Synthetic and Natural Immunomodulators Acting as Interferon Inducers

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Abstract: Interferons are first immunomodulatory molecules that have been shown to display a wide range of applications due to their antiviral, antibacterial, antitumor, and inflammatory activities. Natural and recombinant interferons are among most common biologic therapeutics worldwide. Interferon inducers, however, are less known and have been mostly developed and used in former socialist countries. Despite the fact that they are virtually unknown to the Western world, they represent a substantial market share of modern pharmacopoeia in former socialist republics. This review provides a brief description of most popular interferon inducers including Amyxin, Amizon, Anandin, Arbidol, Blasten, Cycloferon, Galavit, Groprinosine, Hepon, Immunoxel, Dzherelo, Kagocel, Larifan, Ligfol, Likopid, Mebavin, MIGI-KLP, V-5 Immunitor, SCV-07, Milife, Neovir, Poludan, Ragocin, Ridostin, Thymogen and Savratz, some of which were in use for several decades for the same clinical indications as for interferons. The variety and choice offered by the pharmaceutical industry behind the former "iron curtain" certainly deserves the appreciation, familiarity and application prospects for medical and research investigators worldwide.

INTRODUCTION

Immune system is the main regulatory system controlling homeostasis of the body and participates virtually in all (processes) cycles of the life from birth to death. The incompetence of the immune system opens door to infectious, malignant, autoimmune, and inflammatory diseases. There are many modern interventions directed to stimulation, modulation or suppression of the immunity by various routes.

Interferons are extremely important category of protein therapeutics aiding defense against infections and malignancies carrying foreign for host genetic information. Interferons are intra- and inter-cellular signaling proteins of three classes – alpha, beta, and gamma, which differ by their activity, cell origin and cell targets. Natural and recombinant interferons are widely used in the modern therapy of acute and chronic infectious and oncological diseases and some immune disorders. Alpha interferons such as Laferon, Intron A, Welferon, Reaferon, Viferon, Viaferon, Roferon A as well as beta interferons – Betaferon, Feron, Fron, Rebif, and others represent the type I interferons which express high antiviral activity and widely applied in a complex antiviral therapy [1-9]. Gamma interferons such as Iimmukin, Interferonlagen, mega-D-interferon and others represent the type II interferons which increase MHC II level on antigen-presenting cells and regulates the level of inflammatory and immune responses. Gamma interferons were successfully applied for therapy of viral, malignant, and autoimmune diseases [10-14].

However, interferons are species-specific and for the replacement therapy species-specific proteins are necessary, which is a limiting factor for their using in the veterinary and animal experimentations. On the other hand, administration of interferons could activate negative reverse loop of regulation, inhibiting endogenous interferon production and it could be undesirable side effect, particularly in the chronic cases of diseases. To overcome both of the above restricting factors, interferonogens could be successfully applied, as they are not species-specific and stimulate endogenous production of interferon.

Generally, interferonogens have significant advantages comparing to native or recombinant interferons: single administration of interferonogens increases interferons to therapeutic level for up to several days, whilst interferons administration should be multiple and in high dosage as their semi-life is about 20-40 minutes; such high-rate administration of interferons could turn on regulatory machinery of their endogenous synthesis and severe side effects [15,16]; overdosing of interferonogens (and according side effects) is practically impossible as interferon synthesis is still controlled by organism; and, finally, interferonogens are mostly not antigenic and could be used long period repeatedly.

The first successful clinical application of experimental viral interferonogen IVS (inactivated Semliki Forest virus) in therapy of viral ocular infection was performed in the USSR by A.A.Kasparov and colleagues in 1966 [17]. Starting from that several interferonogenes were discovered and investigated, most of them by scientific groups of the former USSR [18].

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Among contemporary immunomodulators with interferonogenic activity the physical, chemical and biological agents could be designated. Physical influence on the immune system by low-intensity laser, ultrasound, low-frequency magnetic field etc. could normalize various immunity subsystems activity, particularly phagocytosis, cellular and humoral immune response by both interferon-dependent and independent pathways [19].

