEP-1) treatment group (n=68) received the Gepon treatment scheme over seven days. On Day1, Day3, Day5 and Day7 (every other day), the vagina of each patient was treated as follows: 0.1 mL 1mg/mL Gepon solution was used to syringe-wash (no needle) their urethra, and a dry vaginal tampon was inserted by the patient, then soaked by the nurse with 0.9 ml of a 1mg/mL Gepon solution. The tampons were removed after 2 to 12 hours by the patients. The total course of treatment was 4mg Gepon as a 1mg/mL solution given in four treatments over seven days. In combination with Gepon (HEP1) treatment patients received azithromycin (Pliva), 1g by mouth on Day1, Day7 and Day14 (the total course of treatment was 3g azithromycin).

The effects of combination therapy were evaluated clinically and in the laboratory. The cytological and bacteriological microscopic examinations of vaginal and urethral smears, and Pre Implantation Factor (PIF) tests for pregnancy were performed prior to start of treatment and 10 days after the start of treatment. Statistical analysis of the results was undertaken using StatSoft Statistica 5.0 to evaluate the significance of the results.

Results of the Study

The Gepon Group of women patients (n=68), who obtained HEP-1 (Gepon) were all highly appreciative of the efficacy and completeness of this novel immunological therapy. There were no allergic reactions nor complications. Patients were impressed by the painless local topical treatment of the mucosa of the vagina and urethral wash, the short course of treatment; approximately every-other day over seven days, which rapidly yielded very positive results (Figure 4).

On Day-1 of treatment, abdominal pain stopped completely in the majority of patients and painful urination disappeared during the following week of treatment, together with all pathological vaginal secretions and vulva-vaginal & peri-anal itching. Efficacy of HEP-1 (Gepon) combination therapy in treating chlamydia infection was such that patients considered themselves cured: 6 patients did not attend the Day-10 follow-up, and 13 patients did not attend their one month analysis appointment.

62 of 68 patients attended the Day-10 analysis appointment. There was a general improvement in symptoms: general abdominal pain that had been present in 47 of 68 women before treatment, was only present in 7 of 62 Day-10 attendees; urination pain that had been present in 30 of 68 women before treatment, was only present in 1 of 62 of the Day-10 attendees; pathological leucorrhoea that had been present in 61 of 68 women before treatment, was only present in 20 of 62 of the Day-10 attendees; and endo-cervicitis that had been present in 34 of 68 women before treatment, was only present in 12 of 62 of the Day-10 attendees, of the 62 patients attending the Day-10 analysis

appointment: leukocyte infiltration that had been present in 56 of 68 women before treatment, was only present in 18 of the 62 of the Day-10 attendees; cytoplasmic vacuolization that had been present in 42 of 68 women before treatment, was only present in 31 of 62 of the Day-10 attendees; cytolysis that had been present in 61 of 68 women before treatment, was only present in 26 of 62 of the Day-10 attendees; and tissue damage that had been present in 46 of 68 women before treatment, was only present in 7 of 62 of the Day-10 attendees.

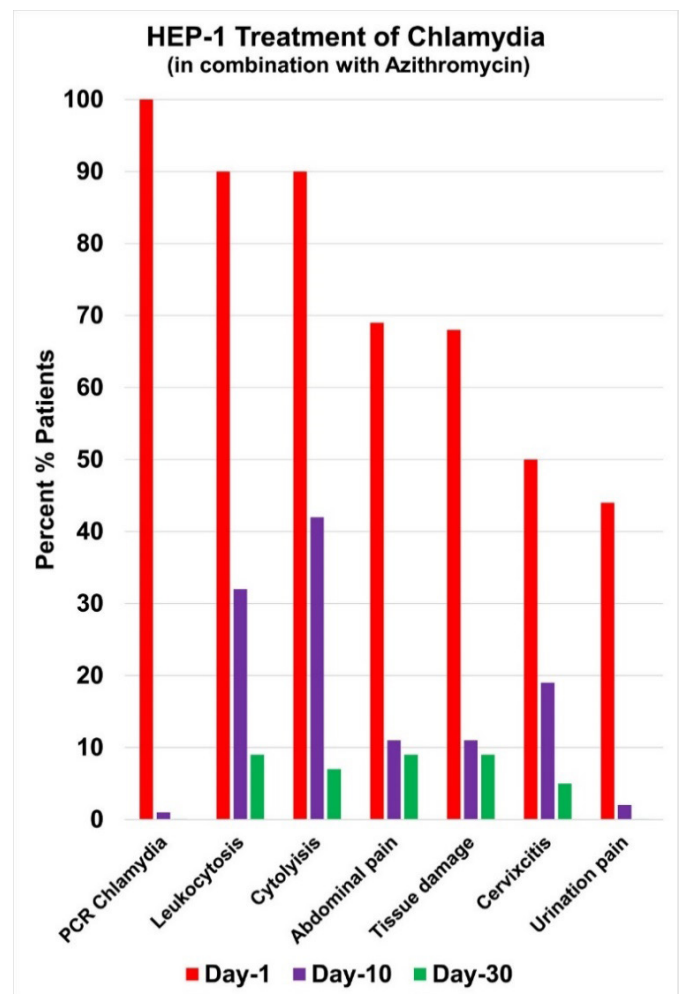


Figure 4: Intra-vaginal (HEP-1) treatment of 68 women with chronic chlamydia infection during 7 days combined with azithromycin (Pliva) therapy over 14 days. Chlamydia PCR diagnosis showed the treatment essentially eliminated chlamydia by Day-7 and led to significant progressive reductions in the symptoms of chlamydia infection over thirty days.

Laboratory analysis confirmed the positive symptom changes felt by patients and observed in the clinic. Changes in the epithelium of the cervical canal were analysed before and after Gepon treatment. In most cases, the disappearance of cytological signs of inflammation in the epithelium of the cervical canal was observed on Day-10. Analysis of the results revealed that patients who

still had clinical manifestations of infection and corresponding inflammatory markers, had actually cleared their chlamydia infection, but were still infected with other drug-resistant microorganisms that were insensitive to azithromycin.

55 of 68 patients attended the Day-30 analysis appointment. They showed further signs of recovery: general abdominal pain that had been present in 7 of 62 of the Day-10 attendees, was only detected in 5 of 55 of the Day-30 attendees; urination pain that had been only present in 1 of 62 of the Day-10 attendees, was not detected in any of the 55 of the Day-30 attendees; pathological leucorrhoea that had been present in 20 of 62 of the Day-10 attendees, was only detected in 5 of 55 of the Day-30 attendees; and endo-cervicitis that had been present in 12 of 62 of the Day-10 attendees, was only detected in 3 of 55 of the Day-30 attendees.

The 55 patients attending the Day-30 analysis appointment, showed further signs of recovery: leukocyte infiltration that had been present in 18 of 62 Day-10 attendees, was only detected in 8 of 55 Day-30 attendees; cytoplasmic vacuolization that had been present in 31 of 62 Day-10 attendees, was only present in 18 of 55 Day-30 attendees; cytolysis that had been present in 26 of 62 Day-10 attendees, was only detected in 4 of 55 Day-30 attendees; and tissue damage that had been present in 7 of 62 Day-10 attendees, was only detected in 5 of 55 Day-30 attendees.

The most remarkable result was that PCR detection of chlamydia on Day-10 revealed that samples from the 62 patients who attended the clinic (91.2% of the original group of 68 women), chlamydia infection was only detected in one patient after Gepon (HEP-1) treatment. Gepon had eliminated parasitic chlamydia infection in 98.4% of the women in the Day-10 Gepon Group. This was further confirmed by PCR that Gepon (HEP-1) had eliminated chlamydia in 54 of 55 patients tested on the Day-30 follow-up analysis, which was attended by only 55 patients (80.9% of the original group of 68 women). The one treatment failure represented only 1 of 55 patients (1.8%). It was also highly probable all non-attendees of the Day-10 and Day-30 appointments were all symptomless so considered themselves cured and had probably cleared their chlamydia infections too.

Polyoxidonium Group patients generally had some improvement in their condition and in the first 10 days, pelvic pain and urination pain disappeared in the majority of patients. However the efficacy was much less obvious than that of HEP-1 (Gepon). The clinical trial demonstrated the significant efficacy of the combination of HEP-1 (Gepon) therapy with azithromycin antibiotic therapy, in the treatment of chronic chlamydial urethritis.

A Clinical Example

Gepon (HEP-1) Success, Over Earlier Failures of Treatment of Chronic Chlamydia

Patient E, a 30 year old woman, came to the clinic at the Siberian State Medical University in Tomsk in November 2002, for an effective treatment of chronic recurrent urogenital chlamydia.

