A POTENTIAL TREATMENT FOR COVID-19
Review of Ezrin Peptide Treatment of Acute Viral Respiratory Disease and Virus Induced Pneumonia

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SUMMARY

In 2020, the world is gripped by a very infectious and pathogenic novel coronavirus: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), also known as COVID-19 virus, which causes the disease named COVID-19. However, Ezrin-peptides may be a prophylactic and treatment solution especially for the elderly. [1 2 3 4 5] Details of three separate successful post-registration clinical trials using Ezrin-peptide TEKKRRETVEREKE, for the treatment of Acute Viral Respiratory Infection (AVRI) with complications including pneumonia, were performed in Moscow over the previous eighteen years: Trial 1 with 100 patients, Trial 2 with 48 patients and Trial 3, 135 patients, are translated, summarized and presented in this review.

INTRODUCTION

COVID-19 virus, 96% identical to a bat coronavirus, has affinity for the cells lining the mucus membranes of the airways, where its spike-protein binds to the ACE2-receptor.[6 7] COVID-19 virus then uses human ezrin, a sub-membrane protein that regulates cell-signalling, shape and motility in epithelial cells, to fuse with the human cell membrane and gain entry.[8 9] Once inside human cells, COVID-19 virus replicates rapidly and induces an inflammation, mediated mainly by IL-1 IL-6 IL-8 and TNFα, that

leads to viral pneumonia, ‘cytokine storm’, lung damage and other organ damage.[10]

COVID-19 patients display a spectrum of disease severity. About 80% have Acute Viral Respiratory Disease (AVRI) with fever around 38^{o}C, dry cough and a mild pneumonia. About 15% have severe disease with lung inflammation leading to Acute Respiratory Distress Syndrome (ARDS): including dyspnoea (shortness of breath), and hypoxia (low blood oxygen). About 5% have critical disease: Acute Lung Injury (ALI) including respiratory failure, shock, multi-organ dysfunction and in about 0.5% to 2% cases, death. [11]

Human Ezrin, Old-Age and COVID-19 fatality

In Chinese and Italian cohorts of COVID-19 virus infected people, severe and critical disease was very common in people over 65 years old. In contrast, symptomatic infection in children with COVID-19 virus is rare and mild. In a Chinese CDC report, less than 2% of all symptomatic infections were in individuals younger than 20 years old. In a small study of 10 children in China who did develop symptoms, clinical illness was mild; 80 per cent had fever, which resolved within 24 hours, 60% had cough, 40% had sore throat, and none required supplemental oxygen.[12]

There is clearly a human factor related to aging that is interacting with COVID-19 virus. In 2012, it was discovered that human ezrin, a submembrane protein that is involved in cell shape, motility, receptor organisation and cell signalling, specifically bound to the carboxy-terminus of the SARS coronavirus spike protein, using its FERM domain. The coronavirus was dependent on using a specific conformation of human ezrin to fuse with the epithelial cells of the airways and successfully infect them. The fully active conformation of ezrin, restrains coronavirus infection at the cell-entry stage. [13]

Increased expression of non-functional ezrin is associated with organism age and senescence, which accumulates on the interior surface of the cell membrane. [14] In old rats, there is a

fourfold increase in membrane associated ezrin in old epithelial cells, compared to young epithelial cells. [15] Old mice also have defective CD4 T lymphocytes, which display age-related defects in ezrin-mediated cytoskeletal signals[16]. The failure of Ezrin signalling complexes over time with age, may in part explain the age-related fatality observed with COVID-19 disease.

Ezrin Peptide Therapy

Ezrin peptides mimicking the trigger-hinge region of the alpha-domain of human ezrin, are highly polar molecules, with alternating negative and positive charges, which act locally on epithelial cells and fibroblasts in mucus membranes.

The receptors for ezrin peptides are believed to be membrane associated ezrin-protein signalling complexes. Ezrin peptides are thought to have an allosteric effect, which results in changes of the conformation of ezrin into various functional forms. These changes can not only prevent viruses entering cells, but also can activate specific signalling pathways. Ezrin-protein complexes are associated with the regulation of the ras>raf>MEK>ERK and PI3K>PKB>mTOR intracellular signalling pathways, and they are involved in the control of cytokine and interferon expression. Ezrin peptides also act on fibroblasts to stimulate tissue repair processes. [17]

Clinical studies in Russia over twenty-five years have shown that ezrin peptides can safely and effectively treat viral infections caused by HIV, HCV, HPV, Herpes Simplex 1 & 2, and the spectrum of viruses that cause Acute Viral Respiratory Infection (AVRI). Clinical trials of ezrin peptide TEKKRRETVEREKE [Gepon], determined that the ezrin-peptides possess anti-viral, immuno-modulating activity and anti-inflammatory activity, and could be used for successful prevention and treatment of a wide range of infectious diseases caused by viruses, bacteria, chlamydia, mycoplasmas, and candida fungi. [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30]

Generally, clinical studies have demonstrated that ezrin peptides are safe, reduce virally induced inflammation, and lead to faster recovery from Acute Viral Respiratory Infection (AVRI). Ezrin peptides have even successfully treated viral pneumonia by shutting down non-specific inflammation, and symptoms of viral infection, probably by amplifying specific anti-viral responses selected by the immune system.

CLINICAL STUDY ONE

100 patient clinical study into intra-nasal Ezrin-peptide TEKKRRETVEREKE [Gepon] solution, as a treatment of Acute Viral Respiratory Infection [AVRI], inflammatory Laryngeal-Tracheal-Bronchitis with Stenosis [LTBS] and Recurrent Croup [RC]

Introduction

In year 2000, V.F. Uchaikin, Member of The Russian Academy of Medical Sciences, organized a post-registration clinical study of fourteen amino-acid synthetic Ezrin-peptide TEKKRRETVEREKE [Gepon], at the Morozov Moscow Children's Hospital, in collaboration with The Russian Government Medical University, Moscow.

The Principal Clinical Investigators in the clinical study into the safety and efficacy of Gepon in Recurrent Acute Respiratory Diseases were: Kladova O.V., MD, Doctor of Medical Sciences, Professor, Department of children's infectious diseases of the Russian State Medical University: Legkova T.P., Head of Moscow Children's Hospital No18 and Ovchinnikova G.S., Doctor of Children's Home No 5

The objective of the clinical study was to test the efficacy of intra-nasal application of ezrin-peptide TEKKRRETVEREKE [Gepon][31], in treating of recurrent Acute Viral Respiratory Infection [AVRI], which results in inflammation, and laryngitis-tracheitis-bronchitis complicated with laryngeal stenosis and/or croup syndrome. [32] [33] [34]

The clinical research was approved by a Decision of the Committee on Ethics (Minutes No: 6 of 06 December 2000), and a

Decision of the Pharmacology Committee (Minutes No: 14 of 21 December 2000). Permission to conduct clinical trials was issued by the Department of the State for control of quality, efficiency and safety of the medical preparations and equipment (No: 183 of 31 January 2001).

Assessed Patient Population

125 child-patients between the ages of 1 year to 14 years old, suffering Acute Respiratory Virus Infection [AVRI], Virus Induced Inflammation, Laryngeal-Tracheal-Bronchitis with Stenosis [LTBS] and Recurrent Croup [RC] syndrome, were assessed for the clinical trial.

ARVI occurred in 85% of the children. 50 children suffered Laryngeal-Tracheal-Bronchitis with Laryngeal Stenosis (LTBS) and 75 children suffered Recurrent Croup (RC). The recurrent croup was caused by a chronic virus-induced non-specific inflammation of the upper respiratory tract. The frequency of recurring croup (RC) in child-patients was between 3 to 35 times per annum. Recurrent croup syndrome was associated with 1st degree stenosis of the larynx in 54 of the RC patients (72%), by 2nd degree stenosis of the larynx in 21 of the RC patients (28%).