As a result of many years of screening several promising interferonogenes were revealed among various kinds of natural and synthetic compounds (fluorenones, acridanones, gossypol derivatives, polynucleotides, ds-RNAs etc.) They have quite high chemotherapeutic index and could be useful for prophylaxis and treatment of viral and other diseases. By chemical synthesis and biotechnology means low molecular weight substances were obtained such as Neovir, Cycloferon, Kagocel, Amixin, as well as high molecular weight substances such as Poludan, Ridostin, Larifan, and others. Others preparations with interferonogenic properties were discovered from natural biological sources, for example, Milife – from fungi; "MIGI-KLP"- from mussel; Immunomax and Immunoxel (Dzherelo) – from medicinal plants; V5 Immunitor – from pooled blood.

In the next chapters we concentrate on some scientifically proven and industrially manufactured interferonogenes and review their properties related to clinical uses.

Hepon. Manufacturer: "Immapharma", Russia

Hepon is synthetic immunomodulator based on tetradecapeptide: Thr-Glu-Lys-Lys-Arg-Arg-Glu-Thr-Val-Glu-Arg-Glu-Lys-Glu, induces alpha and beta-interferons, inhibits inflammatory cytokines, stimulates humoral immunity. Experimentally demonstrated inhibition activity of Hepon on hepatitis C virus replication in human cell cultures [20], antiviral activity of Hepon was also demonstrated for rabies with dose-dependant protection of up to 40% mice [21], Herpes simplex viruses types 1 and 2 with one hundred fold reduction of viral titer *in vitro* and 36% protection after 10 LD50 dose challenge [22]. Hepon-treatment intensifies antibody production against HIV1-antigens [23] and increases concentration of CD4 and NK cells, functionality of neutrophils and CD8 T-cells, and decreases virus load in the blood of HIV-infected patients [24].

Stimulation of activity of intestinal mucosal immunity was demonstrated in several clinical trials [25,26]. In the experimental and clinical studies was proved efficiency of therapy with Hepon and Immunomax (another immunocorrector, developed by the same group) during acute purulent surgical infections [27]. There were no noted contraindications and adverse reactions associated with Hepon.

Cycloferon. Manufacturer: "Polysan", Russia

Cycloferon is a synthetic analogue of *Cytrus Grandis* alkaloid, stimulates B-cells, macrophages and other cells and tissues to produce almost pure type 1 interferons. It was reported to have up to 100-fold upregulation of beta-interferon gene and 10-fold upregulation of alpha-interferon gene in the human blood samples after administration of Cycloferon without affecting essentially the activity of other genes of blood cells [28]. In the placebo controlled multicentered study on totally 16,000 children and adolescents Cycloferon demonstrated clear epidemiological benefit in the prophylaxys of the influenza and other acute respiratory viral infections with 1.5-2.9 –fold decreased morbidity and 41-90% protection index [29]. Its efficiency was demonstrated in chronic infections of upper respiratory tract too [30]. Specific antiviral activity of Cycloferon against adenovirus type 6 *in vitro* [31] and herpes virus on experimental herpetic infection was demonstrated [32]. The author's (D.S.) personal observations in the veterinary hospital have revealed antiviral efficiency of Cycloferon in cases of canine distemper and parvoviral gastroenteritis. The duration of the disease, commonly, decreases for 3-4 days when standard complex therapy was supported by Cycloferon. In the animals with normal immune status Cycloferon induced the formation of the serum interferon in high titers (up to 20,000) with the peak achieved 4-8 hours after the injection and increased survival rate in generalized herpes infection by 30-100% in comparison with the controls. Under immunosuppression caused by gamma-radiation or cyclophosphamide the titers of serum interferon were 4-8 times lower and the protective effect of this preparation was considerably milder [32]. However, in HIV-infected patients the remission period of herpes simplex virus 1 and 2 infections is prolonged after combination of antiviral treatment with Cycloferon [33]. The antibacterial activity of cycloferon was demonstrated for various pathogenic and opportunistic species [34], and correction of the immune status after anti-tumor therapy was also observed [35]. Anti-apoptotic activity of Cycloferon was seen in the hypothalamic neurosecretory centers [36].

