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**N.A. Lebedeva, D.S. Tomin, M.M. Vinokurov**

## **IMMUNOMODULATORS IN THE TREATMENT OF ACUTE RESPIRATORY VIRAL INFECTIONS**

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The scientific review presents a research analysis of acute respiratory viral infections (ARVI) treating methods using drugs available in Russia that have immunomodulatory effect. The article describes the rational usage of this sort of medicine according to the evidence-based medicine methods.

**Keywords:** immunomodulatory, ARVI, flu, children, adults.

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**Introduction.** Acute respiratory viral infection (ARVI) is a widespread group of inflammatory diseases of the upper respiratory tract (URT) in people of all ages and clinical forms. At the moment, ARVI are one of the urgent and priority problems of world health for doctors of different specialties [24]. Despite a large number of studies proving the effectiveness and / or the choice of a particular drug for treatment, ARVI continues to occupy a leading position in the structure of the population morbidity. The choice of drugs for treatment is a subject of debate in the medical community, since ARVI is a nosological group with similar clinical signs, but with a wide range of probable pathogens [8].

According to the WHO, acute respiratory viral infections are one of the most common reasons for seeking medical attention. However, the current data of the epidemiological surveillance of ARVI (as of the 9th week of 2021, the incidence rate of ARVI and influenza in the whole of the Russian Federation was 61.8 per 10,000 population) should be interpreted with caution, due to the increased demand for medical care, as a result of the ongoing pandemic of COVID-19. By comparison, at the 9th week of 2019, the incidence rate in the country was 82.6 per 10,000 population. Consideration should be given to the fact that hygiene and physical distancing measures adopted by states have played a significant role in reducing the transmission of influenza virus [9, 10]. Nevertheless, given the high proportion of patients who do not

seek medical help during the period of active illness, confirm the data that the incidence of ARVI is quite widespread [35].

Immunomodulators - are therapeutic drugs that eliminate the imbalance of the immune system's various parts. These drugs are aimed at normalizing the parameters of immunity. To classify a drug into a group of therapeutic immunomodulatory agents, during preclinical and clinical studies, the ability to change the immunological reactivity of the organism, depending on its initial state, must be proven [11]. These drugs are actively prescribed for the treatment of acute respiratory viral infections in the territory of the post-Soviet space, by doctors of many specialties. Accordingly, the number of articles devoted to the study of the activity of immunomodulators written by Russian-speaking authors is significant. It should be noted that according to foreign researchers, the concept of "immunomodulators" is rather vague. Many drugs have potential, but often virtual, immunomodulatory properties. There are more drugs in the Russian Federation, they can be freely purchased in pharmacies. The role of immunomodulators is not fully understood and their use may be unsafe [25, 30].

**The aim** of this work is to analyze the literature data on the study of the drug activity of immunomodulators in the treatment of ARVI.

### **Assigned tasks:**

1. Study the literature data on the features and effectiveness use of immunomodulators in acute respiratory infections.

2. Evaluate research results from the perspective of evidence-based medicine.

The review includes publications from the following databases: eLibrary, CyberLeninka, PubMed. Search queries were formed with the following criteria: publication date last 10 years, keywords used for search: immunomodulator, ARVI, influenza, children, adults.

Modern medicine has an abundance

of pharmacological drugs used to treat viral infections. A significant difference in the treatment of ARVI in many countries, including the Russian Federation, is the uncontrolled use and sale of immunomodulatory drugs in the Russian Federation without taking into account the principles of evidence-based medicine. International (European and American) clinical guidelines describe the inappropriateness of treatment with nonspecific antiviral drugs due to the lack of proven data indicating a better effect and safety of such drugs as compared to placebo. For example, preparations with the active ingredient imidazolethyanamide pentanedioic acid have not been subjected to randomized placebo-controlled clinical trials; their use does not go beyond Russia. There is an opinion that the early prescription of antibiotics for ARVI reduces the risk of activation of the opportunistic bacterial flora of the upper respiratory tract. But, in this case, the prescription of antibiotics is not only unjustified, but also entails a decrease in nonspecific immunity, the body's ability to produce endogenous IFN, which is directly related to the course and outcome of the disease [31]. Moreover, prolonged use of interferon inducers can lead to IFN-mediated cytokine release syndrome. The doctor should make the decision on the advisability of prescribing systemic antibiotic therapy based on the severity of the disease and the risk of complications.