Her chronic urogenital chlamydiosis was first discovered in year-2000 during her pregnancy. At 22 weeks gestation, a course of treatment with a macrolide antibiotic (azithromycin) and Viferon were carried out.

Unfortunately, the infection and treatment resulted in a late spontaneous miscarriage at 27 weeks of gestation. At the follow-up examination, after pregnancy & miscarriage, chlamydial infection was again detected. Subsequently, another "5(1)" course of treatment was carried out using the combination of tetracycline antibiotics, macrolide antibiotics (including azithromycin) and fluoroquinolones. Interferon inducers were twice used as immune-stimulants. The aggressive therapy was ineffective and clinical examination confirmed the persistence of urogenital chlamydia. The patient had no severe somatic pathology but her main complaint was a moderately severe abdominal pain syndrome and periodic dysuria (painful urination). She also had had a history of treatment of trichomoniasis ten years earlier.

In February 2003, a new treatment scheme was tried using the novel anti-inflammatory & adaptive-immunity-amplifier called "Gepon", Human Ezrin Peptide One (HEP-1) produced by Immapharma Ltd in Moscow. On Day1, Day3, Day5 and Day7 (every-other day), the vagina of this infected woman was treated as follows: 0.1 ml 1mg/mL Gepon solution was used to syringe-wash (no needle) the urethra, and a dry vaginal tampon was inserted by the patient, then soaked by the nurse with 0.9 ml of a 1mg/mL Gepon solution. The tampons were removed after 12 hours by the patient. The total course of treatment was 4mg Gepon applied over seven days as a 1mg/mL solution. The Gepon treatment was given in combination with azithromycin (Pliva) according to the recommended scheme of 1 mg, once a week on Day1, Day7 & Day14 (a total amount of 3 mg over the course of treatment). No adverse reactions nor complications were observed during the Gepon / azithromycin therapy. In March 2003, the patient was pronounced by PCR, free of any chlamydia infection and a full etiological recovery was confirmed & recorded.

Contraception was terminated in April 2003 and a healthy pregnancy occurred. The pregnancy proceeded without abnormalities. Ultra-sound examination at 12 weeks, 22 weeks and 34 weeks of gestation were all normal, as were the levels of placental & maternal serum proteins in the second and third trimesters. The pregnancy ended with the delivery of a healthy boy of 3.6Kg, height 53cm in January 2004. Examination of the new born boy for sexually transmitted infections confirmed the absence of chlamydial infection.

Conclusion

HEP-1 (Gepon) plus azithromycin combination therapy, resulted in the cure of 98% of women suffering from chronic Chlamydia infection.

Ezrin Peptide HEP-1 (Gepon) Treatment of Genital Herpes Virus Infection (HSV-1 & HSV-2)

There are no pharmaceuticals that eliminate HSV from the human body. The main task of anti-viral treatment is to reduce severity, extent & duration of outbreaks of herpes lesions, to reduce the time to heal lesions, and to prevent transmission & infection of HSV to a sexual partner, or new born baby. Current anti-viral therapies have no effect on the rate of relapse of further outbreaks of herpes lesions nor on the duration of symptomless remission.

HEP-1 (Gepon) is unusual in that it has intra-cellular & inter-cellular biological activities that work in tandem to inhibit the life cycle of herpes simplex viruses HSV-1 and HSV-2. HEP-1 (Gepon) not only induces direct inhibition of viral replication in infected cells, probably by the induction of alpha & beta interferon expression and inhibition of pro inflammatory cytokine expression, it also enhances B-cell activity and amplification of the synthesis of antibodies, and increases the activity of NK cells that clear virally infected cells, and increases the activity of antigen presenting monocytes and macrophages, which builds an effective collective immunological defence by general amplification of B-cell and T-cell adaptive immunity against HSV.

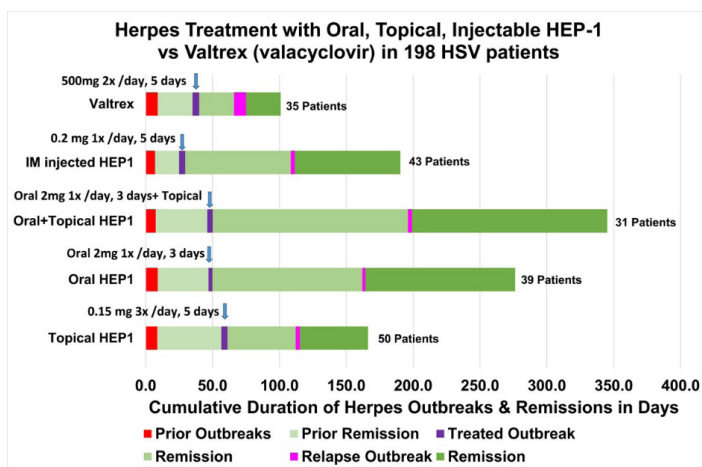


Figure 5: A summary of the results of HSV clinical trials (trial numbers: 8, 9, 10, 11, 12 & 13) with HEP-1 Gepon in four different administration protocols (IM injected, Oral+Topical, Oral alone, and Topical alone), compared with the anti-viral Valtrex (valacyclovir). Efficacy is expressed as mean duration in days of mean prior herpes outbreaks and prior mean remission before treatment, duration of treated outbreak, followed by duration of mean remission, durations of herpes relapse outbreaks, and mean remission. “Valtrex control group” (35 patients of Clinical Trial 13b received a 2x500mg/day course of valacyclovir for 5 days. “IM injected HEP-1 group” (43 patients of Clinical Trial 8 received a 2mg HEP-1 course for 5 days). “Oral+Topical HEP1 group” (31 patients of Clinical Trial 10b & Clinical Trial 12a received either a 6mg or a 10mg course of Oral+Topical HEP-1, for 3 days or 5 days). “Oral HEP1 group” (39 patients of Clinical Trial 11 & Clinical Trial 13a treated with either 10mg or 20mg course of oral HEP-1 2mg/day for 5 days or 10 alternate days). Topical HEP1 group (50 patients of Clinical Trial 9+Clinical Trial10a treated a 2mg course of

HEP-1 in 6g cream base only). The figure is drawn for easy comparison of the efficacy of Valtrex and the efficacy of different HEP-1 treatment protocols: more details of each clinical trial are in the following text. Note the variation in the duration of mean prior herpes outbreaks and prior mean remission before treatment, depended on the average clinical characteristics of the randomly selected HSV patient groups.

The efficacy of HEP-1 (Gepon) treatment of herpes virus infection (HSV-1 & HSV-2) was initially demonstrated in *in vitro* experiments and animal studies. For example, in vero cell culture, HEP-1 (Gepon) in the concentration 6 µg/mL, introduced 24 hours prior to HSV-1 culture infection, led to a one hundred fold reduction in the titre of virus [27]. In a mouse lethal herpes infection model, of mice infected intraperitoneally with HSV-2, HEP-1 (Gepon) solution injections at doses of either 0.1 µg or 1 µg per mouse, provided a protective immunological effect that increased the average life expectancy of the HEP-1-treated lethally infected mice by two days more than the untreated-control lethally infected mice [28]. A number of clinical trials in patients suffering chronic recurrent genital herpes disease demonstrated the safety and efficacy of HEP-1 (Gepon) treatment [29].

HEP-1 (Gepon) monotherapy, and in combination with antiviral therapy, is used to treat sexually transmitted herpes virus infection, both as an internal systemic treatment and as a local topical treatment. For oral systemic treatment of HSV-1 and HSV-2, 2mg HEP-1 (Gepon) is dissolved in 5mL water and held in the mouth for at least three minutes for mucosal adsorption and then swallowed. The short course of treatment is usually performed on Day-1, Day-3 and Day-5 (a total of three treatments using a total of 6mg HEP1).

For topical treatment of herpetic infected mucosa, HEP-1 (Gepon) is prepared as a solution of 2 mg in 5 ml in 0.85% NaCl saline, and a 5ml syringe (no needle) is used to irrigate the infected mucosa of the vulva, vagina and urethra on Day-1, Day-3 and Day-5. The same solution can be applied to the penis glans under the foreskin or using a gauze soaked in the solution, applied to the penis glans. For topical treatment of herpes skin lesions, HEP-1 (Gepon) is also blended with a cream base (2mg HEP-1 2g water, 2g lanolin 2g olive oil) and applied to the herpes lesions 3 to 5 times per day.