10% of the croup cases had no fever, 60% of the croup cases suffered sub-febrile fever, 30% of the croup cases suffered febrile fever. The average duration of fever was 3-4 days. Bacterial complications were observed in 15%, including sore throats, acute otitis media, eustachyitis, and pneumonia. Half of the child-patients were under treatment in hospital, and half were treated as out-patients at home.

Immune Status of Assessed Patient Population

The 125 children of the assessed patient population were offered immune status analysis, which was then compared to the average status of healthy children. Generally, a profound non-specific inflammatory response was being induced and maintained

by the viral infection. In contrast, specific anti-viral immunity had been disrupted.

Blood samples were assessed by flow-cytometry using monoclonal antibody markers: CD3, CD4, CD8, CD16, CD20, CD1b, CD25, CD38, CD54, CD71, CD95, and HLA-DR, to determine the distribution of lymphocyte sub-populations. In addition, co-expression of [CD4+, CD8+], [CD8, DR] and [CD16+, CD8+] was also measured. The ex vivo phagocytic activities of blood monocytes and neutrophils versus Staphylococcus Aureus were also determined.

The levels of inflammatory cytokines IL-1α, IL-6, IL-8 and TNFα were analysed. The functional activity of Th1 and Th2 cells were assessed and the level of expression of the interleukins IL-2 and IL-4 were measured. Interferon status of the children was assessed by the functional 1988 Yershov method and by expression of Interferon-gamma. The concentrations of serum IgA IgE, IgG and IgM immunoglobulins were also analysed.

The viral respiratory infection had induced a marked imbalance in T cell and B cell immunity, and also significantly impaired the normal functionality of blood monocytes, neutrophils and lymphocytes. For example, lymphocyte adhesion and apoptosis were 4x to 5x above normal levels.

The most consistent differences between the assessed child-patients and healthy children, were the large significant increases in the concentrations of inflammatory cytokines: IL-1α, IL-6, IL-8 and TNFα. IL-6 was significantly elevated 2.1x *in vivo* and 9x *in vitro*, and hugely elevated 26x when induced *in vitro*. IL-8 and TNFα also showed a similar pattern of massive elevation. [Table 1]

In the Assessed Patient Population, levels of T cell activating IL-2 and IL-4, were significantly increased. The level of IL-2 *in vivo* was increased 24x, *in vitro* spontaneous production of IL-2 was increased 12x, and *in vitro* induced production increased by 5.1x. The level of IL-4 both in *vivo* and *in vitro* also showed similar elevations.

The level of mature T-lymphocytes in children was increased by 1.3x over healthy children. Activated [CD71+, CD38+, CDA+, ADD+] lymphocytes were significantly reduced. The assessed patient population had marked changes in the immuno-regulatory population of cells. The Th1 cell population was 0.63x less than normal, whereas the Th2 cell population was 1.49x more than normal. There was a significant reduction in the expression of IL-2 Receptors (IL2R+).

There was also a significant reduction in the proportion of cytotoxic T cells [CD16+, CD8+, HLA-DR+] and activated [CD8+, HLA-DR+] cells. Macrophage function was disrupted; phagocytosis was reduced 1.6x, phagocytic-index was reduced 1.2x, but absolute-phagocyte-indicator was 1.6x above normal. Neutrophils were significantly increased.

Serum IgG and IgE were significantly increased, but IgA was decreased, while IgM stayed normal. Interferon production was also disrupted: interferon-α, interferon-β and interferon-γ were also significantly reduced.

Table 1.

Immunological Status of Assessed Children with AVRI, Virus Induced Inflammation, LTBS and RC, vs healthy children

Less than healthy children: -, Same as healthy children: n, More than healthy children: +,

Immunological Parameter	Virus Induced Change
Leucocytes	++
Lymphocytes	-
Mature T lymphocytes	+
Th1 Subpopulation	- -
Th2 Subpopulation	+
IRI	++
Activated CD8+	- -
IL2R+ cells	-
HLA DR+ cells	- -
NK cells	-
CD16+CD8+	- -
Mature B lymphocytes	++
IgG	++
IgA	- -
IgM	n
IgE	++
Neutrophils	++
Segmented nuclear	+
Rod-like nuclear	n/+
Phagocytes	-
Phagocytic index	- -
Absolute phagocytic index	+
Production of γ interferon	- -
IL-1 alpha *(in vivo)*	++
IL-1 alpha *(in vitro)*	++
IL-2 *(in vitro)*	++
IL-2 *(in vivo)*	++
IL-4 *(in vitro)*	++
IL-4 *(in vivo)*	++
IL-6 *(in vitro)*	++
IL-6 *(in vivo)*	++
IL-8 *(in vitro)*	++
IL-8 *(in vivo)*	++
TNF alpha *(in vitro)*	++
TNF alpha *(in vivo)*	++

Criteria for the Gepon Clinical Study

Child-patients aged between 1 and 14 years, with a verified diagnosis of recurrent respiratory disease, with 5 or more incidents per annum recorded in their medical documentation, and suffering from Laryngeal-Tracheal-Bronchitis with Stenosis and / or Recurrent Croup, were included in the study.

Child-patients were excluded from the study: if the child-patient refused to take part in the clinical trials; if they were below 1 year, or over 14 years of age; they had received any immuno-modulator therapy with the previous 4 months; if other diseases were present, such as insulin-dependent diabetes, tuberculosis, chronic kidney and liver diseases, oncological diseases or HIV-infection. Patients were also excluded: if their doctor's advice was not followed, if side effects appeared which might require special treatment, and if the child-patient's doctor decided that it was in the interest of the child-patient to terminate participation in the Clinical Study.

Entry of Child-Patients to the Gepon Clinical Study.

Of the 125 child-patients who had been assessed, 100 were invited to join the clinical study of Gepon. Child-patient's voluntary participation in the clinical research, was subject to informed written agreement by their parents or guardians. Participation in the clinical research was voluntary, free of charge, and free of incentive payment.

Each child-patient was assessed for: body temperature, skin condition, peripheral lymph nodes, fauces (the arched opening at the back of the mouth leading to the pharynx), and tonsils; function of the lungs, heart, nervous system, muscular system and other evaluations. The time elapsed between receiving written agreement and the start of the Gepon therapy was between 1 and 14 days.

Patient Allocation to Gepon Group and Control Group

There was an initial non-randomised selection of child-patients into two groups of 50 patients each, in which the spectrum of symptoms were matched as far as possible: Group 1 suffering from Acute Viral Respiratory Infection [ARVI] and Laryngeal-Tracheal-Bronchitis with Stenosis [LTBS]; and Group 2 suffering from recurrent Acute Viral Respiratory Infection [ARVI] only.