In the practice of a doctor, the issue of prescribing immunomodulators remains the most controversial. A large number of immunomodulatory drugs have been registered, the pharmacodynamic effect of which, according to pharmacological companies, is aimed not only for the treatment of ARVI, but also for its prevention. Numerous works on the complex treatment of diseases contain contradictory conclusions from calls to completely abandon this group of drugs to their unjustifiably frequent prescription [2]. Most often, prescribing by doctors and

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**LEBEDEVA Natalya Afanasyevna** - Ph.D., associate professor Medical Institute M.K. Ammosov NEFU; lebedeva-lor@mail.ru, **TOMIN Dmitry Sergeevich** - resident-otorhinolaryngologist Medical Institute M.K. Ammosov NEFU; **VINOKUROV Mikhail Mikhailovich** - Doctor of Medical Sciences, Professor, Head of the Department, **TEREKHINA Katerina Germanovna** - ordinator otorhinolaryngologist of the FSBI APE.

recommendations by pharmaceutical specialists of medicines (drugs) for the treatment of acute respiratory viral infections and influenza is dictated mainly by a positive assessment of their advertising effectiveness and safety [4]. To confirm the effectiveness and safety of immunomodulators, it is necessary to conduct multicenter clinical trials [15]. Clinical studies to assess the effectiveness and safety of immunomodulators, conducted in Russia, are most often carried out without adherence to generally accepted world standards, principles of randomization and clinical treatment protocols [19].

According to some studies, the appointment of immunotropic drugs is justified in the development of secondary immune deficiency (SIN) URT. One of the manifestations of VIN is frequent illnesses [2, 7].

Polyoxidonium (Azoximer bromide) is one of the drugs that are widespread in the Russian Federation and are classified as synthetic immunomodulators. This drug is devoted to a large number of articles describing the research conducted, while the sample of patients is small, some articles are accompanied by a description of one clinical case [2, 7]. It is worth mentioning that according to the basic norms of evidence-based medicine, works in which one drug is investigated cannot be considered and have a high level of evidence, especially when they contain direct advertising of a particular drug [2, 3, 6, 7, 16, 22, 27, 28].

The mechanism of action of such drugs is described incompletely, or rather it is practically absent, in the pharmacodynamic description only a brief description of the effects is indicated, which, already at this stage, casts doubt on the advisability of these therapeutic agents [34].

A more serious study is presented in the article by S.M. Kharit and A.N. Galustyan, which reflects the results of a double-blind, placebo-controlled, randomized clinical trial of II and III phases of the drug Polyoxidonium. A total of 228 children from 3 to 14 years old took part. The data obtained showed that the complex therapy of ARI significantly reduces the period of normalization of body temperature in comparison with taking a placebo and contributes to the normalization of immunity parameters [29].

The article by T.I. Garashchenko, O.V. Karneev, G.D. Tarasov, I.V. Kim, R.A. Khanferyan describes a multicenter double placebo-controlled study. It includes 155 children aged 1 to 12 years. According to the results of the study, the authors stated the superiority of the use

of Azoximer bromide (AB) in comparison with placebo in complex therapy, and the inclusion of Polyoxidonium in the complex therapy of acute respiratory viral infections in children makes it possible to better control the symptoms of intoxication, reduce the severity of symptoms by the 5th day of therapy, and increase it by 2 times. the number of patients with no symptoms of "Nasal discharge" by the 3rd and 5th days of therapy, to reduce the severity of the infectious-inflammatory process [5]. The use of Polyoxidonium was accompanied by the use of antipyretic drugs. There was no control of the onset of ARVI disease [5].

In the meta-analysis conducted by A.V. Karaulov and A.V. Gorelov selected 5 studies comparing the effectiveness of complex therapy with the use of AB in the treatment of viral diseases and standard symptomatic therapy; in total, 542 children, aged 3 to 18 years old, took part in the study. According to the results of the work, the authors concluded that the addition of AB to ARVI therapy from the first day of treatment makes it possible to reduce the period of temperature normalization, shortens the duration of symptoms of fever and intoxication, and the disappearance of headache, muscle and joint pain. At the same time, the duration of the clinical symptoms of acute inflammation of the upper respiratory tract decreases in general by 1.23 days [13].