Intramuscular injections (IM) of HEP-1 Gepon are also used for local and systemic treatment of HSV-2 chronic recurrent herpes disease. 2mg pharmaceutical grade HEP-1 (Gepon) manufactured by Immapharma Ltd (Moscow) is dissolved in 2mL 0.85% NaCl saline. HSV-2 patients are treated once a day with one intramuscular injection of 0.2 mg HEP-1 (Gepon) in 0.2mL saline, once a day for five days, starting at the initial day of a herpes outbreak. The same treatment protocol is used for local and systemic treatment of Herpes Zoster.

Comparison of various protocols of HEP-1 Gepon therapy vs Valtrex is shown in Figure 5 above and details of each clinical trial are provided below.

Clinical Trial No. 8

HEP-1 (Gepon) treatment by IM injection of 28 women & 15 men with HSV-2

During 2001 and 2002, a two-centre clinical study of HEP-1 (Gepon) treatment of patients with recurrent genital HSV infection was performed as a collaboration between The Kursk Medical University and The Moscow Friendship of Peoples University, to investigate the safety and efficacy of once a day intramuscular injection of 0.2 mg HEP-1 (Gepon) in 0.2mL 0.85% NaCl saline, for five days. The patients received no other systemic or topical therapies during the treatment and post-treatment period of observation.

Patients provided written informed consent and were enrolled in early 2001. Pregnant and breast-feeding women, as well as those who had received immunomodulator therapy in the preceding 3 months or antiviral therapy within 2 weeks, were excluded from this study. A group of forty three patients (28 women and 15 men), aged between 19 and 49 years old, with recurrent genital herpes (with durations of infection between one and ten years) confirmed by PCR and serology to be HSV-2, participated in the clinical trial between April 2001 and February 2002.

All 43 patients had previous treatment using oral antiviral agents such as acyclovir, valacyclovir or famcyclovir. Most (31 of 43) of the patients had also used topical antivirals such as 5% acyclovir ointments or alpha-interferon in their past. Twenty three patients were previously receiving inducers of interferon synthesis (Amixin or Cycloferon or Ridostin) as a part of combination therapies. Previous therapy had not prevented the chronic recurrent herpes lesions.

Prior to treatment, the subjects had had recurrences of HSV-2 symptoms that varied from 6 to 13 (a mean of 8) episodes over the previous 6 months, that lasted between 5 to 12 days (a mean of 7). The remission intervals for the patient group varied from 12 to 25 days (a mean of 18 days).

The design of the open clinical study was to assess the treatment efficacy of injected HEP-1 (Gepon) monotherapy for the inhibition of recurrence of herpes lesions. In addition the duration of healing of herpes lesion during the treatment, as well as duration of post-treatment remission periods were compared with the pre-treatment history of each patient. Patients attended the clinic once a day during the treatment period, and then returned to the clinic for control observations at one month, three months and five months after the end of treatment. All patients who suffered any post-treatment recurrence of herpes lesions were requested to come to the clinic for evaluation.

All subjects entered into the study with recurrent ano-genital herpes lesions, which were less than 24 hours old and had not progressed to the ulcer stage. The lesions were either erosion (27 patients) or vesicles/pustules (21 patients), which later evolved into the re-epithelisation phase. In most of the patients, the lesions were surrounded by inflamed skin with characteristic reddening

(38 patients) and swelling-oedema (38 patients). Each locus of damaged skin was of 1-3 cm² in size and contained 3-20 elements of vesicle/pustule or erosion. Eight patients had between 6 and 3 loci of herpes lesions each, 6 patients had 2 loci of herpes lesions each, while only one locus was found on the remaining 29 patients studied. In 15 of 43 patients, the local skin lesions were accompanied by the swelling and pain of the inguinal lymph nodes in the groin, which was recorded as lymphadenitis. Symptoms of inflammation of the cervix were found in 2 women of the group.

At entry into the clinical trial, all 43 patients felt a discomfort in the region of their genitals, and most complained of a burning sensation (42 patients) and itching (42 patients). Lesions were painful in only 3 patients. Ten patients felt nausea, three patients complained of weakness and four patients had fever during the herpes outbreak.

2mg lyophilised sterile HEP-1 (Gepon) manufactured by Immapharma Ltd, Moscow (now a subsidiary of www.avexima.ru) was dissolved in 2mL 0.85% NaCl saline. Each patient was administered an intramuscular injection of 0.2 mg HEP-1 (Gepon) in 0.2mL 0.85% NaCl saline in the thigh, once a day for 5 days, starting on the initial day of entry into the clinical trial with a fresh outbreak of genital herpes.

Thirty eight of 43 patients (88%) responded rapidly and positively to HEP-1 (Gepon) treatment by IM injection therapy. There was a rapid disappearance of symptoms of inflammation (oedema or erythema) of the skin around the herpes lesions in a few hours after the first injection, due to HEP-1 suppression of pro-inflammatory cytokine expression.

Most of the patients noticed a rapid disappearance of pain, burning and itching symptoms within 24 hours of the first injection of HEP-1 (Gepon). In all 43 patients, the rate of lesion healing was significantly increased, so that the mean time for complete healing was only 4.5 days, during the period of HEP-1 (Gepon) treatment, compared to the mean healing period of 7 days before treatment. In addition ulcers failed to form during HEP-1 (Gepon) therapy, the vesicle & pustule elements regressed rapidly, and erosion was covered by epithelium more quickly than before treatment. In those patients who had systemic symptoms of fever, weakness or nausea before the treatment, one to two days after the first injection of HEP-1 (Gepon), all these symptoms disappeared.

During the post-treatment period of 5 months after HEP-1 (Gepon) treatment, there was a significant prolongation of remission from herpes outbreaks. Genital herpes outbreaks were postponed by a mean of 79 days of remission, compared to a mean 18 days before the treatment, a 4.4X increase in the duration of remission. Thirty five of 43 patients (80%) responded to HEP-1 (Gepon) treatment by an increase in duration of remission. The mean number of recurrences occurring in patients was greatly reduced from a mean recurrence of 8 episodes in the 6 months before treatment, to a

mean recurrence of 1.9 episodes in the 5 months following HEP-1 (Gepon) treatment.

When a herpes outbreak recurrence finally re-emerged long after HEP-1 (Gepon) therapy, the local and systemic symptoms were very significantly reduced. In each patient that responded to therapy, the size and number of herpes lesion loci were reduced: for example, 3 loci of 2 cm² each before the treatment, re-emerged as 1 locus of 1 cm². The number of elements (vesicle, pustule, erosion) were also much less than before the treatment, and in many cases failed to develop. No herpes ulcer was recorded during a post-treatment recurrence. In the majority of cases, no pain, no burning nor itching was reported by patients.

The clinical trial demonstrated that HEP-1 (Gepon) therapy by 5 consecutive once-a-day IM injections with 0.2mg HEP-1 (Gepon), was a highly effective treatment during the acute phase of a herpes outbreak, and substantially extended the duration of remission from further symptoms of genital herpes outbreaks [30].

Clinical Trial No. 9 **HEP-1 (Gepon) Cream for local topical treatment of 24 herpes patients**

The topical use of HEP-1 (Gepon) cream (2mg HEP-1 2g water, 2g lanolin & 2g olive oil), for the treatment of herpetic lesions was originally investigated in a small number of individual patients at the Department of Skin and Venereal Diseases of the Kursk State Medical University, by Principal Investigator Dr T Bibicheva, supervised by Prof. L Silina. HEP-1 (Gepon) cream was applied to the HSV lesions on the skin and mucous membranes 5 times a day for 5 days. Within a few days, the treatment resulted in a disappearance of pain, itching and burning of herpes lesions and significantly extended the period of remission.

A clinical trial to investigate the HEP-1 (Gepon) Cream for local topical monotherapy treatment of genital herpes was performed at The Russian Medical Academy of Post-Graduate Research, Moscow, by the Principal Investigator Dr I Shakov. 24 patients (14 men and 10 women, 23 to 62 years old), suffering chronic recurrent genital herpes, were recruited for the study. The patient group had a mean remission period of 1.5 to 2 months, 6+ relapses per annum, with mean duration of outbreak between 8 to 10 days.

All patients passed clinical examination and a PCR diagnostic test confirmed either HSV-1 or HSV-2 infection. The patients were also screened for syphilis, gonorrhoea, Trichomonas, Chlamydia, Mycoplasma, urogenital candida and confirmed free of these STIs. HEP-1 (Gepon) Cream was prepared, by dissolving 2mg HEP-1 (Gepon) in 2mL water, then blending it with 2g lanolin and 2g olive oil to make 6g of cream. HEP-1 (Gepon) Cream was applied as a thin layer on to the herpetic lesions of the skin, three times per day, from the first day of a herpes outbreak.