Amyxin (Amixine). Manufacturer: "Lancepharm", "Dalhimpharm", "Masterlek", Russia; and Odessa Physico-Chemical Institute, Ukraine

Amyxin (Tilorone) induces alpha, beta, and gamma interferons by intestinal epithelium, hepatocytes, and granulocytes.In the animal models, 4-24 hours after oral administration, maximum levels of interferon are reached in the intestine, liver and blood, resulting in efficient prevention and therapy of chronic enteritis and hepatitis [37]. Besides potent interferonogenic activity, Amyxin causes activation of NK and phagocytes in peripheral blood [38]. Interestingly, linkage of RNA-Amyxin complex to bead carriers improves interferonogenic properties and proves that mechanism of such activity requires the contact between the effector and the cell surface without its penetration into the cell [38]. Antiviral properties of Amyxin are well documented on a range of viruses. Thus, experimental Haemorrhagic fever studies reveals 52% protection of animals by combined Amyxin-Virosole therapy which was superior to the effect of their monotherapy [40], although some regimens of Amyxin only provided protection up to 61% with oral administration and up to 65% with subcutaneous injection [39]. Preventive Amyxin therapy in population groups with high hemorrhagic fever with renal syndrome (HFRS) risk prevents development of HFRS and acute respiratory viral infection [41]. In the same study it was shown that Amyxin in chronic viral hepatitis (CVH) improved general condition of the patients, removed jaundice of the skin and sclera, normalized activity of aminotransferases and blood bilirubin level. Virus replica-

tion was stopped in 25% cases of chronic HBV and in 1.6% cases of chronic HCV infection [39]. The 33% lethality reduction by Amyxin was demonstrated in experimental West Nile Fewer *in vivo* [40], while antiviral effect of RNA-Amyxin molecular complex was registered *in vitro* for three virus-cell systems: vesicular stomatitis virus (VSV) - murine fibroblast L929 cells, Venezuelan equine encephalitis virus (VEEV) - swine embryo kidney (SEK) cells and encephalomyocarditis virus (EMCV) - established piglet testicular (EPT) cells [42]. The administration of Amyxin simultaneously with polyvalent vaccination of pups in context of emergency prophylaxis, seemed to reduce cases of vaccination failure, although efficiency of Amyxin in cases of developed canine distemper and parvovirosis was insignificant even at early stages of diseases. The efficacy of Amyxin for flu and acute respiratory viral infections' prophylaxis and treatment was demonstrated in a controlled trial of the risk group of medical personnel [43]. Amyxin in combination with herpes vaccination was highly efficient (87.9-90.9%) for the treatment of herpetic keratitis and prevented the relapse of the disease [44].

Arbidol. Manufacturer: "Dalchimpharm", "Masterlek", Russia

Arbidol (ethyl-6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylthio)methyl]-indole-3-carboxylate hydrochloride monohydrate) stimulates humoral and cellular immunity, posses interferonogenic and antioxidant activity. Arbidol was shown to have effects on nonspecific defense factors, on capacity to induce interferon and to activate phagocytes in particular. Arbidole-treated patients with lower baseline immunity showed improvement in immunological parameters (in the counts of CD4 and CD8 lymphocytes, B lymphocytes, in the levels of serum immunoglobulins). Arbidol produces a high preventive and therapeutical effects in influenza A and B and other acute respiratory viral infections, prevents postinfluenza complications, reduces the incidence of exacerbations of chronic diseases in postinfluenza patients [45]. In the randomized, double-blinded, placebo controlled trial was revealed that the median duration of naturally acquired influenza was 72.0 hours in Arbidol group and 96.0 hours in placebo group. The median area under the curve (AUC) of decreased total score were significantly higher in Arbidol group than in placebo group, thus Arbidol was effective and well tolerated in the treatment of early naturally acquired influenza [46]. Specifically, reproduction of human IVA antigenic strains H1N1, H2N2, H3N2, remantadin-sensitive and remantadin-resistant strains of influenza virus as well as pathogenic for humans strains of avian influenza virus H5N1 and H9N2, were inhibited *in vitro* by Arbidol [47]. Efficiency of arbidol against bird flu virus H5N1 isolated from wild birds and poultry in Russia was proved *in vitro* [48, 49], and in the treatment of humans during avian influenza outbreak [50]. The wide spectrum of antiviral activity against respiratory viruses has led to the assessment of its efficiency on hepatitis C virus in cell culture. Long-term Arabidol treatment of Huh7 cells chronically replicating a genomic length genotype 1b replicon resulted in sustained reduction of viral RNA and protein expression, and eventually cured HCV infected cells. Besides, pre-treatment of human hepatoma Huh7.5.1 cells with 15 microM ARB for 24 to 48 hours inhibited acute infection with JFH-1 virus by up to 1000-fold [51].