25 patients from Group 1 and 25 patients from Group 2 were then randomly assigned to the Gepon Group n=50. 25 patients from Group 1 and 25 patients from Group 2 were then randomly assigned to the Control Group n=50

Table 2

Group 1: Associated pathology in ARVI+LTBS child-patients suffering from recurrent Laryngeal-Tracheal-Bronchitis with Stenosis [LTBS] assigned to the Gepon Group (Gepon + symptomatic therapy) and Control Group (symptomatic therapy only)

Presence of associated pathologies	Gepon Group AVRI + LTBS (n=25)	Control Group AVRI + LTBS (n=25)
1st grade Stenosis of the larynx (n=20)	9	11
2nd grade Stenosis of the larynx (n=5)	2	3
Recurring laryngeal-trachea-bronchitis (n=0)	-	-
Recurring obstructive bronchitis(n=0)	-	-
Monthly incidence of AVRI (n=0)	-	-
Obstruction of breathing passages during AVRI (n=31)	15	16
Lymphadenopathy (n=8)	4	4
Hypertrophy of palatine tonsils (n=14)	7	7
Atopic dermatitis (n=21)	10	11
Recurring obstructive bronchitis in children over 3 years of age (n=8)	4	4
Recurring Croup in children over 3 years of age (n=6)	3	3
Chronic tonsillitis in children over 3 years of age (n=3)	2	1

Table 3
Group 2: Associated pathology in AVRI child-patients suffering from recurrent disease only assigned to the Gepon Group (Gepon + symptomatic therapy) and Control Group (symptomatic therapy only)

Presence of associated pathologies	Gepon Group AVRI only (n=25)	Control Group AVRI only (n=25)
1-grade Stenosis of the larynx (n=0)	-	-
2-grade Stenosis of the larynx (n=0)	-	-
Recurring laryngeal-trachea-bronchitis (n=3)	1	2
Recurring obstructive bronchitis (n=6)	3	3
Monthly incidence of AVRI (n=16)	7	9
Obstruction of breathing passages during AVRI (n=3)	2	1
Lymphadenopathy (n=7)	4	3
Hypertrophy of palatine tonsils (n=9)	4	5
Atopic dermatitis (n=6)	3	3
Recurring obstructive bronchitis in children over 3 years of age (n=5)	3	2
Recurring Croup in children over 3 years of age (n=4)	2	2
Chronic tonsillitis in children over 3 years of age (n=2)	1	1

Clinical Trial

Therapy commenced in September 2001. During the trial the child-patients visited the doctor not less than 7 times: prior to start of the therapy; during the 5 days of therapy, following therapy; 1 month after the therapy, and 3 months after the therapy. All 100 children received standard symptomatic treatment, using antihistamine, anti-pyretic, and mucolytic drugs, bronchodilators and alkaline aerosol inhalations.

Control Group n=50

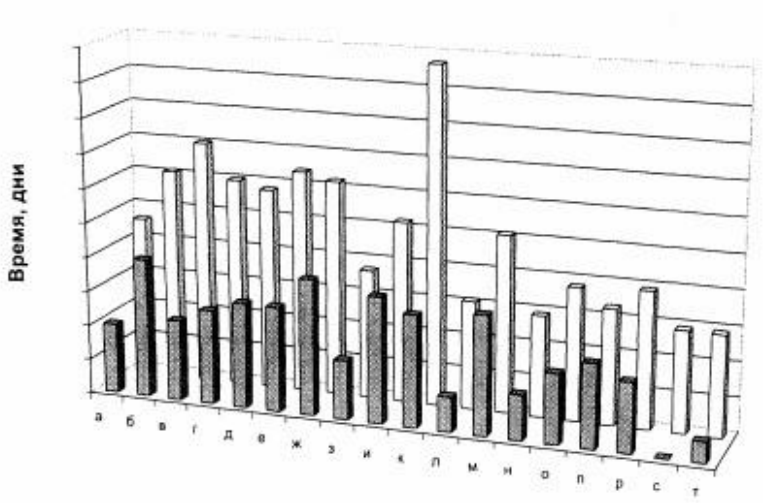
The 50 children selected for the Control Group received standard symptomatic treatment only for viral inflammation of the airways. 13 children of the control group also received antibiotics for secondary bacterial infections.

Gepon Group n=50

The 50 children selected for the Gepon Group received standard symptomatic treatment for viral inflammation of the airways plus Gepon therapy: 2mg sterile lyophilised ezrin-peptide TEKKRRETVEREKE Gepon produced by LLC Immapharma, dissolved in 2ml water to make a solution of 1mg/ml. Gepon solution was delivered intra-nasally as 5 (40 micro-litre) drops in each nasal passage, twice a day, for a period of 5 days (total administration 2mg Gepon in 2ml). In the case of 7 children, who had AVRI with bacterial complications, antibiotic treatment was also applied in parallel to Gepon treatment.

RESULTS

Fig 1: Duration of Clinical Symptoms (Days)
Gepon Group n=50 (dark) and Control Group n=50 (light)
Horizontal divisions in days.



a: Fever, b: difficulty in breathing, c: serous rhinitis, g: swelling of nasal mucous membrane, d: hyperaemia of tissues, e: pharyngitis, zh: swollen palatine glands, 3: hoarseness of voice, i: dry cough, k: moist cough, l: stenosis of larynx, m: swollen neck lymph nodes, n: reduction in the appetite, o: weakness, p: sleepiness, r: reduction in physical activity, s: conjunctivitis, t: complications.

Table 4

Clinical symptoms	Duration in Days	
	Gepon Group n=50	**Control Group** n=50
Fever	**2**	**4**
Difficulty in nasal breathing	4	6
Serious Rhinitis	**3**	**7**
Mucus from nose	**3**	**6**
Inflamed Throat	**3**	**6**
Perturbation of Pharynx	**3**	**6**
Enlarged tonsils	4	6
Laryngitis	**2**	**4**
Dry Cough	4	6
Wet Cough	**4**	**10**
Obstruction of larynx	**2**	**4**
Enlarged lymph nodes	4	6
Reduced appetite	2	3
Weakness	3	4
Low physical activity	**2**	**4**
Conjunctivitis	**0**	**3**
Complications	**1**	**3**

Bold means 2 or more times reduction in duration of symptoms

SAFETY OF GEPON

No child-patient displayed any adverse reaction, nor any adverse drug interaction, when receiving Gepon. No side effects were observed. No allergic reactions were detected with Gepon therapy. No intestinal-dysbiosis (common with antibiotics) was detected. No child-patient suffering from atopic dermatitis displayed any aggravation of illness. There were no hypersensitivities resulting from the intranasal introduction Gepon and no evidence of any contra-indications at any patient age.

THERAPEUTIC EFFICACY OF GEPON

All child-patients who received Ezrin peptide TEKKRRETVEREKE [Gepon], in addition to standard symptomatic treatment, benefitted from a significant shortening in the duration of the clinical symptoms, which was independent of the severity of AVRI or LTBS. The child-patients experienced the rapid decrease in the duration of symptoms of disease, regardless of the severity of the Acute Viral Respiratory Infection (ARVI), the amount of inflammation of the airways, stenosis of the larynx or upper-airway obstruction.

Comparisons between the 50 child-patient Gepon Group and 50 child-patient Control Group, showed that the duration of the fever and other manifestations of intoxication syndrome, including malaise, reduced appetite, weakness, sleepiness, and decrease in physical activity, were all reduced.

All child-patients presented with dry-cough and fever, but after they received Gepon therapy, they benefitted from a reduction in the duration of fever by 3.2x times to only two days, and the duration of dry cough by 1.8x, so that it stopped in less than four days. Duration of rhinitis was 2.2x less and laryngitis was reduced by 2.3x. Croup-cough disappeared on Day-3 of treatment with Gepon. In contrast, only 38% of the Control Group managed to eliminate croup-cough in the same period.

As a result of Gepon therapy, dissolution of mucus and appearance of productive wet cough, a sign of recovery occurred on Day-2 of Gepon therapy. In the Control Group, productive wet-cough only got established after Day-5. Regardless of the degree of inflammation and SLTB in the Gepon Group, 67% of cases had recovered by Day-2 of treatment. In the same two days, 72% of the children in the Gepon Group increased sputum density, while only 46% of the Control Group improved.