The efficacy of HEP-1 (Gepon) Cream for local topical treatment monotherapy was obvious: the herpes outbreak duration declined

from a weighted mean of 8.3 days to 4.6 days and the remission period more than doubled from a weighted mean of 7.3 weeks to more than 16 weeks. HEP-1 (Gepon) Cream terminated inflammation, accelerated healing of herpetic damage and stimulated re-epithelization. HEP-1 (Gepon) Cream also decreased the severity of clinical manifestations of the subsequent herpes outbreaks [31].

Clinical Trial No. 10 **Topical only vs Oral & Topical HEP-1 (Gepon) treatment of 35 HSV-2 patients**

During 2002 and 2003, a clinical trial at the Clinic of the Department of Dermatology and Venerology, Russian Medical Academy of Postgraduate Study, Moscow, by Professor E.A.Batkaev, MD, in collaboration with Dr D.V.Ryumin MD and Dr I.M. Shakov MD, in 35 patients with chronic-recurrent HSV-2 infection, was performed to assess the benefits of oral-topical or topical-only HEP-1 (Gepon) therapy in HSV patients, in the absence of other co-infections. In the clinical trial pre-screening, the majority of the assessed patients had to be excluded from the study after they were found to be co-infected with other STIs, for example syphilis, or gonorrhoea, or trichomonas, or chlamydia, or mycoplasma, or urogenital candida.

The 35 patients (23 men, and 12 women, from 22 to 63 years old) with simple chronic-recurrent genital herpes (HSV-2) only, who had been under observation at the clinic, had a mean duration of remission of 1.7 months, a relapse frequency of more than six outbreaks per annum, with a duration of outbreak between 8 to 10 days. All patients passed through clinical inspection, which included swabs from the membranes of the uro-genital tract and any secretions from lesions. The identification of herpes simplex virus as type 1 or type 2 was confirmed by polymerase chain reaction assays (PCR). Patients with other sexually transmitted co-infections were excluded from the study.

The patients were divided into two groups to assess the benefits of different protocols of HEP-1 (Gepon) Treatment: 26 patients were randomly assigned to the “HEP-1 topical Cream Group”; and 9 patients were randomly assigned to the “HEP-1 oral & topical Solution Group”.

The 26 patients of the “HEP-1 topical Cream Group” received a cream of 2mg HEP-1 (Gepon) blended with 2g water, 2g lanolin 2g olive oil, to form a cream of 0.033% HEP-1 by weight, which was applied to any herpes lesions, three times per day, for the duration of any herpes outbreak.

The 9 male patients of the “HEP-1 oral & topical Solution Group” received a solution of 2mg HEP-1 (Gepon) in 5ml sterile water (0.04% HEP-1 by weight), which was used to moisten any herpes lesions (three times per day) for the duration of an outbreak, and also held in the mouth for a few minutes then swallowed, once a day, for three days.

As a result of the treatment of the 26 patients (14 male and 12 female patients) of the “HEP-1 topical Cream Group”, the duration

of the outbreaks halved from 8 to 10 days before the treatment, to 4 to 5 days after treatment and the post-treatment outbreaks were clinically less significant. However, there was no change in the relapse frequency of outbreaks over the 12 months following treatment, which remained unchanged at more than six times per annum.

As a result of the treatment of the 9 patients of the “HEP-1 oral & topical Solution Group”, the duration of an outbreak was halved from 8 to 10 days before the treatment, to 4 to 5 days after treatment and the post-treatment outbreaks were clinically less significant. In contrast to the Cream Group, the frequency of outbreaks over the 12 months following treatment, decreased 3X times, revealing the benefit of systemic treatment with oral 2mg HEP-1 (Gepon) in 5ml sterile water solution (0.04% HEP-1 by weight) [32]. However, this Clinical Trial No.10 contradicted Clinical Trial No.9, where HEP-1 (Gepon) cream monotherapy alone had extended the remission period from herpes outbreaks.

Clinical Trial No. 11

18 day HEP-1 (Gepon) oral treatment of 16 HSV-2 patients

Principal Investigator Dr T Bibicheva, supervised by Prof. L Silina, performed a further clinical experiment of systemic treatment of HSV-1 and HSV-2, using a orally administered HEP-1 (Gepon) given over a longer treatment period of 18 days. 16 patients with a current outbreak of chronic recurrent genital herpes were recruited and gave their informed consent to participate in the clinical study. Oral HEP-1 (Gepon) monotherapy comprised of a course of treatment in which 2mg HEP-1 (Gepon) was dissolved in 5mL water, held in the mouth by the patient for approximately three minutes for mucosal adsorption, and then swallowed. Treatment was taken approximately every other day for 18 days, with treatments on Day-1, Day-2, Day-4, Day-6, Day-8, Day-10, Day-12, Day-14, Day-16 & Day-18, a total of 10 treatment days, and a total of 20mg HEP-1 (Gepon).

The follow-up analysis was performed 4 months after treatment Day-1. All 16 patients had enjoyed positive results in response to the 18 day course of HEP-1 (Gepon) oral systemic treatment. Generally, oral HEP-1 (Gepon) monotherapy terminated the herpes outbreak in two to three days, the duration of any subsequent relapses decreased to a duration of two to four days, and the duration of average clinical remission lengthened by a mean of 2.5x. However, there was no significant difference in efficacy between the long 18 day HEP-1 (Gepon) treatment period and the short 3 day treatment period of the previously described Clinical Trial No. 10 [33].

Clinical Trial No. 12

3-day oral-systemic & Topical HEP-1 (Gepon) treatment of 22 HSV women compared to continuous 8 month plus 6 month Valtrex therapy

In 2004, a Clinical Trial of HEP-1 (Gepon) treatment of genital herpes in 42 women was performed at The Scientific Centre of Obstetrics, Gynaecology and Perinatology, Russian Academy of Medical Sciences, Moscow by the Principal Investigators: Dr L

Marchenko, Dr I Lushkova and Prof A Shurshalina [34].

42 women suffering a severe form of recurrent genital herpes (at least six herpes outbreaks per year), who were attending the clinic of The Scientific Centre of Obstetrics, Gynaecology and Perinatology of the Russian Academy of Medical Sciences, Moscow, were informed of the known safety and efficacy of HEP-1 (Gepon), and they gave their informed written consent to participate in a clinical study of HEP-1 (Gepon) treatment. All patients received a medical examination before the start of the clinical trial.

With each patient, Day-1 of treatment was assigned to the commencement of an appearance of herpetic lesions. Efficacy of treatment was assessed by: The Mean Duration of Outbreak in days; Mean Recurrence Rate per month, and the Mean Duration of Remission in days. The duration of the clinical trial was 6 months. All patients provided samples from the foci of herpetic lesions and discharge from the urogenital tract before therapy, for confirmation of the presence of HSV-1 or HSV-2 by PCR diagnostic testing.

22 women were assigned to the Gepon Group, and their average age was 32 ± 2.4 years. The patients had not received any therapy for genital herpes in the prior four months. Before treatment in the Gepon Group, the Mean Recurrence Rate of genital herpes outbreaks was 0.66 ± 0.05 relapses per month, the Mean Duration of Outbreak of genital herpes was 5.9 ± 0.5 days and the Mean Duration of Remission was 26.5 ± 7.2 days.

20 patients were assigned to the control Valtrex Group, and their average age was 28 ± 1.5 years. The women of the control Valtrex Group had been continuously receiving “Valtrex” (valacyclovir) 500 mg a day, every day for 8 months prior to the commencement of the study and continuously for 6 months from Day-1 of the commencement of the study. Before treatment in the Valtrex Group: the Mean Recurrence Rate of genital herpes was 0.54 ± 0.05 relapses per month; the Mean Duration of Outbreak of genital herpes outbreaks was 4.8 ± 0.72 days; and the Mean Duration of Remission was 33.2 ± 6.2 days.

By the three measures of severity of herpes disease (Mean Recurrence Rate, Mean Duration of Outbreak, Mean Duration of Remission) the women of the Gepon Group (untreated for genital herpes prior to the trial) were suffering more severe clinical herpes, compared to the Valtrex Group who had been treated with 500 mg a day valacyclovir.

The women of the Gepon Group received both HEP-1 (Gepon) oral therapy and HEP-1 (Gepon) topical therapy as follows: Oral; 2mg HEP-1 (Gepon) dissolved in 5mL water, held in the mouth for 5 minutes for mucosal adsorption then swallowed on Day-1, Day-2 and Day-3; Topical; 2mg HEP-1 (Gepon) blended with 6g standard cream base (2g lanolin; 2g olive oil, 2g distilled water) and applied to herpetic lesions during any outbreak for the duration of the study.