Amizon. Manufacturer: "Pharmac", Ukraine

Amizon (N-methyl-4-benzylcarbamidopyridinium jodide) – derivative of isonicotinic acid belongs to analgetic group and among anti-inflammatory, antifever and analgetic properties expresses interferonogenic activity increasing 3-4 fold endogenous interferon in plasma, enhancing humoral and cellular immunity. Antiviral and immunomodulatory activity of amizon was clinically demonstrated on patients with hepatitis B and C with renal lesions [52] and chronic toxic hepatitis [53]. Clear clinical improvement was detected in 149 patients with Mumps treated by complex therapy with amison in comparison to 177 patients obtaining the same conventional treatment without amizon [54]. Antiinflammatory activity of amizon enhance its positive interferonogenic influence on patients with acute infectious inflammation [55].

Neovir. Manufacturer: "Pharmavit", Russia, "Pharmsynthez", Russia

Neovir (for veterinary use Camedon. Manufacturer: MEDITER, Russia) – sodium 10-methylencarboxylate-9-acridone – induses high titres of endogenous interferon, particularly alpha-interferon with peak interferonogenic activity at few hours after intramuscular injection prolonging up to 16-20 hours. Antiviral activity of Neovir was demonstrated on patients with chronic viral hepatitis B and C [56], and individual therapy programs for such patients were developed [57]. Very powerful interferonogenic activity of Neovir allowed to use it successfully on the spectrum of bacterial diseases [58,59]. Some positive effect of Neovir on steroid hormones receptors in uterus cancerous tissues was shown [60]. Moreover, Neovir exerted the direct cytotoxic action on HT-29 and K-562 cells, intact and transfected with mdr1 gene. Preliminary incubation of cells with Neovir for 24 h efficiently increased the cytotoxic effect of doxorubicin and vincristine. The enhancement of toxic action of doxorubicin for HT-29 cells had, as a rule, additive character, while for HT-29 MDR1 cells the interaction was synergistic (CD(50) was decreased by 2.85- and 8.67-fold respectively). The effect of vincristine toxicity enhancement didn't depend on mdr1 gene expression and had synergistic character. Neovir enhanced the cytotoxic effect of doxorubicin in relation to K-562 and K-562 MDR1 cells by 3.18-fold and more than by 100-fold respectively. Preincubation of HT-29 cells with Neovir has resulted in 2000-fold decrease of 5-fluorouracil CD(50) and in 36.6-fold for HT-29 MDR1 cells. Thus, the effect of Neovir seems to have no relation to the action on the mechanisms of multiple drug resistance and may be mediated through some other pathways [61]

Kagocel. Manufacturer: "Nearmedic plus", Russia

Kagocel – is a potent inducer of so-called "late interferons', a mixture of alpha and beta interferons, produced by T- and B-lymphocytes, macrophages, granulocytes, fibroblasts, endothelial other cells after oral administration of one dose of Kagocel the peak titer of interferon is registered in the intestine in four hours, although peak titer in blood registered

in 48 hours, and interferonogenic response lasts up to 5 days. *In vitro* kagocel indused production of alpha and gamma interferons and interleukin 2 by human long-term cell cultures of different origin: J-96 and J-41 (monocytic leukemia), SW-13 (adenocarcinoma), and MT-4 (T-cell leukemia) [62]. The antiviral effect of Kagocel on the reproduction of Herpes simplex virus including its mutant strains resistant to basic antiherpetic medicine Acyclovir was demonstrated. Kagocel inhibited reproduction of Herpes virus type 1 and Herpes virus type 2 in noncytotoxic concentrations. Kagocel was also demonstrated to inhibit the reproduction of Herpes virus type 1, resistant to combination of Acyclovir and phosphonoacetic acid [63].