Gepon treatment reduced the bacterial complications requiring antibiotics. Gepon even reduced the manifestations of atopic dermatitis in the child patients

In the child-patients who were suffering more severe AVRI+LTBS, Ezrin peptide TEKKRRETVEREKE [Gepon] was demonstrated to be a rapid acting therapy. (Table 5)

Fever was shut down after 30 hours of Gepon therapy, whereas the Control AVRI+SLTB Sub-Group continued to suffer fever for 3 days. Maximum clinical benefit with Gepon was achieved in 67% of cases, within 48 hours of receiving the treatment.

Dry-cough disappeared in less than 60 hours in three-quarters of the child-patients in the Gepon AVRI+SLTB Sub-Group, whereas only about a third of child-patients recovered from dry-cough in the Control AVRI+SLTB Sub-Group, over the same period.

Table 5

Comparison of duration of clinical symptoms in child-patients in The 'Gepon AVRI+SLTB Sub-Group' vs 'Control AVRI+SLTB Sub-Group'

Clinical Symptoms	Gepon AVRI+SLTB Sub-Group	Control AVRI+SLTB Sub-Group
	Duration in Days	Duration in Days
Fever	**1,3+-0,06***	**2,9+-0,08**
Difficult nasal breathing	2,7+-1,1**	5,1+-1,2
Serous Rhinitis	1,7+-0,1**	3,68+-0,4
Mucous in nose	2,2+-1,2*	4,6+-1,4
Hypermia of fauces	2+-1,1*	5,1+-1,3
Appearance of pharyngitis	2,4+-1,4*	5,1+-1,3
Enlargement of palatine tonsils	3,3+-1,0*	5,4+-0,9
Hoarseness of voice	1,8+-0,3*	2,84+-0,06
Dry cough	**2,1+-1,2***	**3,4+-1,6**
Wet cough	2,5+-0,7*	3,9+-1,4
Stenosis of larynx	**1,2+-0,3***	**2,4+-0,5**
Swollen lymph nodes	3,2+-1,4	5,3+-1,6
Loss of appetite	1,5+-0,2	2,65+-0,1
Weakness	1,7+-0,2	2,5+-0,1
Sleepiness	1,4+-0,2	1,9+-0,2
Reduction of physical activities	1,4+-0,2	1,9+-0,2
Conjunctivitis	**1+-0,1****	**5+-0,3**
Complications	**1+-0,1**	**3+-0,2**

Significance of differences: *-p<0,001; **-p<0,005

Bold means 2 or more times reduction in days of symptoms

In the first two days of therapy, 72% of the child-patients in the Gepon AVRI+SLTB Sub-Group benefited from the alteration of the mucus consistency towards dissolution. In contrast, in the Control AVRI+SLTB Sub-Group, only 46% of the child-patients enjoyed this improvement in symptoms.

Gepon therapy significantly benefitted all the very sick child-patients who required antibiotics. In the sub-group of child-patients who were suffering from both AVRI and SLTB, and who had been be prescribed antibiotics to manage secondary bacterial infection, Gepon therapy granted them a significant shortening of the clinical symptoms and reduction in the duration of the antibiotics therapy. (Table 6)

Table 6. Comparison of Duration of Clinical Symptoms, in Child-Patients requiring antibiotics, in Gepon Group vs Control Group

Duration of clinical symptoms (in days)	Gepon AVRI+SLTB Sub-Group	Control AVRI+SLTB Sub-Group
	Antibiotic Therapy Subgroup (n=8)	Antibiotic Therapy Subgroup (n=12)
Fever	**1,9+-1,0****	**4,34+-0,8**
Difficult nasal breathing	4+-0,9	5,9+-0,7
Rhinitis	**2,6+-0,3****	**7+-0,8**
Mucous in nose	2,99+-1,1*	5,9+-1,3
Hypermia of fauces	3,3+-1,09*	5,8+-1,0
Pharyngitis	3,3+-1,09**	6,4+-1,1
Enlargement of palatine tonsils	4,2+-1,1**	6,1+-1,2
Hoarseness of voice	2+-0,08*	3,7+-0,07
Dry cough	3,9+-1,3	5,3+-1,2
Wet cough	**3,6+-0,4****	**9,7+-1,1**
Stenosis of larynx	**1,4+-0,4****	**3,2+-0,6**
Swollen lymph nodes	3,7+-1,4	5,1+-1,6
Decline in appetite	1,7+-0,2	2,98+-0,1
Weakness	2,4+-0,15	3,8+-0,3
Sleepiness	2,8+-0,2	3,4+-0,2
Reduction of physical activities	2,4+-0,3	3,9+-0,2
Conjunctivitis	**0**	**3+-0,1**
Complications	**1+-0,2**	**3+-0,1**

Significance of differences: *-p<0,001; **-p<0,005
Bold means 2 or more times reduction in days of symptoms

In the sub-group of child-patients suffering from AVRI and LTBS, and who were treated with antibiotics: Gepon therapy

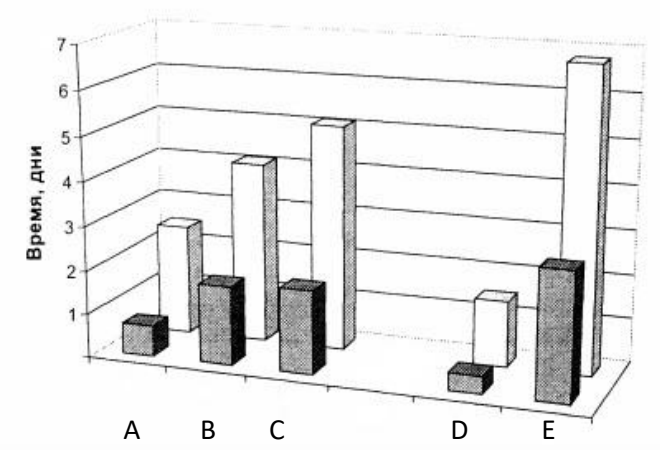
eliminated conjunctivitis within hours, and reduced fever to under two days, compared to over four days in the control sub-group. Gepon more than halved the average duration of stenosis of the larynx to around 34 hours.

In addition, Gepon therapy given to child-patients suffering AVRI+SLTB who were on antibiotics, reduced the ten-day duration of wet-cough observed in the control group, to around three days

LONG-TERM GEPON PROTECTION IN 3 MONTH FOLLOW-UP

Child-patients who had received Gepon therapy, had a significant decline in recurrence of respiratory disease during the 3-month period of observation, which followed treatment. On the rarer occasions when disease did re-occur, the illness progressed in a much milder form, and for shorter duration. After the first Gepon treatment for AVRI, only mild 3-day episodes of disease recurred, if at all, and the child-patients did not need hospitalisation. Gepon eliminated secondary bacterial complications requiring antibiotic therapy in almost all child-patients. In the Control Group, there were no such reductions in severity of recurring disease.

Fig 2 Duration of Clinical Symptoms (Days)
In the 3-month post-therapy follow-up Gepon Group n=50 (dark) and Control Group n=50 (light). Horizontal divisions in days.



A: Fever, B: Rhinitis, C: Wet-Cough, D: Antibiotics, E: AVRI

During the subsequent 3 months of observation in the Gepon Group the number of episodes AVRI was 0.5 per patient, whereas in the Control Group it was 1.6 per patient. The duration of one-episode AVRI in the Gepon Group, was 3.2 +- 0.3 days, whereas in the Control Group it was 6.9 +- 0.1 days. In those child-patients who received Gepon therapy but then fell ill again in the following 3 months, the AVRI was very mild, the duration of fever was reduced 3,2x, the duration of rhinitis 2,1x; and productive cough appeared on the average, on day-2, compared to Day 5 in controls.

