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Upper respiratory tract infection in children – immunostimulating treatment

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Abstract

This paper is a review of publications on viral infections of the upper aerotract in children. Recurring infections can be a consequence of the lack of treatment, inappropriate therapy or accompanying diseases. It is possible that an impaired condition of immunity leads to recurring infections. In this review a great deal of attention has been given to the mechanisms and the various stages of viral infection, and the onset of an organism's defense mechanisms against viruses. The function of the immunomodulatory and immunostimulatory medical product, namely inosine pranobex has been evaluated in *in vitro* and *in vivo* studies. A review of the antiviral activity of inosine pranobex and the onset of cellular and humoral immunity has been presented.

Inflammation of the respiratory tract in children, especially reoccurring inflammations are frequent problem for youngsters, their parents and doctors conducting therapy. It mostly affects children in their preschool age and early school age, and the seasons predisposing for the occurrence of symptoms in form of rhinitis, sore throat, subfebrile temperature or fever very often with tiring cough are the transition periods between summer and fall and between winter and spring. Parents are not only interested in their children's recovery, but also in recurrence of the disease and how it could be evaded.

Inflammations of the upper respiratory tract are mostly initiated by viral infections. It is estimated that about 60-90% of children are appointed to the doctor due to the viral infection of the upper respiratory tract (1). The most common attacking are rhinoviruses, RS viruses, adenoviruses, influenza virus, parainfluenza virus, Coxackie virus. It should be borne in mind that the most common therapeutic procedure is staying in bed, application of warming and diaphoretic agents, consumption of lots of fluids and airing the room where the patient is recovering. Nowadays old methods of treatment are experiencing their renaissance, including **Chinese bubble.** Available at the market bubbles with a valve allow safe blood extravasation and mobilization of immune mechanisms. Unfortunately due to the problem with pacification of sick children in bed and the need of increased awareness and time needed, a lot of parents willingly administer antibiotics that were prescribed as a preventive measure. Moreover, it allows parents to send their children to the kindergarten or school. The application of the antibiotics or anti-inflammatory drugs without justification of administration is more harmful than helpful. Broad-spectrum antibiotics used for several days are the cause of significant havoc in digestive tract. It mostly affects saprophytic bacteria, which presence does not only maintain proper biocenosis, but is also a source of stimulation for developing immune system. It is not a secret that the abuse of antibiotics is on the rise not only in Poland and that the antibiotic resistance among bacteria grows exponentially (2).

Antibiotics taken "just in case" trigger weakening of the immune system. It may lead to a vicious circle when after one antibiotic treatment and convalescence a new infection occurs, conditioning recommendation of new administration of antibiotics, which results in another decrease in immunity facilitating another infection (2).

In case of reoccurring or chronic bacterial infections, bacterial vaccines are used; they include Broncho-Vaxon, Luivac, Polyvaccinum, Ribomunyl, Uro-vaxom, I.R.S 19, Panodia and others. These non-specific vaccines have immunostimulating properties. They stimulate

the non-specific defensive mechanisms of the organism that protects against new infections. More and more successful are antiviral vaccines that either prevent the infection or alleviate the symptoms. There should be mentioned vaccines against influenza (Influvac), measles (Rouvax), mumps (Mumpsvax) or rubella (Ervevax)/

Basing on many observations it is proven that the use of non-specific immunostimulating drugs is effective in secondary immune disorders – the relapses are less common and infection symptoms are present for a shorter period of time and they are alleviated (3,4,5).

The difficulty in treating viral diseases, especially those with recurrence nature, is associated with variety of viruses, but mostly it is due to the lack of effective causative remedy.

It should not be forgotten that viral infection may have different intensification – from asymptomatic to a severe pulmonary infection, not to mention about impending bacterial superinfection. A proposed symptomatic treatment should take into consideration: patient's age, his overall condition and the intensity of the symptoms. The purpose of the symptomatic treatment in viral infection or the respiratory tract is to alleviate pain ailments, lower fever, clear the nose and reduce serous running nose as well as to manage a dry paroxysmal cough with coughing up thick mucous secretion.