Poludan. Manufacturer: "Lens Pharm", Russia

Poludan – complex of polyadenilic and polyuridilic acids in equimolar ratio – induces mostly alpha interferon and some beta and gamma interferons. Subconjunctival injection of poludan increases the level of the interferon in blood and tears more than 10-fold and 7-fold after three hours respectively. The daily injections support elevated level of interferons which, dramatically influenced on ophtalmoherpes [64]. The same group of clinical ophthalmologist developed very promising method of viral and non viral eye lesions treatment. The method of local express auto-cytokine therapy (LEACCT) consists in using an experimentally tested autologous complex of cytokines (alpha-, beta-, gamma-interferons, interleukins 2, 8, tumor necrosis factor alpha etc.), which is produced by joining the autoblood of patients with poludan. The administration (subconjunctivally and as instillations) of the autoblood-poludan mixture was effectively used for herpes- and adenovirus keratoconjunctivitis, slow re-epithelization after laser keratectomy and in eye burns (178 patients). Apart from the external LEACCT procedures, a 1-4-time injection of the mentioned mixture into patient's anterior chamber used in endothelial herpetic keratoiridocyclitis, initial bullous keratopathy, severe keratoconus and in injuries of the anterior lens capsule (117 patients). The clinical-study results (main group -295 patients) show that the increased visual acuity ranging from 0.05 to 1.0 was registered in 85% of cases [65]. The epidemiological effectiveness of poludan for prevention of acute respiratory viral infections was shown on group of (101 students). The placebo group (96 students) received the distilled water. In the students receiving poludan the incidence of acute respiratory diseases was significantly lower than in the control group ($p = 0.058$), decreasing to two times [66]. Similar data was obtained for prophylactic activity in the cases of the polyethiologic group of acute respiratory viral infection during the seasonal peak of the disease, with a coefficient of efficiency of 2.1 and corresponding protection index of 52.7%. Having the same chance of getting infected, individuals protected with these drugs often have the disease in a milder or asymptomatic form [67].

Ridostin. Manufacturer: "Vecterpharm", Russia, "Diapharm", Russia

Ridostin – mixture of double – stranded and single – stranded RNA sodium solts – potently induses interferone production and stimulates phagocytosis. Intraperithoneal injection of ridostin to mice induses intensive blood accumulation of interferon with peak at 8 hours, albeit interferone level was low in the respiratory tract and brain. Contrastly, intranasal and aerogenic administration of ridostin induced interferon mainly in the upper respiratory tract and lung [68]. Intracerebral injection of ridostin induced accumulation of interferon in the brain and serum [69]. Combined treatment with killed vaccine and ridostine by the scheme of urgent prophylaxis (3 days before challenge) demonstrated 100% protection of Aujeszky's disease infected minks, 75% protection of foot-and-moth infected pigs, and 50% protection of canine distemper infected dogs. Clinical symptoms of dogs developed canine dictemper was mild and delayed 23-25 days post infection [70].

Larifan. Manufacturer: "Pharm", Riga, Latvia

Larifan - double stranded RNA of f2-phage – potently indused interferone after systemic or local administration. Larifan demonstrated high antiviral efficacy against Omsk haemorrhagic fever virus (strain "Ondatra") in experiments with laboratory animals. This drug prevented the death of 65% infected mice and significantly decreased infection severity in rabbits [71]. However, this virus reproduction on cell culture was suppressed mildly whilst human adenovirus serotype 2 wasn't suppressed by larifan *in vitro* at all [72].

Savratz. Manufacturer: "SRIEM", Russia

Savratz – oxybenzylamine derivative – demonstrated high interferone-inducing capacity with early and late peaks of interferone production (4-8 and 48-96 hours after administration) depending on the route of administration [73]. Savratz showed antiviral activity *in vitro* against hepatitis C virus on cell cultures SW-13 and MT - 4 [74].

Groprinosine. Manufacturer: "Polfa", Poland

Groprinosine – inosine pranobex – induces interferon, stimulates macrophages activity and lymphocytes proliferation, with specific damage to viral genetic machinery. Antiviral properties of groprinosine were demonstrated in 35 patients with acute virus hepatitis of average severity, who developed, after short-term improvement of general status, a negative dynamics of clinical and laboratory indexes. The 21 patients have received traditional treatment, 14 patients additionally were prescribed groprinosine within 5-10 days. It was shown, that addition of groprinosine to combination therapy positively influenced the disease course, promoted a rapid regress of clinical symptoms, normalization of biochemical indexes of liver function and decreased duration of hospitalization [75].