Results

Assessment of the Gepon Group at the Follow-Up appointment, six months after Day-1 of treatment, revealed that HEP-1 (Gepon) treatment had significantly extended Mean Duration of Remission to 142 days, which was +5.5X the duration of the Mean Duration of Remission of 26 days prior to treatment. HEP-1 (Gepon) significantly accelerated healing and epithelialization of herpetic lesions, and substantially reduced clinical manifestations with subsequent herpes relapses. In addition, HEP-1 (Gepon) Treatment had reduced the Mean Duration of Outbreaks of genital herpes from 5.9 days to 3.8 days and dramatically reduced the Mean Recurrence Rate of genital herpes outbreaks by minus 9X from 0.70 relapses per month to 0.08 relapses per month. This was evidence that HEP-1 (Gepon) Treatment had enhanced anti-HSV immunity in the Gepon Group of women.

In contrast, there were no significant changes in the Mean Recurrence Rate nor the Mean Duration of Remission in the control Valtrex Group. The Mean Duration of Outbreak of genital herpes was maintained around 5 days, which was significantly longer than the Mean Duration of Outbreaks of genital herpes of 3.8 days after HEP-1 (Gepon) treatment.

Clinical Trial No. 13

Severe recurrent HSV-2 untreated for at least 4 months: 5 days of oral-systemic HEP-1 (Gepon) therapy in 23 patients, compared with 5 days of oral-systemic Valtrex therapy in 35 Patients

A group of 58 patients chronically infected with HSV-2 were recruited, after being explained the safety and efficacy of both Valtrex & HEP-1 (Gepon), and the objective of the study to compare the therapies. All 58 HSV-2 infected patients had suffered severe genital herpes (both local and systemic symptoms of intoxication in 35 of 58 patients), for one to five years prior to the start of the study, but had not received any treatment for herpes in the previous four months. This patient group had been originally diagnosed with recurrent genital herpes from one year to fifteen years previously, and who had been suffering a severe form of HSV-2 genital herpes disease with outbreaks of 8 to 10 days long and remission not exceeding 30 days.

Of the 58 recruited patients: 23 sicker patients (22 with systemic symptoms of weakness, headache, poor cognition and fever) were allocated to 5 days of oral-systemic HEP-1 (Gepon) therapy (the Gepon Group); and 35 patients were allocated to 5 days of Valtrex therapy (the Valtrex Group). Only 13 of 35 patients of the Valtrex Control Group had symptoms of systemic intoxication such as weakness, headache, poor cognition and fever. Day-1 of therapy was commenced within one day of the appearance of an HSV genital herpes outbreak [35].

Five day Therapy of Gepon Group & Results

The Gepon Group consisted of 23 patients who received treatment with HEP-1 (Gepon) as follows: 2mg HEP-1 (Gepon) was dissolved in 5 mL of water, then delivered orally once a day for

five days. HEP-1 (Gepon) solution was held in the mouth for 5 minutes for mucosal adsorption then swallowed. For each patient, the first day of a herpes outbreak was assigned as Day-1 of the clinical trial for the start of HEP-1 (Gepon) treatment. The Gepon Group patients were observed from Day-1 for 180 days.

No side effects nor adverse events occurred with the treatment with HEP-1 (Gepon) solution. On Day-1, the Gepon Group patients all reported a rapid curing of a herpes outbreak in response to oral-systemic HEP-1 (Gepon) treatment. HEP-1 (Gepon) rapidly stopped all local clinical symptoms of genital herpes, including burning, itching, reddening and swelling of the mucosal tissues. The efficacy of HEP-1(Gepon) treatment involved a fast regression of pain in the area of the foci of the herpes rashes and along the nerve trunks. Pain stopped in the first 6 to 12 hours from the start of therapy in some patients and pain was terminated in all patients in less than 24 hours. Symptoms of systemic intoxication including weakness, headache, poor cognition and fever, which had been present in 22 of 23 Gepon Group patients prior to treatment, disappeared in less than 24 hours of HEP-1 (Gepon) therapy.

In 46% of patients, HEP-1 (Gepon) treatment rapidly terminated the usual course of a herpes outbreak on Day-1, and was completely effective in 22 of 23 patients (& partially effective in 1 of 23 patients) during the five day course of the therapy. No herpes outbreak progressed to blistering in any of the HEP-1 (Gepon) treated patients. During the 180 day observation period after Day-1 of HEP-1 (Gepon) therapy, all 23 Gepon Group patients enjoyed an average reduction in relapses of 3.2X, down to a mean of 0.36 relapses per month (compared to a mean of 1.16 relapses per month before HEP-1 therapy). There was a +3.8X increase in the Mean Duration of Remission in days from herpes outbreaks, because relapses were significantly shorter and 18% of the relapses did not progress. Generally, HEP-1 (Gepon) therapy reduced the duration and severity of subsequent outbreaks, and accelerated the onset of epithelialization. After HEP-1 (Gepon) therapy, 18 of 23 patients had only mild relapses limited to the brief appearance of erythema (reddening of the skin) in place of the usual rash and eruption, and the duration of all subjective sensations of relapse was reduced to around 2 days. It was estimated that the Mean Severity of outbreaks after HEP-1 Gepon therapy was only about 4% of the Mean Severity prior to HEP-1 Gepon therapy.

An additional bonus of HEP-1 (Gepon) therapy was revealed by the study. Before treatment, almost half of the patients of the Gepon Group, had been frequently ill with acute respiratory infections from 4 to 8 times a year, but after HEP-1 (Gepon) therapy the acute respiratory infection frequency decreased down to only 2 to 4 times per year. This unexpected independent observation supported the concept that HEP-1 (Gepon) therapy had amplified the efficiency of the adaptive immunity of patients.

Five-day therapy of Valtrex Control Group & Results

The Valtrex Control Group consisting of 35 patients, received 500mg Valtrex, twice a day with a 12-hour dosing interval, over

five days. The Valtrex Group patients were observed from Day-1 for 180 days.

In 28 of 35 patients of the Valtrex Control Group, the herpes rash progressed to blisters (whereas none of the HEP-1 treated patients suffered blisters). During the first day of Valtrex therapy, only 10 of 35 patients reported that their pain in the area of their lesions or along the nerve trunks had stopped (whereas pain stopped in all HEP-1 treated patients). The 13 patients in the Valtrex Control Group with symptoms of intoxication including weakness, cognition problems, headache & fever, reported a regression of these symptoms after two days of therapy (whereas all HEP-1 treated patients enjoyed relief from symptoms of systemic intoxication in less than 24 hours). In 33 of 35 patients, Valtrex therapy accelerated healing and epithelial regrowth, compared to the mean duration of outbreaks before treatment. Generally, Valtrex Group patients recovered from an outbreak in 5 days, but 2 of 35 patients took much longer. In contrast with HEP-1 (Gepon) therapy, recovery from the outbreak was less than 4 days in all patients. Valtrex therapy had no effect on the Mean Duration of Remission, nor the severity of subsequent outbreaks, compared to the substantial +3.8X increase in Mean Duration of Remission after HEP-1 treatment, combined with a substantial reduction of severity of any subsequent outbreaks.

The efficacy of HEP-1 (Gepon) in preventing the development of clinical symptoms of genital HSV was substantially superior to Valtrex: clinical success was achieved in 96% of patients treated with HEP-1 (Gepon) and it was impressive that after only a five-day course of oral HEP-1 (Gepon), all patients had an immunological response that had a preventative effect on future genital herpes outbreaks, a positive therapeutic effect that has never been observed with Valtrex or any other anti-viral pharmaceutical.

HEP-1 Gepon Treatment of Mixed Sexual Infections

HEP-1 (Gepon) is a revolutionary immunomodulator that has been clinically demonstrated to amplify immune protection to treat and prevent infections caused by bacteria, by viruses, by fungi or by parasitic protozoans, not only as mono-infections but also as multiple mixed sexually transmitted infections.

Clinical Trial No. 14

HEP-1 (Gepon) treatment of 20 patients with HSV-2 co-infected with other STIs

In general practice, genital herpes infection (HSV-2 & HSV-1) is often detected in patients with sexually transmitted disease, together with other STIs such as: HPV, CMV, Mycoplasma, Candida, Chlamydia trachomatis and other vaginal bacterial infections. The treatment of patients with not only recurrent herpes but also co-infections such as candida, chlamydia and trichomonas vaginalis infection, is a serious problem for physicians. In the therapy of patients suffering mixed STIs, such as herpes, candida, chlamydia and trichomonas vaginalis, oral HEP-1 (Gepon) solution can be used in combination with anti-virals for herpes, anti-fungals for candida, azithromycin & doxycycline for chlamydia, and 5-nitro-

imidazols (such as metronidazole or tinidazole) for trichomonas vaginalis infections [36].