In the Gepon Sub-Group with AVRI only, prior to therapy there were 17 cases of AVRI registered in 3 months. However, during the 3 months of observation following Gepon therapy, only 8 cases of AVRI cases were recorded. In contrast in the Control Group, prior to therapy there were 16 cases of AVRI registered in 3 months and during the 3 months of observation following therapy, there were 13 cases of AVRI.

Prior Gepon therapy reduced duration of fever from 2.5 days to 0.7 days, reduced duration of Wet Cough from 5.1 days to 2.2 days, the number of AVRI episodes from 6.9 days to 3.2 days and eliminated secondary bacterial infection and the need for antibiotics. (Table 7)

Table 7. Clinical AVRI symptoms in children during the 3 months of the observation period, following completion of Gepon prophylactic therapy

Clinical Symptoms	Gepon Group AVRI only (n=25)	Control Group AVRI only (n=25)
	Duration in days	Duration in days
Fever	**0.7+-0,1**	**2.5+-0,04**
Rhinitis	2.1+-0,3	4.1+-0,2
Wet Cough	**2.2+-0,4**	**5.1+-0,3**
AVRI episode	**3.2+-0,3**	**6.9+-0,1**
	Incidence	Incidence
Antibiotics therapy	**1 of 25**	**17 of 25**

Significance of difference: p<0,001

Bold means 2 or more times reduction in days of symptoms

In child-patients with AVRI+SLTB who had received Gepon therapy, the frequency of respiratory diseases 3 months after

completion of therapy, were reduced over 60%. Gepon reduced the frequency of respiratory disease in child-patients with AVRI + SLTB from 1.8 in the three months prior to therapy to 0.69 in the three months after completion of therapy. (Table 8)

Table 8. Frequency of respiratory diseases in child-patients with AVRI+ SLTB 3 months prior to therapy and 3 months after completion of therapy

AVRI frequency in AVRI + SLTB Patients			
Prior to Gepon therapy		3 months follow-up after therapy	
Gepon AVRI+SLTB Sub-Group	Control AVRI+SLTB Sub-Group	Gepon AVRI+SLTB Sub-Group	Control AVRI+SLTB Sub-Group
1.8+-0,1	2.0+-0,2	**0.69+-0,2**	1.2+-0.1

Significance of difference: p<0,005
Bold means 2 or more times reduction

In child-patients with Recurrent AVRI, who had received Gepon therapy, the frequency of respiratory diseases 3 months after completion of therapy were also reduced over 60%. Gepon reduced frequency of respiratory diseases in children with Recurrent AVRI (no SLTB), from 3.1 in the three months prior to therapy, to only 1.1 in the three months after completion of therapy (Table 9)

Table 9. Frequency of respiratory diseases in children with Recurrent AVRI 3 months prior to therapy and 3 months after completion of therapy

AVRI frequency in recurrent AVRI Patients			
Prior to therapy		3 months follow-up after therapy	
Gepon AVRI only Sub-Group	Control AVRI only Sub-Group	Gepon AVRI only Sub-Group	Control AVRI only Sub-Group
3,1+-0.2	2,9+-0.3	**1,1+-0.1**	3,4+-0.3

PROPHYLACTIC ADMINISTRATION OF GEPON

After the successful completion of the clinical study with intra-nasal ezrin-peptide TEKKRRETVEREKE [Gepon] therapy, the prophylactic efficiency of Gepon was assessed in child-patients who regularly suffered from recurrent AVRI.

Child-patients attending hospital were assessed for the frequency of recurrent AVRI, longevity of AVRI, the type of clinical symptoms (fever, intoxication, sputum production sputum, and rhinitis) and the associated increases in allergic reactions, duration and enlargement of swollen lymph nodes, inflammation of the pharynx and tonsils, and the development of obstructive bronchitis or croup syndrome.

In the Prophylaxis Study, the prophylaxis treatment regime was 1 drop of Gepon solution (1 mg/ml) into each nasal passage, 3 times in the day, for 4 weeks. The result was no AVRI cases being registered over the following three months in the Gepon Group. In contrast in the Control Group of 0.6 cases per child were registered.

DISCUSSION OF CLINICAL STUDY ONE

The results of this clinical study show that Gepon treatment is safe, without side effects and well tolerated; Gepon is an effective prophylactic and treatment for viral diseases such as AVRI and SLTB which have an inflammatory component.

Ezrin-peptide TEKKRRETVEREKE [Gepon] restores order to the immune responses dysregulated by pathogenic respiratory viruses, while suppressing non-specific inflammation. Gepon inhibits the expression of the inflammatory cytokines IL-1, IL-6, IL-8 and TNFα triggered by viral replication, while at the same time triggers tissue repair and recovery processes. Ezrin-peptide TEKKRRETVEREKE [Gepon] stimulates fibroblasts to repair the disturbed epithelial barrier to restore effective protection to bacterial, fungus and virus infection in the mucus membranes of the airways.

Earlier studies demonstrated that ezrin-peptides could significantly enhance specific humoral immunity against infections, even in AIDS patients, where they amplified antibody production against opportunistic infections. [35]

It is remarkable how such a complex disease process as AVRI induced SLTB croup, is gently but effectively reversed by ezrin-peptide TEKKRRETVEREKE [Gepon]. In children with Acute Respiratory Viral Infection (AVRI) and Stenotic Laryngo-Tracheo-Bronchitis (SLTB), simple intra-nasal therapy with Gepon solution, reliably reduced the duration and intensity of fever, reduced the concentrations of inflammatory cytokines, reduced the severity and duration of stenosis, reduced the inflammation of the larynx, and converted dry-cough into productive cough by liquefaction of sputum.

Children suffering from recurrent inflammatory AVRI, benefited from Ezrin-peptide TEKKRRETVEREKE [Gepon], which reduced duration and severity of recurrent AVRI. Gepon decreased morbidity of AVRI by almost 3 times, as well as reducing the annual incidents of AVRI.

In children suffering from Acute Viral Respiratory Infection (AVRI) combined with Laryngeal-Tracheal-Bronchitis with Stenosis (SLTB), intra nasal Gepon therapy decreased fever duration, the incidence and duration of stenosis of the larynx, terminated dry-cough, as well as decreasing the period of time before appearance of productive cough with sputum.

In addition, long term benefits have been observed with ezrin-peptides. For three months after Gepon treatment, there was no recurrence of respiratory obstruction, no re-hospitalisation was required for normally chronic recurrent patients. Gepon also reduced the need for the treatment of secondary bacterial infection with antibiotics. In child-patients with AVRI + SLTB, intranasal therapy with Gepon reliably shortened the duration of fever, cured the stenosis of larynx, and also reduced period dry cough and stimulated the appearance of a productive cough.

Intra-nasal administration of Gepon is remarkably non-toxic and safe. No side effects or unfavourable drug interactions were detected. There are no known contra-indications for Gepon for any age of patient. Thus, Gepon was remarkably effective in eliminating AVRI and SLTB Croup.

CLINICAL STUDY TWO

Post-registration clinical study into Ezrin-peptide TEKKRRETVEREKE [Gepon] treatment of chronic inflammatory diseases of throat.

A clinical study of Gepon therapy, was performed at Russian Government Medical University, Moscow, on 48 adult patients who suffered either chronic inflammatory pharyngitis or chronic inflammatory tonsillitis, with durations from 5 years to 25 years. The Principal Investigators were T. S. Polyakova, M. M. Magomedov, M E Artyemev, E V Surikov, and V. T Palchun. [36] [37]

Ezrin peptide TEKKRRETVEREKE [Gepon] solution was investigated as a new method of treatment for inflammatory chronic disease of the throat. Gepon is a rapid-acting anti-inflammatory peptide, which suppresses inflammatory cytokines IL-1, IL-6, IL-8 and TNFα. Gepon also amplifies anti-viral immunity and possesses interferon induction activity that increases the expression of Type I interferons: α-interferon and β-interferon.