Milife. Manufacturer: "Vilar", Russia, "Dija", Russia

Milife – biomass of Fusarium sambicium fungi strain VSB-917 – stimulate production of alpha and gamma interferons, normalize humoral, cellular immunity and cytokine homeostasis. Milife administration to mice led to rapid and significant increase in total leukocyte and lymphocyte count in peripheral blood that persisted for at least 3 weeks after a 6 days treatment. Cellularity of lymph nodes, bone marrow and thymus increased significantly at days 4 and 6 of treatment, but returned to pretreatment levels after Milife discontinuation. Though total splenocyte numbers did not change

dramatically, there occurred delayed increase in CD4+ cells in the spleen 3 weeks following treatment. Preferential accumulation of CD4+ cells was also found in peripheral blood, with the peak at day 6 of treatment. As a result, CD4/CD8 ratio in blood and spleen was significantly higher in treated than in untreated mice. Splenocytes from treated mice proliferated more vigorously in response to Con A. When added *in vitro*, Milife also mildly co-stimulated Con A-induced proliferation of splenocytes from intact animals [76].

Mebavin. Ragosin. Manufacturer: "IBC", Uzbekistan

Mebavine and ragosin – soluble gossypol derivatives – possess interferonogenic and inflammation-regulatory activity. Anti-inflammatory activity of mebavin was similar to prednisolone as revealed on patients with adjuvant arthritis [77], without suppression and even with stimulation of immunity [78].

Prodigiosan. Manufacturer: MBRC "Alexis", Georgia

As a polysaccharide extracted from Serratia marcescens and other bacteria Prodigiosan activates enzymatic activity of macrophages and stimulates phagocytic processes.Like other polysaccharides compounds Prodigiosan possesses the direct antibacterial activity and increases efficiency of antibiotics in therapy of infections caused by a wide spectrum drug-resistant bacterial strains [79]. Its interferonogenic properties were demonstrated both *in vivo* and *in vitro* [80,81], and its antiviral efficiency was confirmed in complex therapy of viral respiratory diseases [82] and hepatitis B [83]. In the later research efficiency of prodigiosan combined with ibuprofen was more pronounced than monotherapy with reaferon (alpha 2-interferon) in terms of decreasing of total serum IgE levels. Interestingly, another remedy - prodigiosin isolated from the culture broth of Serratia marcescens B-1231 possessed anti-autoimmune properties by suppressing progression of autoimmune diabetes and collagen-induced arthritis [84].

Rusam. Manufacturer: "Bryntsalov A", Russia

Extraction from thermophilic strain C of S. aureus possess antiallergic activity and stimulate cellular immunity and both type of interferon production. Clinical trials in bronchial asthma patients demonstrated high interferonogenic and anti-autoimmune activity [85].

MIGI-K. Developer: "VNIRO", Russia

MIGI-K preparation – a result of acidic hydrolysis of mussels flesh – contains several pharmacologically active compounds: melanoidines, peptides carnosin and taurin, amino acids, polyunsaturated lipids, vitamins and minerals. MIGI-K demonstrated antitumor, immunostimulating, antioxidant and radioprotective properties. Preparation secured radioprotection in trials after Chernobyl accident [86] and demonstrated strong antioxidative properties on animal models significantly or completely preventing intensification of lipoperoxidation and depression of antioxidative systems (superoxide dismutase, glutathione peroxidase, nonprotein thiols, lipoantioxidants) in skin and liver of UV-irradiated rats [87]. Interferonogenic activity of MIGI-K allowed recommending it as food addidtive in viral hepatitis and respiratory infections [88].

Blasten. Manufacturer: SIC "Enzypharm", "Enzyme", Ukraine

Immunomodulatory preparation from cellular walls of Lactobacillus Delbrueckii demonstrated potent immunostimulation of all types of immunity with very wide therapeutic limits. Clinical trials proved efficiency of blasten in complex treatment of oncological diseases [89], respiratory and surgical infections [90]. Very low toxicity and adjuvanticity comparable with complete Friend's adjuvant led to recommendation of Blasten to wide use in medical practice by health authorities of Ukraine.

Maxidin. Developer: "Niarmedic-plus", Manufacturer: "Micro-plus", Russia

Maxidin (germanium bis(pyridine-2,6-dicarboxylate)) potently induces interferon and normalizes immunity in secondary immunodeficient conditions. Maxidin is effectively used in immune disorders and viral diseases of animals [91].