Following the next steps of viral infection it should start from the reaction just after the penetration of the virus to the organism when the multiplication occurs in lymphoepithelial lymph lumps. **At first, there is a vascular phase when the necrosis of airways' epithelium occurs and the cilia of the mucocilary system are paralyzed.** As a result of infection there is an activation of primary and secondary inflammation mediators. TNF (tumor necrosis factor) is released as well as interleukine 1, 6, 8, bradykinines, histamine, prostaglandins, leukotriens and nitrate oxide (6,7). The accumulation of those compounds in focal inflammation results in the vasodilatation, swelling, pain and increased body temperature. The increase in the permeability of the blood vessels results in the runny nose. Interleukine 6 (IL-6) activates hypothalamus resulting in the increased body temperature (8).

Due to the viruses destructing cells, phospholipase A is being activated and arachidonic acid is released from cellular membrane. Arachidonic acid under the influence of cyclooxygenase 2 (COX2) is converted into prostacyclines and prostaglandins responsible for vasodilatation and the increase of their permeability. Similar effect is triggered by phosphatidylholine (PAF). Both prostaglandins, leukotriens (LTC4, LTD4, LTF4) and PAF are responsible for increased contractions of the smooth muscles of bronchi (8). A similar effect have inflammation agents such as histamine and bradykinin. Bradykinin lowers the threshold of nociceptors, so as a result it increases the sensitivity to pain and attracts granulocytes to the focal inflammation. Vasodilatation and pain sensation is also conditioned by the synthesis of nitrate oxide (6).

Second phase of the viral infection is so-called cellular phase. It is characterized by the production of thick secretion and formation of cellular infiltration. Liquid mucous of

respiratory tract is getting thicker due to the formation of mucopolysaccharido-protein complexes and polymerization of mucopolysaccharides as a result of disulfide bridges formation. Viscous mucus sticks together cilia of mucociliary apparatus making it harder to purify the respiratory tract and the mucus is residing. The latter may facilitate the bacterial superinfection. That results in the next phase of infection – bacterial infection of the respiratory tract (5).

While analyzing the development of the viral infection it should be remembered that viruses cannot replicate without cells – that is why they may be called intracellular parasite. Before penetration virus binds to the cell through receptors. Virus, for example influenza virus consists of RNA (genome), protein capsid (it consists of glycoprotein enzymes on its surface – neuraminidase (N) and hemagglutenin (H) and lipoprotein sheath).

At first **absorption** occurs and the virus adheres to the surface of the cell by binding to the specific receptors with receptor-binding protein. Secondly, the process of **penetration** occurs and the virus penetrates to the cell using different mechanisms. It may occur as a fusion when the virus with its lipid sheath blends with cell membrane. There may also occur viropexis when there is a similarity of cellular proteins and viral spikes. It allows the penetration of the virus to the cytoplasm. Non-enveloped virus can penetrate to the inside of the cell by endocytosis. Next step is uncoating of the virus – the release of genetic material. Before the genome is being replicated, the production of **early proteins** that are demanded for the replication and changes in the cellular metabolism. **Replication** of the genome and its form is dependent on the type of genetic material. It may be the **integration** of the viral genome with host's genome. **The production of late proteins** is on the basis of the new genetic code. These are mostly structural proteins that are building the capsid and proteins allowing the proper **build of virions** with the uprise of nucleocapsids. **The release of virions from the cell** takes place after their integration. Non-enveloped viruses are mostly released after the death of the cell and its decomposition while enveloped viruses germinate from the surface of the cell. Lipid layer of the virus is most commonly a fragment of host's cell membrane (9).

The defensive mechanisms of the organism against viral infections include: anatomical and physiological barriers, activated innate immune mechanisms and acquired immunity (which develops much slower than predecessors). The development of acquired immunity is mostly stimulated by the innate immune mechanisms. Undoubtedly to initiate the development of innate immunity it is mandatory to recognize the virus penetrating to the host cell. Viruses, similarly to other pathogens are identified by pathogen-associated molecular pattern (PAMP) recognized by pattern recognition receptors (PRR) (10).

The organism does defend against the viral infection on some stages of invasion of the pathogen. First is response of the innate immune system as a non-specific reaction, mainly dependent on lymphocytes Th1. The following actions occur: phagocytosis, activation of natural killer cells (NK cells), increased activity of cytototoxic lymphocytes, production of interferon (mostly IFN-gamma), synthesis of cytokines and chemokines, increase of body temperature (fever has a virostatic properties). Crucial role belongs to interferon (IFN) type I

that regulate the development of immunological response against viral infection on many stages (11,12).