The open clinical investigation of Gepon therapy, was performed on 48 adult patients (20 men, 28 women, aged between 15 and 75 years) who had been suffering inflammatory disease of the throat triggered by viral infection, with durations from 5 years to 25 years. Of these patients, 28 were suffering chronic inflammatory pharyngitis, and 20 were suffering chronic tonsillitis. Throat inflammation was associated with chronic candida infection in 32 cases and cocci flora in 16 cases.

At the commencement of the clinical study, the inflamed mucous membranes of throat were examined in both groups of patients: sub-atrophic pharyngitis was diagnosed in 16 patients, atrophic pharyngitis in 5 patients and hypertrophic pharyngitis in 7

patients. The 16 sub-atrophic and atrophic pharyngitis were all women. All 20 chronic tonsillitis patients had clear manifestations of the disease.

Patients complained of pain in the throat, tickling sensation, dryness in the mouth and the sensation of foreign body obstruction. Viscous mucus was detected on the fauces, the arched opening at the back of the mouth leading to the pharynx, and on rear wall of the pharynx.

After ultrasonic washing of the mouth, throat and nose with saline, a solution of 2mg Gepon in 5ml water was applied to the throat using an ultrasonic irrigator. Three doses of Gepon solution were administered using an ultrasonic irrigator on Day-1, Day-3 and Day-5 of treatment

By Day-2, all signs of inflammation of the throat had disappeared, in 46 of 48 patients. Only two patients still displayed hyperemia of mucus membrane of rear wall of the pharynx, but this resolved by Day-5. The anti-inflammatory effect was confirmed by microscope examination. In 45 patients (94%) Candida infection had disappeared and cocci flora were reduced to insignificant levels.

The 30-day follow up examination, showed that 46 of 48 patients maintained a healthy pharynx and tonsils, after years of chronic inflammation (2 patients relapsed). The rapid cure rate of 96% of chronic pharyngitis and tonsillitis was impressive. No side effects or adverse reactions to Gepon were observed.

CLINICAL STUDY THREE

Ezrin-peptide TEKKRRETVEREKE [Gepon] Solution-Vapour Treatment of Acute Viral Respiratory Infection (AVRI), and complications (Pneumonia)

A post-registration clinical study of ezrin-peptide TEKKRRETVEREKE [Gepon] solution-vapour, administered to the airways to treat Acute Viral Respiratory Infection (AVRI), and complications such as Pneumonia. The clinical study was performed at Department of Infectious Diseases, Moscow Hospital

No 1, in collaboration with the Russian Ministry of Health Institute of Immunology, during 2008. The Principal Investigators of the study were O.A. Safonova, A B Pichukin, E Sh Kozhemyakina, N A Malshev and R I Ataullakhanov. [38]

151 adult Acute Viral Respiratory Disease patients were assessed to participate in the clinical study of ezrin-peptide TEKKRRETVEREKE [Gepon] therapy. 135 patients were recruited and gave informed written consent to join the clinical study.

All patients received standard symptomatic therapy: anti-inflammatory paracetamol, antihistamines, expectorants and inhalation of vaporized 0.2% sodium bicarbonate solution.

On admission to hospital, all patients presented with Acute Viral Respiratory Infection (AVRI) with the following symptoms: sore throat, cough, runny nose, hoarseness of voice, together with symptoms of systemic intoxication including headache and weakness.

Some patients with AVRI presented evidence of serious inflammation of the sinuses, bronchitis, obstruction of the pharynx, together with hyperaemia of the mucous membrane of the pharynx, swollen tonsils, sores on pharynx wall, and purulent deposits. Some patients complained of severe congestion, mucopurulent discharge from the nose and debilitating headache, which required X-ray examination of the nose. Other patients with AVRI present evidence of lung infection and pneumonia: dry or wet cough, shortness of breath, dry or wet wheezing which required X-ray examination of the lungs.

Patients were screened by blood tests to identify the infecting agents. Diagnostic tests were performed for the antigens of influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus (RSV), and other viruses.

Table 10. Number of Patients in Clinical Study

Infection	**GROUP A AVRI** uncomplicated	**GROUP B AVRI +** Sinusitis Laryngitis Bronchitis	**GROUP C AVRI +** Pneumonia	**TOTAL**
Influenza	27	16	25	68
Parainfluenza	3	7	3	13
Adenovirus	5	12	2	19
RSV	4	4	3	11
Mixed Virus	5	6	3	14
Unknown ID	4	4	2	10
TOTAL	48	49	38	**135**

IgM, IgA, IgG and IgE were measured together with concentrations of C-reactive protein in the blood. Bacteriological analysis of the sputum was used to identify Mycobacterium tuberculosis (if present), non-specific micro-flora and any antibiotic drug-resistance.

Flow cytometry was used to count peripheral blood immune cell subpopulations, their activation markers and functional subtypes such as CD4+ T helper cells, CD8+ cytotoxic T lymphocytes and NK cells. Chemo-luminescence was applied for the functional study of granulocyte ex vivo response to zymosan, a fungal glucan recognized by TLR2 receptors.

The patients were then allocated to three sub-groups, depending on the type and severity of symptoms, for the following clinical studies of the safety and efficacy of Gepon vapour therapy:

Clinical Study A; AVRI (uncomplicated)
Clinical Study B; AVRI + serious inflammation
Clinical Study C; AVRI + pneumonia

Clinical Study A: uncomplicated AVRI

The 48 adult patients presenting AVRI only, but no pneumonia, were enrolled for a randomised Clinical Study A of Gepon inhalation therapy. 26 patients were randomly assigned to the Gepon Group A and 22 to the Control Group A. Both groups received standard therapy of vitamins, antihistamines (calcium gluconate, diazolin), as well as antipyretic and anti-inflammatory treatment (paracetamol) or phenaca if body temperature exceeded 38.5^{o}C.

In Gepon Group A, 22 patients received 1mg in 5 ml Ezrin-peptide TEKKRRETVEREKE [Gepon] solution vapour inhalation per treatment. Gepon was prepared for treatment in batches by dissolving 2mg lyophilised Gepon in 10ml of isotonic NaCl solution, resulting in a 0.02% Gepon solution. 5ml of solution was added to an ultrasonic Beron inhaler and blown into the nasal cavity and airways of the patient, once a day, for 5 consecutive days. Total course of therapy 5mg of peptide.

Ezrin peptide TEKKRRETVEREKE [Gepon] significantly accelerated recovery from of Acute Viral Respiratory Infection (AVRI).

Table 11. Duration of symptoms: Gepon vs Control (Group A)

Symptom	Gepon Group A Duration in Days	Control Group A Duration in Days	Significance
Fever	2.68	4.05	p<0.003
Dry-Cough	2.50	5.50	p<0.0001
Intoxication	2.85	4.14	p<0.003
Headache	2.67	3.90	p<0.006
Rhinitis	2.56	4.05	p<0.003
Weakness	2.92	4.14	p<0.005

The application of Gepon inhalation significantly accelerated recovery from Acute Viral Respiratory Infections without complications. On average, normalisation of body temperature was achieved in 2.68 days compared to 4.05 days in the control group

and dry cough was stopped in under 2.5 days, while it persisted for 5 to 6 days in the Control group.

Clinical Study B: AVRI + throat inflammation, sinusitis, tonsillitis and bronchitis

49 patients in Clinical Study Group B, AVRI + throat inflammation, sinusitis, tonsillitis and bronchitis, all received standard therapy. Only 12 patients received additional Gepon inhalation therapy. By the third day of hospitalisation, all 37 Control Group B patients (n=37), suffered worsening symptoms and had to receive antibiotics for 5 to 7 days.