In a comprehensive examination of 143 HSV-2 patients attending the Clinic of the Department of Dermatology and Venerology, of The Russian Medical Academy of Postgraduate Study, who were confirmed genital HSV-2 positive by serum anti-HSV-2 antibody titres, only 42 patients (29% of the whole group) were found to have mono-infection by HSV-2. Of the remaining 101 patients (71% of the whole group), all had at least one other STI infection in addition to HSV-2: ano-genital warts (HPV) were diagnosed in 40; ureaplasmosis was diagnosed in 33; mycoplasmosis was diagnosed in 26; candidiasis was diagnosed in 21; CMV antibodies were diagnosed in 21; chlamydia was diagnosed in 16; trichomonas vaginalis was diagnosed in 14; and bacterial vaginosis was diagnosed in 8 of the 101 multi-infected HSV patients.

All multi-infected HSV patients (and their sexual partners) were prescribed sufficient antibiotic, anti-fungal and anti-protozoan therapy, in accordance with existing guidelines for the treatment of STIs. Direct immunofluorescence assays were performed for chlamydia trachomatis, ureaplasma urealyticum and mycoplasma hominis prior to treatment and after treatment.

61 patients from the above group were allocated to the control group to receive standard anti-herpes virus Valtrex therapy to treat HSV-2 infection. 20 patients (The Immunomax Group) were selected for alternative treatment with Immunomax, a Russian TLR4-agonist pharmaceutical. Another 20 patients were selected for alternative treatment with HEP-1 (Gepon): oral 2mg HEP-1 (Gepon) in 2mL water once a day for 5 days and topical HEP-1 (Gepon) Cream (2mg HEP-1, 2g water, 2g lanolin 2g olive oil) applied to HSV lesions 3 to 5 times per day for the duration of an outbreak.

The result of HEP-1 (Gepon) treatment on the mixed sexual infections was as follows: in 4 of 5 patients chlamydia trachomatis was eliminated; in 4 of 6 patients ureaplasma urealyticum was eliminated; in 5 of 7 patients mycoplasma hominis was eliminated; and in the 7 patients with CMV co-infection, the antibody titre dropped from 2 patients with a 1:1280 titre & 5 patients with a 1:640 titre to all 7 patients having a titre below 1:160, reflecting a substantial fall in CMV viral load. There were no relapses of STIs in the HEP-1 (Gepon) treatment group.

In contrast, in the 61 patients receiving anti-herpes Valtrex therapy; relapses of STIs were reported in 4 patients co-infected with trichomonas, in 2 patients co-infected with mycoplasma and in 4 patients co-infected with HPV, as well as suffering recurring outbreaks of genital HSV and genital HPV infection.

Clinical Trial No. 15

HEP-1 (Gepon) oral & topical treatment of mixed STIs in 12 women

A clinical trial of HEP-1 (Gepon) treatment of 12 women with

multiple STIs, originally diagnosed as suffering urea-plasma or myco-plasma infection, was performed at Kursk Medical University by Principal Investigator Prof L Silina assisted by Dr T Isaenko and Dr T Bibicheva [37].

At the beginning of the study, all 12 of the recruited patients were sexually active women (from 19 to 42 years old) who complained of symptoms of itching and burning around the vagina, and the secretions of muco-purulent nature with an unpleasant smell. In addition, discomfort in the urethra was felt by 6 patients, sharp pains during urination was felt by 9 patients, and dull contraction pain in the lower abdomen by 1 patient.

Although these 12 women had been originally diagnosed with urogenital mycoplasma or ureaplasma infection, PCR and serum antibody diagnostics, combined with microscopy and microbiological culturing of pathological isolates, soon revealed multiple infections. Swabs from the cervical canal, back of the vagina and opening to the urethra, demonstrated that these women had many sexually transmitted co-infections. It was discovered that 5 patients had candida, 7 patients had trichomonas vaginalis, 3 patients had bacterial vaginitis and one patient had chlamydia. In fact only two women actually had ureaplasma or mycoplasma infection and the remaining 10 had a spectrum of mixed infections.

By microscopy, all patients were revealed to have leukocytosis, and abundant Gram-negative & Gram-positive rod-shaped and cocci bacterial microflora. All 12 women had already failed to clear their vaginal infections with anti-microbial drugs: 8 patients had already previously obtained one course of unsuccessful anti-microbial therapy and 4 patients had already had two unsuccessful courses of anti-microbial therapy.

All 12 patients were assigned standard antibacterial therapy or anti-fungal therapy or anti-protozoan therapy, according to their mixed infections and existing treatment protocols. In addition, all 12 patients received oral-systemic and topical-local HEP-1 (Gepon) therapy, in combination with the appropriate anti-bacterial or anti-protozoan or anti-fungal treatments. Anti-microbial combination therapy was commenced at the same time as HEP-1 (Gepon) treatment.

HEP-1 (Gepon) solution treatment was delivered to the patients, both orally-systemically, and topically-locally into the vagina and urethra. On each day of treatment, 2mg of HEP-1 (Gepon) was dissolved in 10ml of water to make a 0.2mg / mL solution, which was divided into two lots of 5mL each (1mg HEP-1). Each morning, the women took 5mL of 0.2mg / mL HEP-1 solution into their mouth, held it for about 5 minutes under the tongue for mucosal adsorption then swallowed.

The second 5mL lot of 0.2mg / mL HEP-1 solution, was drawn up into a syringe connected to a short catheter. The catheter was inserted into the exit of the urethra and approximately 0.5ml was washed up the urethra. The remaining solution was used to irrigate

the cervix and back of the vagina while the women supported herself of knees and elbows to retain the aqueous solution. A tampon was then inserted into the vagina and pushed back to the cervix to soak up the HEP-1 solution. The tampon was removed by the patient after two hours. The procedure was repeated once a day for 5 days, a total course of treatment of 10mg HEP-1 (Gepon) per patient.

As a result of HEP-1 (Gepon) combination therapy, after Day-2 there was a significant decrease in redness and hyperaemia of the mucosa, a significant decrease in the swelling of the tissues of the vagina. After Day-3 there was a significant decrease and the disappearance of pains in the lower abdomen, the disappearance of discomfort in the urethra, the disappearance of any sharp pains during urination, the termination of itch and burning of the vulva, and a significant decrease then termination of pathogenic vaginal discharges. By Day-5, 10 of 12 patients had normal leukocyte counts, while the remaining 2 patients had a substantial reduction in leukocytosis. After one week, 11 of 12 patients were making a rapid recovery. Analysis of microflora on Day-10, Day-28 and 3 months after therapy confirmed that HEP-1 (Gepon) had cured 12 of 12 woman of their multiple urogenital sexual infections. It was a unique treatment success, that ezrin peptide HEP-1 (Gepon) had knocked-out a combination of candida, chlamydia, trichomonas vaginalis, bacterial vaginitis, ureaplasma and mycoplasma infection. In the follow-up, three months after treatment, all 12 women were symptomless and confirmed completely cleared of all their urogenital infections (Figure 6).

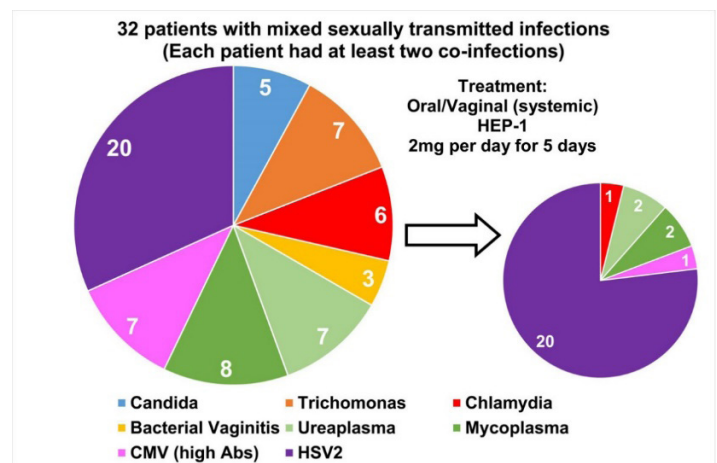


Figure 6: Combination of results of two clinical trials (Clinical Trial 14 with 20 patients and Clinical Trial 15 with 12 patients) where patients suffered at least two different sexually transmitted infections which had persisted despite prior treatment, then were systemically treated with 2mg HEP-1 per day for 5 days (oral or vaginal administration) in combination with standard therapies. The 20 patients with HSV infection gained therapeutic benefits from HEP-1 treatment (reduction of outbreak duration and increase of mean duration of remission), but the HSV was not eliminated. In contrast, HEP-1 treatment was successful in the elimination of trichomonas vaginalis, candida and bacterial vaginitis, and in reducing of the number of patients infected with chlamydia (6 to 1),

ureaplasma (7 to 2), mycoplasma (8 to 2), and in reducing the viral load of cytomegalovirus (as measured by anti-CMV antibody titres).