Second step is the reaction of immunocompetent cells. Further activation of macrophages occurs, followed by increased phagocytic activity, release of lymphokines and increased cytotoxicity associated with antibodies reaction. The following cytokines are released: tumor necrotizing factor (TNF), interleukine 6 (IL-6), IL-12 and many chemokines. Also the synthesis in inflamasomes of IL-1β, IL-18 i IL-33 occurs (11,13,14).These humoral agents activate cells taking part in innate immunity mechanisms as well as cells essential for the activation of acquired immunity. They do induce inflammation and regulate the course of immune response against viruses. Other crucial role is played by plasmocytoid dendritic cells (they are the reservoir of IFN type I in the early stage of infection), lymphocytes T CD8+, lymphocytes Th and lymphocytes B. There is more and more information about mastocytes also being responsible for defensive mechanisms against viruses. Some authors suggest that mastocytes participate in the pathogenesis of diseases caused by viruses (15).

Next stage is the increased humoral response, dependent on lymphocytes Th2. It is mostly characterized by production and the release of antibodies. Moreover, complement system is responsible for cellular degradation and induction of the release of inflammatory agents and opsonization of antigens (14).

In general, immune response in viral infection is directed by many mediators, however the most dominant role is played by the conjugated regulatory mechanisms dependent on lymphocytes Th1 and Th2. There are several interactions between lymphocytes Th1 and Th2 – the inhibition of reactions dependent on lymphocytes Th1 by interleukin-10 (secreted by lymphocytes Th2) and vice versa – the inhibition of reactions dependent on lymphocytes Th2 by interferon gamma (secreted by lymphocytes Th1). Co-inhibition and selective stimulation allows remaining at equilibrium state during the viral infection. In cellular and humoral response different immunocytes are involved. A cascade reaction is released by the activation of target cells (14). Macrophages activated by INF-gamma and TNF-beta (released by lymphocytes Th1) stimulate the latter by releasing IL-12. This feedback is mandatory for autoregulative processes. Lymphocytes Th2 are activated by mastocytes, while lymphocytes Th2 by releasing IL-3, IL-4, IL-10 which stimulate mastocytes. Mast cells are present in great numbers in mucous membrane of respiratory tract, being localized just under the epithelium in the proximity to blood vessels. It allows easier and faster contact with attacking viruses (15).

There are a lot of data proving that mast cells are the target cells of some viruses (denga virus, adenoviruses, reoviruses) and even some of them may replicate in mastocytes. Viral infection may trigger degranulation of mast cells and the release of strong pro-inflammatory mediators. At some point, developing inflammatory process is defense mechanism of the organism but overly intensified may trigger to pathology (10). In people with properly functioning immune system (immunocompetent) the infection ends with recovery but the virus may remain in body in an “asleep” form from a few hours to even several years. In latent period virus remains in the form of provirus so its genetic material is

inbuilt into the genome of the host. When a drop of immunity occurs the virus may activate and start replicating in host cells and attacks many cells at one time. In this way some of the neoplasms may occur (lymphomas) (16).

During the acute phase of infection (that lasts for 3 to 5 days) the treatment is only symptomatic. The drugs mostly used include: vasoconstrictors (they do reduce the swelling and permeability of the vessels thus reducing exudation) and wide spread of anti-inflammatory drugs. Other medicines include: alpha-sympathomimetics, paracetamol, anti-histamines, non-steroidal anti-inflammatory drugs (NSAID), antitussives or alleviating cough.

Most therapeutic methods are based on limiting the development of the infection that transforms viral disease into chronic one. The infection may reoccur (virus latency) or reappear after a very long period of time, leading even to the death (16).

Medicine is lacking in the methods that would inhibit the proliferation of viruses. The problems are: intracellular localization of the virus (if it affects cells of immunity system it weakens the organism significantly), its mutations, inhibition of the major histocompatibility complex (MHC) expression – after penetrating cells some viruses inhibit the presentation of theirs characteristics by MHC and they cannot be destroyed by cytotoxic lymphocytes, the phenomena of rejecting antibodies when virus disconnects the antibody connected to it (12).

The symptomatic treatment sometimes is beneficial for the development of viruses. Examples include lowering body temperature and decreasing the effectiveness of antiviral defense of organism. The relief of the symptoms gives just a subjective feeling of health improvement while in the effect it inhibits defensive response.

In all kind of infection, including viral infections the most important is immunity of the organism that allows fighting with microorganisms in acute inflammation and moreover – to prevent recurrences or developing chronic condition. That dictates the increasing interest in the use of immunestimulating drugs.