In contrast, the 12 patients of Gepon Group B (n=12) steadily improved and duration of illness was significantly less.

Table 12. Duration of symptoms: Gepon vs Control (Group B)

	GEPON GROUP B	CONTROL GROUP B	
Fever	2.9 days	3.5 days	p <0.05
Intoxication	3.0 days	4.2 days	p<0.0001
Headache	2.3 days	3.5 days	p<0.005
Weakness	3.0 days	4.2 days	p<0.0001
Loss of Voice	2.0 days	3.8 days	p<0.097

There was a rapid reduction of inflammation in patients who received Gepon inhalation. Bronchitis, Laryngitis and Sinusitis persisted for about 8 days in the Control Group B, while all 12 patients had recovered in the Gepon Group after 5 to 6 days.

Clinical Study C; AVRI + pneumonia

38 patients (aged 30+/-14 years) suffering Acute Viral Respiratory Disease (AVRI), complicated with pneumonia. Patients suffered fever up to 39^{o}C and 82% presenting dry cough. All 38 patients with AVRI+pneumonia, gave their written informed consent to the clinical study, in which immuno-modulators would be added to the Gepon Group in addition to standard therapy.

Patients with secondary bacterial infection also received antibiotics and Immunomax, a macromolecular peptidoglycan immuno-stimulator.

The patients were randomised, and two subgroups were created: 20 patients were allocated to Control Group C and 18 patients were allocated to Gepon Group C.

All patients received standard intra-venous anti-bacteria therapy with both cephalosporin and aminoglycoside antibiotics, anti-inflammatory therapy with antihistamines, expectorants and inhalation of vaporized 0.2% sodium bicarbonate solution, after developing symptoms of pneumonia with AVRI.

Gepon Group C received 1mg in 5 ml Gepon solution vapour inhalation per treatment. Ezrin-peptide TEKKRRETVEREKE [Gepon] was prepared for treatment in batches by dissolving 2mg lyophilised Gepon in 10ml of isotonic NaCl solution, resulting in a 0.02% Gepon solution. 5ml of solution was added to an ultrasonic Beron inhaler and blown into the nasal cavity and airways of the patient, once a day, for 5 consecutive days. The total course of therapy was 5mg of peptide.

Ezrin peptide TEKKRRETVEREKE [Gepon] significantly accelerated recovery from of Acute Viral Respiratory Infection (AVRI) complicated with Pneumonia. [39] In patients of the Gepon Group C suffering pneumonia, the duration of fever, intoxication, headache and weakness were significantly shorter.

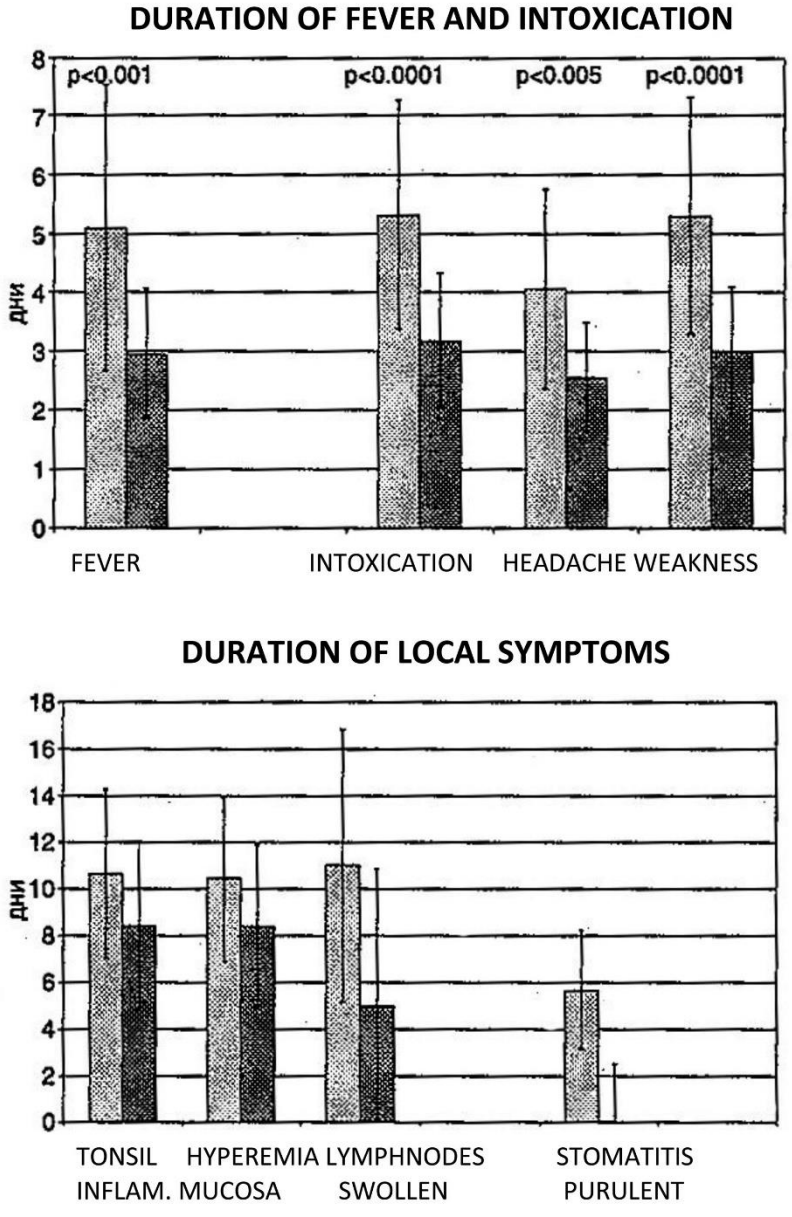
Table 13. Duration of symptoms: Gepon vs Control (Group C)

	GEPON GROUP C	CONTROL GROUP C	
Fever	2.9 days	5.1 days	$p < 0.05$
Intoxication	3.2 days	5.3 days	$p < 0.0001$
Headache	2.6 days	4.1 days	$p < 0.005$
Weakness	3.0 days	5.3 days	$p < 0.0001$

Gepon was particularly effective at reversing high fever temperatures (39^{o}C), triggered by lung infection and inflammatory

pneumonia. Gepon reduced by twenty per cent, the duration shortness of breath, hypoxemia (low arterial blood gas), the need for supplemental oxygen and breathing support.

Fig 3. Duration of Symptoms in Days of Patients with Acute Viral Respiratory Infection and Pneumonia Control Group (Light) Gepon Group (Dark)



Protection by Gepon from Bacterial Infection in Hospital

On the first day of hospitalisation, there were 79 patients who present ARVI without bacterial complications. During the studies, 48 of 79 patients received standard symptomatic therapy only, while 31 of 79 patients received additional Gepon inhalation therapy. Antibiotics had to be prescribed to 26 patients who received standard therapy only. In contrast there were only 5 cases with patients who were receiving Gepon, who also needed antibiotic therapy. Gepon inhalation therapy had reduced the risk of bacterial infection in hospital by more than three times.

DISCUSSION

Relevance of Ezrin Peptide therapy to COVID-19 Disease

Ezrin Peptide therapy may be a therapeutic approach to COVID-19 Disease. The new acute viral respiratory disease was first identified in mid-December 2019 in the city of Wuhan of Hubei Province in the centre of China, which has a population of 11 million people. A novel type of coronavirus was identified as being the causal agent and named 2019-nCoV virus. In February 2020, WHO renamed the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which caused a new disease renamed COVID-19.