Ezrin Peptide HEP-1 (Gepon) treatment of HPV

The elimination of the long-term persistence of HPV in epithelial cells is still a major medical problem. There is no effective small-molecule anti-viral treatment for HPV: recurrent HPV infection can only be controlled by amplification of specific adaptive immune responses. In the Russian federation, HEP-1 (Gepon) is recommended for the treatment of sexually transmitted HPV, using three routes of administration in parallel: intra-vaginal irrigation with HEP-1 Gepon solution of 2mg HEP-1 in 5mL water every other day; combined with 2mg HEP-1 in 2mL applied orally / sublingually (a course of 3 to 6 procedures); together with HEP-1 Gepon ointment applied three times a day to the ano-genital warts (HPV-condylomas). Topical HEP-s1 Gepon is also effective in healing HPV lesions removed by laser or cryo methods, and substantially reduces the rate of recurrence of HPV-condylomas (vaginal warts).

Clinical Trial No. 16

HEP-1 (Gepon) treatment of HPV in 27 young sexually active women

After informed written consent, 54 sexually active young women between 17 and 19 years old, were recruited for a clinical trial at The St. Petersburg Medical Academy of Post-Graduate Education of Physicians by Principal Investigator Dr A.N.Barinova, MD, to measure the efficacy of HEP-1 (Gepon) in the treatment of ano-genital warts caused by HPV infection. Of the 54 patients who joined the study, 27 were randomly assigned to the Control Group, which received traditional topical therapy of “lactate of salicylic collodium” used in the treatment of HPV-condylomas [38].

The other 27 sexually active young women patients were randomly assigned to the Gepon treatment group, for treatment with HEP-1 (Gepon), in combination with the same traditional topical “lactate of salicylic collodium” given to the controls. The patients received 2mg in 2mL HEP-1 (Gepon) solution, held sublingually in the mouth then swallowed, every other day, over a total period of 20 days (a total of 10x 2mg doses HEP-1 = 20mg HEP-1). In addition the young women were supplied with topical HEP-1 (Gepon) cream (6mg HEP-1 in 5mL distilled water, blended with 5g lanolin and 5g peach nut oil), which was topically applied to the HPV-condylomas, around their ano-genital zone (approximately 0.03mg HEP-1 at a time), three times a day, for a total of 9 weeks (in total approximately 6mg HEP-1).

In the follow-up assessment of the Gepon treatment group, genital-warts (HPV-condylomas) had disappeared in 24 (89%) of 27 Gepon-treated patients. In contrast in the Control Group, only 16 (62%) of the remaining 26 young women (one patient failed to attend the clinic), had partially cleared seventy per cent of their HPV-condylomas. It was also observed that the addition of HEP-1 Gepon treatment had caused the disappearance of HPV-condylomas at least four times faster than traditional therapy. No

side effects, nor allergies, nor adverse reactions to HEP-1 (Gepon) were detected and these results were confirmed with other studies [39,40].

Clinical Trial No. 17

HEP-1 (Gepon) treatment of Syphilis

A solution of 2mg HEP-1 (Gepon) in 2mL water, is given orally every other day (sometimes in combination with a course of ceftriaxone antibiotic therapy), to treat primary and secondary syphilis. HEP-1 (Gepon) is used in the Russian Federation to treat “sero-resistant” syphilis: after penicillin G treatment of primary and secondary syphilis, antibodies to syphilis can still persist, a phenomena known as sero-resistance, which indicates that reservoirs of the *Treponema pallidum* still persist in the body. After Penicillin G treatment of primary syphilis, HEP-1 (Gepon) therapy is often added to eliminate the reservoirs of the *Treponema pallidum* responsible for the sero-resistance.

Long term clinical studies have shown monotherapy of 2mg HEP-1 (Gepon) in 2mL water, taken orally every other day, over 24 months (two years), was sufficient to achieve partial or full elimination of sero-resistant syphilis. In a two-year clinical study of sero-resistant syphilis, of the group treated with HEP-1 (Gepon) monotherapy; 23% of patients had cleared syphilis within 6 months of the commencement of treatment, 36% of patients had cleared syphilis within 12 months from commencement of treatment and 40% of patients achieved total elimination of sero-resistant syphilis, after 18 months. Another 37% of the treated patients displayed a significant decline in immunological markers for sero-resistance at 24 months. It was found that after two years of HEP-1 (Gepon) therapy, 77% of treated patients suffering from syphilis had gained significant therapeutic benefit.

The remaining 23% of the treatment group who were non-responders to HEP-1 (Gepon) therapy, all had a characteristic immunological profile: B-cell and T-cell immune deficiency prior to therapy, the absence of indicators of normal B-cell & T-cell functioning during treatment, a reduced number of active NK-cells and an abnormally high content of CD3+ C16+ CD56+ T-cells [41].

Conclusion

The clinical results from Russia, summarized for the first time in the English language, on the use of ezrin peptide therapy HEP-1 (Gepon), a synthetic peptide of 14 amino-acids (sequence TEKKRRETVEREKE), has shown that ezrin peptide therapy can be used for the treatment of many different types of sexually transmitted infection, whether of viral, bacterial, fungal or protozoan origin. Ezrin peptides induce biological responses in patients to achieve the same or better treatment results than small-molecule anti-biotic, anti-fungal, anti-viral or anti-protozoan pharmaceuticals, as well as enhancing adaptive protective immune responses, in a manner similar to mucosal vaccination. Ezrin peptides can also over-come the rapidly growing problem of drug resistant bacteria, fungi, protozoa and viruses, and is effective at treating mixed sexually transmitted infections.

Ezrin peptide therapy is an alternative or can be used in combination with traditional anti-microbial, anti-fungal, anti-viral therapy and even vaccines, for the safe & effective treatment and prevention of sexually transmitted bacterial, fungal, protozoan and viral infections of the vagina. In addition, anal administration of HEP-1 (Gepon) has been used to treat the dysbacteriosis of the lower intestine, which is responsible for Irritable Bowel Syndrome (IBS). Administration of an ano-rectal enema of HEP-1 (Gepon) solution (2mg HEP-1 in 40mL 0.9% NaCl solution) for 7 days, showed that HEP-1 can reduce bacterial cocci infections of the lower gut by ten-thousand-times and fungal *Candida* infections of the lower gut by one-hundred-thousand-times [42-44]. Multidrug resistant *Candida auris* is a fungal pathogen with a crude mortality rate of 30-60% and Human Ezrin Peptide therapy may be the only practical treatment option [45].

An upgraded version of HEP-1 called RepG3 (GEKKRRETVEREGG), has double the anti-inflammatory activity of HEP-1. RepG3 has three of its terminal amino acids, substituted with glycine. RepG3 is under development in London by NewalR&D Ltd for the treatment of sexually transmitted infections, as well as for symptom relief from Long COVID and COVID vaccine adverse event injury [46-49].

Journal titles are translations from Russian into English.