Many of laboratory and clinical researches, conducted since eighties evaluate positively the use and effectiveness of inosine pranobex in viral infections. *In vitro* and *in vivo* examinations prove its retroviral effect and its participation in stimulation cellular and humoral immunity.

Inosine pranobex, inosiplex (Groprinosine) is a synthetic compound, made of 1 inosine molecule and 3 molecules of 4 (acetylamino) - 1- (diethylamino-2-propranol) benzoate in the ratio 1:3 (17,18). This drug has a complex activity. On one hand it has the ability to inhibit the replication of the virus while on the other hand it presents the ability to stimulate the immune system. Inosiplex activates both: lymphocytes T and phagocytic cellular function. Moreover, it increases mitogen-dependent and antigen-dependent synthesis of the DNA in lymphocytes (19). This has an impact on the appearance of differentiation markers of immature precursors of T-cells, the increase of suppressor and helping functions of T-cells as well as the increased production of lymphotoxins. Clinical research of the effectiveness of

inosine were mostly concentrated on viral infections such as herpes virus infection, influenza, zoster, hepatitis A- and B-type and HIV infection (19).

Clinical research documented significant decrease in antibiotics therapy in children with reoccurring respiratory infections that had Groprinosine prescribed in dose 50mg/kg of body weight/day for 10 days (18). Laboratory research revealed increased number of lymphocytes and the improvement of theirs function due to the Groprinosine therapy. The following population of lymphocytes were observed: CD3+ and its subpopulation CD3+/CD4 (helper), CD3+/CD8+ (cytotoxic), CD19+ (lymphocytes B), CD15+56+ (natural killer cells – NK), CD3+/HLA-DR (active T-lymphocytes). The tendency of increase in immunoglobulins IgG, IgA and IgM was observed (18). It was proved that the increase in LCD3+ and TCD4+ may favorably prevent reoccurring viral infections due to its antiviral and immunostimulating function (20,21). Inosiplex penetrates to the interior of lymphocytes and decreases the synthesis of viral RNA (22).

The effectiveness of inosiplex according to many authors is dependent mostly on the dose and more importantly – the frequency of aplication. Much higher effectiveness was obtained when inosiplex was applied six times a day, not two-three or four times per day (23).

Inosine according to the newest research – is not only a strong immunomodulator but also has a neuroprotective properties. Inosine increases degradation of mast cells, weakens the production of pro-inflammatory mediators by macrophages, lymphocytes and neutrophils (24).

Purine nucleosides, such as adenosine and its most important metabolite inosine participate in intracellular processes and serve as monomeric precursors of RNA and DNA. These nucleosides are also present in small amount in extracellular space but during infection or hypoxia their concentration increases significantly. After binding with purine receptors, inosine may pass information to the inside of the cell. Moreover inosine may impact the function of the cell beyond the receptors (25).

Immunomodulating effect of the inosine is expressed in stimulation of mast cell degradation by selective binding them with purine receptor A3. It is proved that there is no such effect in mice in which the A3 receptors are not present (24). In contrast to pro-inflammatory effect of mast cells, inosine is a strong anti-inflammatory agent in macrophages and lymphocytes observed *in vitro* (26,27).

Inosine pranobex (groprinosine) induces interferon, stimulate the activity of macrophages and lymphocytes proliferation as well as activates natural killer cells (NK) (28). Antiviral properties of groprinosine were proved in patients with acute viral hepatitis of medium intensity. Thanks to the combination of conventional treatment and this drug, better therapeutic effect was obtained with faster regress of symptoms, normalization of biochemical results of liver functions and shorter hospitalization period (29). In *in vitro* examination it was proven that after isopronasine therapy in patients with acquired immune deficiency syndrome

(AIDS) the return of proper or nearly proper values of IL-2, expression of Tac-gene and absorption of IL-1 (30). That suggest the immunostimulating properties of isopronasine.

Thanks to antiviral properties groprinosine does find its application in treating or supporting therapies in following diseases: influenza, acute and chronic viral inflammation of the airways, adenovirus 6 infection, viral otitis media, viral keratitis, rhinitis, mumps, parwovirus infection, measles, shingles, rabies, hepatitis type A, B and C, herpes simplex caused by virus type 1 and 2, HIV, hemorrhagic fever, acute encephalitis, subacute sclerosing encephalitis and others (7,17,28).

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