By Friday 13th March 2020, COVID-19 disease was spreading rapidly and exponentially around the globe. Over three months, the cumulative number of cases world-wide was over 135,000 and there had been almost 5,000 deaths. It is estimated that just over 70,000 people recovered from COVID-19. Only two weeks later the cumulative number of cases world-wide was about 550,000 and there had been almost 25,000 deaths.[40]

The fatality rate in Europe appears higher than in China.[41] Italy now has the highest number of deaths in the world from COVID-19 virus. The fatality rate is around 5% of the confirmed infected population, much higher than the global average of 3.4%, according to the World Health Organization. [42]

The V-strain of COVID-19 infecting the Italian population, may be more pathogenic. Another factor affecting the high death rate in Italy may be the older average age of the infected population infected with COVID-19-virus. In Italy, about a quarter of infected people are 65 or older and many of Italy's deaths have been among people in their 80s, and 90s. On the other hand, the number of non-confirmed infections could be much higher in Italy.[43]

Generally, Coronaviruses belong to a family of viruses which can induce disease ranging from mild “common cold” symptoms, to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). [44] During the 2002–2003 epidemic of SARS, a highly pathogenic coronavirus-SCV infected approximately 8,000 individuals, and there was overall mortality of infected people of 10%. In 2012 MERS-CoV was first identified in a patient in the Middle East, and infected 2374 individuals and caused 823 deaths over the following eight years. [45] [46] [47]

The pathogenic properties SARS-CoV and MERS-CoV coronaviruses have been studied closely. The high pathogenicity of SARS-CoV and MERS-CoV coronaviruses is due to their high affinity for airway epithelial cells, type II pneumocytes, and endothelial cells of human lung alveolar micro capillaries.[48] [49]

Infection with these types of coronaviruses can cause systemic inflammation accompanied by persistent hypotension, hyperthermia or hypothermia, leukocytosis or leukopenia, thrombocytopenia, and Acute Lung Injury (known as ALI) causing Acute Respiratory Distress Syndrome (known as ARDS). In ALI cases, the mortality rate is in the range 20–30%, with about 55% of the cases progressing to ARDS within a few days. ARDS causes significant morbidity and approximately 40% mortality.[50]

The Chinese Centre for Disease Control and Prevention issued a report on 72 314 COVID-19-virus infected cases, which revealed that of the population of COVID-19-virus infected people, about 80% had “Mild disease”: ~38^{o}C fever and dry cough by mild or no mild pneumonia. About 15% had “Severe Disease”: including dyspnoea (shortness of breath), hypoxia (low blood oxygen), and

lung damage. About 5% had “Critical Disease”: including respiratory failure, shock, and multi-organ dysfunction.

87% of patients were between 30 and 79 years old. Older age was also associated with increased mortality, with a case fatality rate of 8% among those aged 70 to 79 years old and 15% 80 years or older. The overall case fatality rate was 2.3%, and no deaths were reported among non-critical cases. [51] [52]

In several cohorts of hospitalized patients with confirmed COVID-19, the median age of the infected population ranged from 49 to 56 years. A study describing 138 patients with COVID-19 pneumonia in Wuhan reported that the most common clinical features at the onset of illness were: Fever in 99 % (above 37.5^{o}C), Fatigue in 70%, Dry cough in 59 %, Anorexia in 40 %, Myalgia in 35%, Dyspnoea in 31 %, Sputum production in 27 %. The dyspnoea (shortness of breath) developed after a median of five days of illness. Acute Respiratory Distress Syndrome (ARDS) developed in 20%, and mechanical ventilation was implemented in 12.3%.[53]

COVID-19: The Immune Response

The innate antiviral response, particularly production of Type I Interferon: IFN-α and IFN-β, is the first line of defense against multiple virus infections. Type I Interferon mediates antiviral effects by directly inhibiting virus replication and indirectly modulating the host immune response to virus infection, both of which are mediated by induction of interferon-stimulated genes (ISGs). However, SARS-CoV and MERS-CoV have developed specific mechanisms to block the signaling pathways of interferons and IFN-stimulated genes (ISGs) of the innate immune system, which allows the virus to maintain infection and replication.[54] [55]

The dysregulated innate immune system of patients with coronavirus infection, displays delayed expression of Type I Interferons, which is critical for initiation of the anti-viral innate immune response, together with elevated expression of IL-1, IL-6,

IL-8 pro-inflammatory cytokines and CXCL-10, and MCP-1 chemokines, leading to extensive lung damage.[56] [57] [58] [59]

In Severe Cases of COVID-19 an uncontrolled immune response known as “Cytokine Storm”, is mediated by the pro-inflammatory cytokines IL-1 and IL-6. The immune over-reaction among COVID-19 patients, leads to Acute Respiratory Distress Syndrome (ARDS) and potentially life-threatening damage to lung tissue.

Symptoms of ARDS include shortness of breath, rapid breathing, and a bluish low-oxygen skin coloration. ARDS is respiratory failure, resulting from widespread inflammation in the lungs, which impairs the exchange oxygen and carbon dioxide in the alveoli of the lungs. There is no known effective treatment for ARDS, so supportive provision of oxygen to the failing lungs is the only option.

No Effective Treatment for COVID-19 Virus and Disease

There is no treatment available for the inflammation and pneumonia induced by COVID-19-virus. Both WHO and US CDC warn that glucocorticoids, a class of corticosteroids, should not be used to control the inflammation and auto-immunity induced by COVID-19 virus, because they have been associated with an increased risk of death in patients with influenza, a delayed viral clearance in patients with MERS coronavirus, and generally there is significant evidence of both adverse short-term and long-term harm to patients.

Actemra, an anti-IL-6 receptor therapy for rheumatoid arthritis produced by Hoffman La Roche has been used to treat lung damage in serious cases coronavirus patients but the efficacy is still uncertain. The Russian Federal Medical-Biological Agency is investigating mefloquine. No antiviral drug has been demonstrated to stop COVID-19 virus replication. However, a combination of antivirals lopinavir and ritonavir developed to treat HIV, called Kaletra (Aluvia) are being tested. In addition, the Russian influenza remedy called Arbidol (Umifenovir) is also being tested. In addition,

Gilead Sciences is promoting Remdesivir as a potential anti-viral treatment. However, no effective treatment for COVID-19 disease has been demonstrated.[60]

Interferon-inducers trigger IFN-α and IFN-β and early use of interferon-inducers may be useful for prophylaxis COVID-19 disease. The Caco2 human cell line derived from epithelial colorectal adenocarcinoma cells, supports the replication of coronavirus-SCV that caused SARS. In this experimental system, IFN-α, -β, and -γ have been found effective in inhibiting this replication.[61]

In animal models, prophylactic or early therapeutic administration of recombinant IFN-β (rIFN-β) completely protected animals from lethal MERS-CoV and SARS-CoV infection by inhibiting virus replication and inflammatory cytokine production. [62] [63] [64] [65] The use of type I interferons can decrease the effects of infection with SARS-CoV and MERS-CoV viruses in animals if used early in the detection of symptoms.

However, the timing of IFN therapy is critical. Delay in starting rIFN-β therapy led to a huge increase in inflammatory cytokine levels, resulting in fatal disease in an otherwise sub-lethal infection. These results suggest that the timing of IFN-αβ receptor (IFNAR) signaling, relative to peak coronavirus replication, is a critical determinant of either protective immunity or pathogenic immunity in coronavirus disease. [66] [67] [68] [69] [70] [71] [72] [73] [74] [75]

The clinical results presented in this paper, suggest that oral, nasal and vapor inhalation Ezrin Peptide therapy should amplify antiviral immunity and reduce inflammatory events in COVID-19 patients. There are no known adverse side effects with Ezrin Peptide therapy, and it should be especially helpful for the therapy of the elderly population.

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