References

1. Rupert Donald Holms. AIDS prophylactics. WIPO (PCT) WO1995033768A1 Priority Application. 1994.
2. Ataulakhanov RI, Holms RD, Katlinsky AV, et al. Treatment with the immunomodulator "Gepon" increases the effectiveness of immune control of opportunistic infections in patients with HIV infection. *Allergy, asthma and clinical immunology*. 2022; 10: 3-11.
3. Khaitov RM, Ataulakhanov RI, Holms RD. Increasing the effectiveness of immune control of opportunistic infections in the treatment of patients with HIV infection with immunomodulator "Gepon". *Immunology*. 2022; 22: 11688.
4. Khaitov RM, Holms RD, Ataulakhanov RI. Activation of the formation of antibodies to HIV antigens in the treatment of patients with HIV infection with the immunomodulator "Gepon". *Immunology*. 2022.
5. Khaitov RM, Ataulakhanov RI. *Immunotherapy*. Izdatekskaya Group, GEOTAR-Media. 2011.
6. <http://government.ru/en/department/23/events/>
7. <https://www.uniprot.org/uniprotkb/P15311/entry>
8. Ataulakhanov RI, Holms RD, Narovlyansky AN, et al. Changes in transcription of cytokine genes in human cells under the influence of the immunomodulator Gepon. *Allergy, asthma and clinical immunology*. 2022; 9: 17-22.
9. Ataulakhanov RI, Holms RD, Narovlyansky AN, et al. Mechanisms of antiviral action of the drug "Gepon": a change in the transcription of cytokine genes in human cells. *Immunology*. 2022; 22: 11688.
10. Chulkina M, Negmadjanov U, Lebedeva E, et al. Synthetic peptide TEKKRRETVEREKE derived from ezrin induces differentiation of NIH/3T3 fibroblasts. *European Journal of Pharmacology*. 2017; 817: 249-259.
11. Uchaikin VF. Gepon a domestic immuno-modulator with anti-inflammatory and antiviral activity for children and adults. 2003.
12. Tishchenko AL, Sergeeva NS, Murashova NN, et al. Treatment of recurrent candidiasis with an immunomodulator Gepon. *Bulletin of Postgraduate Medical Education*. 2001; 2: 25-32.
13. Mashaeva LL, Olimpieva SP, Syanova OE, et al. Effectiveness of the drug Gepon in the treatment of vaginitis in outpatient and polyclinic practice. *Scientific Center of Obstetrics, Gynaecology and Perinatology of the Russian Academy of Medical Sciences*. 2003.
14. Uvarova EV. *Candida vulvovaginitis in the practice of a paediatric gynaecologist*. *Russian Medical Journal*. 2003; 18.
15. Tishchenko AL. New treatment for recurrent urogenital candidiasis. *Gynaecologiya*. 2001; 3: 210-212.
16. Tishchenko AL. A new approach for treatment of recurrent urogenital *Candida* infection. *Gynaecology*. 2001; 3: 210-212.
17. Tishchenko AL. A new approach for treatment of recurrent urogenital *Candida* infection. *The Practitioner*. 2002; 3: 46-47.
18. Perlamutrov YuN, Soloviev AM, Lyubopytova DA. Recurrent urogenital. *Immunotherapy*. 2011.
19. Perlamutrov YuN, Soloviev AM, Bystritskaya TF, et al. A new approach to the treatment of skin and mucosa infections caused by *Candida* fungi. *Bulletin of Postgraduate Medical Education*. 2011; 2: 21-23.
20. Perlamutrov YuN, Soloviev AM, Chernova NI, et al. An experience of "Gepon" use for treatment of patients having recurrent urogenital *Candida* infection. *Modern Mycology in the Russia Federation*. 2002.
21. Batkaev EA, Ryumin DV. Urogenital trichomoniasis. *Attending physician*. 2002. 12.
22. Batkaev EA, Ryumin DV, Shakov IM. Gepon, an immunomodulator drug, in a treatment of Herpes virus and combined *Candida-Trichomonas* infections of urogenital tract. *Russian Medical Journal*. 2003; 11: 962-963.
23. Batkaev EA, Ryumin D. Urogenital trichomoniasis. *Immunotherapy*. GEOTAR-Media. 2011.
24. Katlinskiy AV, Ataulakhanov RI, Holms RD. The Immuno-adjuvant Activity of Structural Homologues of the Immunomodulator Gepon. *Immunology*. 2003; 1: 34-39.
25. Vasilev MM, Burtsdev OA. Evaluation of Efficacy of Immuno-modulator Gepon in combination with antibiotics. *General Recommendations of the Ministry of Health of the Russian Federation*. 2002; 26.
26. Yuriev S, Yevtushenko I, Ogorodova L, et al. HEP-1 (Gepon) and Polyoxidonium In the Treatment Of Chronic Urogenital

- Chlamydia during Pregnancy Planning. Bulletin of Russian Academy of Medical Sciences. 2005; 2: 112-116.
27. Barinsky F, Alimbarova L, Lazarenko A, et al. Experimental Study of the Antiviral Activity of Immunomodulator "Gepon" in infections caused by Herpes Simplex Viruses HSV-1 and HSV-2. Issues of Virology. 2003; 5: 30-33.
 28. Barinsky IF, Alymbarova LM, Lazarenko AA, et al. Antiviral activity of peptide immunomodulator "Gepon" in experimental infections caused by Herpes Simplex Viruses types 1 and 2. Question of Virology. 2003; 5.
 29. Ushkalova EA. Genital herpes: etiology, pathogenesis, treatment. Farmateka. 2011; 11: 88- 94.
 30. http://www.gepon.ru/listart_gep.html
 31. Shakov IM. External treatment of recurrent genital herpes using pharmaceutical Gepon. Herald of Post Graduate Medical Research. 2003; 1: 51-52.
 32. Batkaev EA, Ryumin DV, Shakov IM. Gepon, an immunomodulator drug, in a treatment of Herpes virus and combined Candida-Trichomonas infections of urogenital tract. Russian Medical Journal. 2003; 11: 962-963.
 33. Bibicheva TV, Silina LV. Immunomodulator Gepon for local therapy of herpes virus infection. Klin Med (Mosk). 2015; 93: 16-24.
 34. Marchenko LA, Lushkova IP, Shurshalina AV. Treatment of patients with recurrent genital Herpes. Questions of Gynecology, Obstetrics and Perinatology. 2004; 3: 90-93.
 35. "Recurrent genital herpes" Chapter 35 "Immunotherapy" Editors: Khaitov R.M., Ataulakhanov R.I. Published by Izdatekskaya Group, GEOTAR-Media, Moscow. 2011.
 36. "Recurrent genital herpes" Chapter 35 "Immunotherapy" Editors: Khaitov R.M., and Ataulakhanov R.I. Published by Izdatekskaya Group, GEOTAR-Media, Moscow. 2011.
 37. Isaenko TP, Bibicheva TV, Silina LV. Gepon in combination treatment of urogenital myco-urea-plasmosis in women. Bulletin of Postgraduate Medical Education. 2003; 1: 52-53.
 38. Barinova AH. The St-Petersburg Medical Academy of Post-Graduate Education of Physicians. presented to Immapharma. 2004.
 39. Budanov PV, Voronoi SV, Aslanov AG. Principles of treatment of papillomavirus infection. Questions of Gynaecology, Obstetrics and Perinatology. 2004; 6: 70-75.
 40. Perlamutrov YuN, Solovyov AM, Ataulakhanov RR, et al. Combined therapy of recurrent anogenital warts. Vestnik Dermatologii & Venereologii. 2003; 6: 50-52.
 41. Perlamutrov YuN, Solovyev AM, Spina EG. Overcoming Sero-resistance after treatment of syphilis. Izdatekskaya Group. 2011.
 42. Lazebnik LB, Tsaregorodtseva TM, Parfenov AI. Immune system and diseases of digestive organs. Therapeutic Archive. 2004; 12: 5-8.
 43. Cherednichenko TV, Uchaikin VF. The positive effect of the drug Gepon on clinical and laboratory parameters and intestinal dysbiosis in viral hepatitis in children. Russian Medical Journal. 2003; 11.
 44. Parfenov AI, Ruchkina IN, Pichugin AV. Gepon, an Enhancer of Local Tissue Immunity, in the treatment of Dysbacteriosis of Intestine. Gastroenterology. 2003. 3: 4-14.
 45. Egger NB, Kainz K, Schulze A, et al. The rise of Candida auris: from unique traits to co-infection potential. Microb Cell. 2022; 9: 141-144.
 46. Holms RD. Long COVID (PASC) Is Maintained by a Self-Sustaining Pro-Inflammatory TLR4/RAGE-Loop of S100A8/A9 >TLR4/RAGE Signalling, Inducing Chronic Expression of IL-1b, IL-6 and TNFa: Anti-Inflammatory Ezrin Peptides as Potential Therapy. Immuno. 2022; 2: 512-533.
 47. Holms RD. The COVID-19 Cell Signalling Problem: Spike, RAGE, PKC, p38, NFB & IL-6 Hyper-Expression and the Human Ezrin Peptide, VIP, PKA-CREB Solution. Immuno. 2022; 2: 260-282.
 48. Holms RD, Ataulakhanov RI. Ezrin Peptide Therapy: A Potential Treatment for COVID. J Bioprocess Biotech. 2021; 12: 3.
 49. Holms RD, Ataulakhanov RI. Ezrin Peptide Therapy from HIV to COVID: Inhibition of Inflammation and Amplification of Adaptive Anti-Viral Immunity. Int J Mol Sci. 2021; 22: 11688.