The study of the use of Polyoxidonium in foreign literature is described in a single article by P. Pruzinec, N. Chirun, A. Sveikata. The sample consisted of 502 patients, the results confirm the safety of use and no effect on the kidneys, however, studies of the effectiveness of the pharmacological action have not been described [33].

Another quite popular drug is Cycloferon. There is much less research on its effectiveness. One of these is the study of V.A. Isakov and D.V. Isakov: in which the effectiveness of the tablet form of cycloferon is studied in the complex therapy of viral respiratory tract infections in adults. The duration of fever was 1.8 times and intoxication 1.4 times shorter than in the comparison group. The catarrhal syndrome and the general duration of the disease turned out to be less prolonged, complications developed less frequently [12].

Systematic review and meta-analysis of N.K. Mazin, I.V. Sheshunov, P.V. Mazin, V.P. Mazin, A.L. Kovalenko, V.A. Zaplutanova: based on the results, they claim a milder course ARVI, when using tableted Cycloferon as a prophylactic and therapeutic agent in both adults and children

[18].

In the article by A.V. Karaulova, with the study of the less popular immunomodulatory drug Groprinosin, it is concluded that it is an effective immunomodulator even in the case of allergic diseases. The goal of immunotherapy is to eliminate the pathological focus, reduce the severity of the inflammatory response, improve the clinical picture of the underlying disease, and reduce the need for antibacterial and anti-inflammatory therapy. [fourteen]

In the work of M.S. Savenkov, A.A. Afanasyev, G.M. Balakirev, the medicinal effect of the drug Groprinosin (inosine pranobex), advertising of which occupies a significant part of the entire article, on respiratory tract diseases is also investigated. However, the emphasis is on the concomitant herpesvirus infection, and as the authors note, the treatment of such diseases is multifaceted and requires further study. [26]

When assessing the effectiveness of Groprinosin in the study by T.A. Kryuchkova, the duration of admission is described for at least 7 days, while the drug was taken for another 2 days, even after the symptoms disappeared. Given the average duration of ARVI, which is less than a week, it makes no sense to expose the child to excessive drug load. [17]

The work of O.Yu. Filatov, O.V. Kashaev, M.A. Gordeev, O.A. Paevskaya describes the therapy of 220 patients with moderate acute respiratory infections with the immunomodulatory drug Derinat. It is noted that the injected drug is successfully used both in patients with an active inflammatory process and in complications after suffering a cold [28].

In the articles of Yu.V. Marushko and co-authors, A.P. Babkin. with a team of authors, the use of Derinat is effective in the complex treatment of acute respiratory viral infections, while the proven effectiveness of the drug is only 5 days, when, according to the assurances of the authors, increases the secretion of immunoglobulins A in the mucous membranes of the nasal passages by 3 times. [1, 20]

The meta-analysis of the effectiveness of Derinat carried out by V.I. Moerchuk, V.S. Bortnitsky and co-authors describes several studies conducted in the period from 2010 to 2015, a sample of patients, their number does not allow us to call the article fully a meta-analysis. [21 ] There are no new studies proving the effectiveness of the drug against diseases of the upper respiratory tract.

Priority in the treatment of ARVI is given to symptomatic therapy, the effect of which is aimed at relieving symptoms and reducing patient discomfort [32]. The

predominant symptoms of ARI are fever, nasal congestion, and coughing. In order to reduce swelling of the nasal mucosa and, consequently, improve respiratory function, the use of decongestants is recommended, in a short course of up to 5-7 days [19]. The pathogenesis of cough in ARI is due to mechanical irritation of the mucous membrane of the posterior pharyngeal wall and larynx by nasal secretions. It should be remembered that antitussive therapy in children should affect the improvement of bronchial drainage, therefore, it is advisable to prescribe mucolytics (acetylcysteine, carbocysteine) [23].

**Conclusion.** For the Republic of Sakha (Yakutia), which has harsh climatic conditions, as well as a high seasonal incidence of ARVI, the selection of adequate immunomodulatory therapy is important. The search for adequate ways to treat ARVI remains relevant today, despite the large number of available drugs sold in pharmacy chains. The literature review confirmed the relevance of randomized scientific research on the search for effective immunomodulators in ARVI, the demand for immunomodulators and adaptogens from local northern raw materials on the market.

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