Immunoxel (Dzherelo). Manufacturer: "Ekomed" Kiev, Ukraine

This immunomodulator contains the wide spectrum of biologically active substances derived from herbs. The preparation possesses interferonogenic and potent anti-inflammatory activities. Series of clinical trials have demonstrated that Dzherelo induces protective immune response to a broad range of bacterial and viral infections and positive immune activity in autoimmune conditions and cancer as well. Dzherelo has been recommended by the health authorities of Ukraine as an adjunct therapy for TB and seasonal flu [92]. When Dzherelo and anti-tuberculosis therapy (ATT) or antiviral therapy are combined, it improves clinical symptoms and produces higher cure rate than in patients than on chemotherapy alone. It has been shown to achieve faster and superior rate of mycobacterial clearance, reduce HIV burden, accelerate healing of pulmonary lesions, decrease inflammation markers and pro-inflammatory cytokines, liver damage, improve hematology picture, i.e., increased hemoglobin levels, CD4 counts, and enhance significantly quality of life such as weight gain, fever, respiratory function, physical fitness, well-being and better mood. Immunoxel has been shown effective even against multidrug (MDR-TB) and extensively drug-resistant TB (XDR). The details of these beneficial outcomes were published earlier [93-100].

SCV-07. Manufacturer: "Verta", St.Petersburg, Russia. Licensee: "Sciclone", San Mateo, USA

Scv-07 or gamma-D-glutamyl-L-tryptophan, is a synthetic dipeptide with potent immunomodulatory and antimicrobial activity. Verta and SciClone Pharmaceuticals are developing SCV-07, the lead product in a series of immnunostimulants from Verta, for the potential treatment of tuberculosis and hepatitis C virus infection. Phase II clinical trials of the compound are ongoing [101]. SCV-07 has also shown potential in treatment of herpes infection

Immucor GA-40 and GA-47. Manufacturer: "Alexis", Georgia

Chromatographically purified polypeptide complexes extracted from plants demonstrated antitumor and immunomodulatory activity in all arms of immunity, including stimulation of interferon production.

Likopid. Manufacturer: "Peptek", Moscow, Russia

Likopid or N-acetyl glucosaminyl-1-4-N-acetylmuramyl-L-alanine-D-isoglutamine dipeptide, is a synthetic analogue of the fragment of cell walls of bacteria. It stimulates the functional activity of macrophages and synthesis of cytokines. It is clinically used in adjuvant therapy for chronic immunodeficiency conditions, low current and recurring inflammatory infectious diseases at various sites [102]. Due to broad spectrum activity Likopid is also used for treatment of cytomegalovirus infection and pulmonary tuberculosis [103].

Galavit. Manufacturer "Medikor" Moscow, Russia

Galavit is a monosodium α-luminol or monosodium 5-amino-2-3-dihydro-1-4-phthalazine dione. Galavit inhibits production of inflammatory cytokines such as TNF-alpha, IL-1 through regulation of metabolic activity of macrophages. As such it has been found useful for various clinical indications as follows: gastrointestinal infections of various origins; viral hepatitis; herpes infections; urogenital infections, i.e., chlamidia, endometriosis and other bacterial and fungal infections [104].

V5 Immunitor. Manufacturer: "Monserum", Mongolia

This product is made from hydrolyzed pooled blood of hepatitis B and C carriers by using unique technology. The hepatitis viruses are killed by heat- and chemical inactivation and then formulated into a tablet. The principle for production of V5 is not much different from established principles with old-fashioned killed vaccines, i.e., Hepatitis B vaccine made from pooled plasma. V-5 is available as 850 mg coated pill, ten of which are sealed in a "blister" pallet, with 30 pills per one package. The recommended dose is one-two pills per day. The preparation is stable at ambient temperature for five years. Studies in chronic hepatitis B and C patients have shown nearly 100% efficacy, without any adverse effects, and with positive outcome achievable within one month from treatment initiation [105,106].

Ligfol (Olipifat). Manufacturer: "Ligpharm", Moscow, Russia

Ligfol is obtained as a result of hydrolysis of wood lignin that is reduced to a sterile liquid for injection and has been in veterinary use since 2000. This preparation is quite unusual, bearing in mind its origin and broadness of clinical applications. It has been found useful in the management of stress; as an antioxidant; anti-tumor agent; enhancer of healing; hepatoprotector; hematopoiesis stimulant; inducer of cell-mediated immunity and interferon synthesis. These properties may appear unrelated to each other but there are published clinical studies that lend support to these claims [107-109].

Anandin. Manufacturer: "Meditere", St. Petersbourg, Russia

Anandin is an injectable and topical preparation of modified sugar, glucosamine-propyl-carbocridone, developed by Travkin and Yakovleva in 1990-1995. It has been used in Russia over the last ten years in humans but predominantly in the veterinary practice without any significant toxicity. Main indications are for acute and chronic viral and bacterial infections; inflammatory conditions; as an enhancer of healing process; and for a variety of immune disorders. In animals it is commonly prescribed for parvovirus enteric infections, pestiviruses, bovine herpes, infectious bovine rhionotracheitis (IBR), bovine viral diarrhea (BVD), hepatitis, and many other viral infections of unknown etiology [110,111].

Imunofan. Manufacturer: "Bionox", Moscow, Russia

This immunomodulator consists of a short synthetic peptide, (Arg-α-Asp-Lys-Val-Tyr-Arg), which imitates the action of thymopoietin. It is provided as a rectal suppository, injectable solution or intranasal spray. According to Russian studies the pharmacological effect is due to three main modes of action: correction of immune response; restoration of antiodixadant/peroxidation processes; and inhibition of multidrug resistance through interaction with transmembrane pumps responsible for drug resistance. Imunofan is prescribed for a wide range of clinical conditions including as adjunct for cancer therapy; acute and chronic pyogenic infections; opportunistic infections such as Cytomegalovirus; Toxoplasma gondii; Klebsiella pneumonia; Herpes virus; Chlamydiae and Cryptococcus neoformans; HIV; acute and chronic viral hepatitis; diphtheria; as adjuvant for vaccination; and psoriasis.Although it is unlikely, Imunofan may cause inflammatory reactions in certain individuals [112-114].

Thymogen. Manufacturer: "Cytomed", Russia

This preparation is perhaps best know interferon inducing immunomodulator. It was originally discovered by Khavinson et al., and has been sold in Russia since 1991 [115]. It is very simple dipeptide (L-Glu-L-Trp) that is orally available and has been used for innumerable clinical conditions ranging from cancer to infectious diseases and other unrelated uses especially in the neurological or neuroendocrine context. The number of references on PubMed alone is by an order of magnitude higher than for any other of above reviewed substances. Thymogen is fully synthetic but since it has been discovered by screening other preparations of thymic extract, Thymalin and Vilon, it appears to affect various immune responses by mimicking the function of the thymus.

CONCLUSIONS

There are several dozen clinically deployed immunomodulators in Russia and former Soviet block countries. Most popular ones are listed in this review (Table **1**). They have been used with various success rates in a large number of patients, but are practically unknown in the English-language medical literature. We hope that this review provides a glimpse into current situation and perhaps will stimulate further research in this exciting area.

Table 1. Summarized Data on Immunomodulators as Compiled from Available Literature Sources, Authors Own Clinical Observations, and Personal Communications

Category of Preparations	Commercial Name	Clinical Indications
Synthetic, low-molecular	Anandin Amyxin Arbidol Amizon Cycloferon Hepon Galavit Groprinosine Imunofan Likopid Maxidin Neovir Thymogen	Rabies, hepatitis A, B, C virus, TB, herpes simplex virus type 1 and 2, HIV, influenza, acute and chronic respiratory viral infections, adenovirus type 6, mumps, canine distemper, parvovirus, panleukopenia, viral hemorrhagic fever, West Nile fever, vesicular stomatitis virus, Venezuelan equine encephalitis virus, encephalo-myocarditis virus, chronic enteritis, surgical infections, keratoconjunctivitis, rhinitis, secondary immunodeficiencies, malignant diseases.
Synthetic, high-molecular	Poludan	Ophathalmoherpes, influenza, acute and chronic respiratory viral infections, viral hepatitis B, rabies, HIV.
Natural, low-molecular	Kagocel Ligfol Mebavin Ragocin Savratz	Herpes simplex, influenza, acute and chronic respiratory viral infections, hepatitis C, rabies, enteroviruses
Natural, high-molecular	Ridostin Larifan Prodigiosan	Influenza, acute and chronic respiratory viral infections, Aujeszky's disease, foot-and-mouth disease, canine distemper, rabies, Omsk haemorrhagic fever, herpes virus
Natural, complex	Blasten Dzherelo Immunoxel Milife Rusam V5 Immunitor MIGI-K	Influenza, TB, acute and chronic respiratory viral infections, oncological and autoimmune diseases, malignancies, viral hepatitis, purulent wounds

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