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A NEW APPROACH TO ETIOTROPIC THERAPY ARVI IN CHILDREN

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A B S T R A C T

Aim. Confirmation of the efficacy and safety of the drug riamilovir (Triazavirin®), 100 mg capsules, in children aged 12–17 years with the diagnosis of acute viral respiratory infection (ARVI).
Materials and methods. The multicenter study included 269 patients diagnosed with acute viral respiratory infection (ICD-10 code: J00, J02, J02.9, J04, J04.0, J04.1, J04.2, J06, J06.0, J06.9) in the presence of clinical manifestations and confirmation of the etiology of the disease by laboratory tests (PCR method). Patients were included in the study after one of the patient's parents/adoptive parents and the patient signed an informed consent to participate in the study. The interval between the appearance of the first symptoms of the disease and the inclusion of the patient in the study did not exceed 36 hours.
Results. As a result of a clinical study, the efficacy and safety of treatment with riamilovir (Triazavirin®) in sick children aged 12–17 years with a diagnosis of ARVI was shown. A decrease in the duration of the disease was shown when using the drug riamilovir (Triazavirin®) compared with the control group. No serious adverse events were detected during the study.
Conclusion. As a result of the conducted clinical study, the high efficacy, safety and good tolerability of the drug riamilovir in the treatment of children aged 12–17 years with a diagnosis of ARVI was established. It is recommended to use the drug riamilovir in clinical practice as an etiotropic therapy in children aged 12–17 years with a diagnosis of ARVI due to its high efficacy and safety.

K E Y W O R D S

Acute viral respiratory infection, ARVI, children, riamilovir, etiotropic antiviral therapy.

Introduction

In clinical practice, there is a collective concept of “acute respiratory viral infections” (ARVI), which implies a number of diseases mainly of the upper respiratory tract with manifestations of catarrhal-inflammatory syndrome and intoxication. The spectrum of ARVI pathogens that annually cause epidemics in the world in the autumn-winter period includes RNA and DNA viruses of various families, most often rhino-, boca-, adeno-, metapneumo-, coronaviruses, parainfluenza viruses, and respiratory syncytial viruses. It has been noted that some rhino-, adeno- and enteroviruses can induce stable immunity, which is type-specific, which does not exclude infection with other serotypes of viruses. And

in case of infection with parainfluenza viruses, respiratory syncytial viruses, coronaviruses, stable immunity is not formed [1].

The share of ARVI in the overall structure of infectious diseases is 86.5–95%, depending on the season and age. Viral infections in children account for more than 95%, bacterial infections up to 3%, and the rest account for less than 1% of cases. The epidemic situation regarding the incidence of ARVI, including influenza, is determined by children - more than 63.2%. According to the World Health Organization, every 3–5th child and 5–10th adult suffer from influenza every year worldwide [2, 3].

ARVIs are among the 5 leading causes of death in the world and pose a serious problem for the public health of countries, regardless of the level of economic development, but are most relevant for developing countries [4].

Currently, the medical community's attention is focused on the incidence of acute respiratory viral infections in children and influenza in adults, as there is an underestimated burden of coinfection with 2 or more viruses, which is exacerbated by the ongoing COVID-19 pandemic. In addition, there are various reasons why many respiratory viruses are not routinely detected and can therefore be considered diagnostically and clinically ignorable [5–7].

The procedure for providing care implies that a child with ARVI is usually observed in an outpatient setting by a pediatrician. Inpatient treatment (hospitalization) may be required if complications develop and febrile fever develops for a long time. Complications of ARVI in most cases are determined by the addition of a bacterial infection. Thus, there is a risk of developing acute otitis media against the background of nasopharyngitis, especially in young children, usually on the 2nd–5th day of illness. Its frequency can reach 20–40% [8, 9]. In addition, a respiratory infection can be a trigger for exacerbation of chronic diseases, most often bronchial asthma and urinary tract infections [1].

The incidence of ARVI is highest between September and April, with the peak incidence occurring in February and March. As of 41 weeks 2022 (10/17/2022–10/23/2022) in the territory of Bukhara. During the inter-epidemic period for influenza, the incidence of ARVI is caused by respiratory viruses of non-influenza etiology (rhinoviruses, parainfluenza viruses, adenoviruses, respiratory syncytial viruses, etc.) [10].

The current clinical recommendations of the Ministry of Health for the treatment of influenza and ARVI in adults emphasize the importance of early prescription of etiotropic therapy for viral infections and the need to make efforts to find new etiotropic antiviral drugs aimed directly at the life cycle of viruses, namely, inhibiting the process of viral replication. One of the etiotropic antiviral drugs recommended by the Ministry of Health for the treatment of influenza and ARVI in adults is the drug riamilovir [11, 12].

The basis for including the drug riamilovir in the clinical recommendations of the Ministry of Health were the results of multicenter randomized comparative clinical studies in patients over 18 years of age with diagnoses of ARVI and influenza, which established the high antiviral efficacy, safety and good tolerability of the drug riamilovir in the treatment of viral infections [13–17] .

In addition, therapy with the drug riamilovir has statistically significant advantages in various indicators compared to both the placebo group and the comparison group (oseltamivir) [18, 19].

The results obtained in adult patients made it possible to plan and conduct a multicenter, randomized, double-blind, comparative, placebo-controlled study of the effectiveness and safety of the drug riamilovir (100 mg capsules) in children aged 12–17 years diagnosed with ARVI.

The purpose of the study is to confirm the effectiveness and safety of the drug riamilovir capsules 100 mg in children 12–17 years old diagnosed with ARVI.

To achieve this goal, it was planned to solve the following tasks:
- to evaluate the effectiveness and safety of the drug riamilovir, 100 mg capsules, in comparison with placebo as part of the treatment of ARVI in children aged 12–17 years;
-to study the pharmacokinetics of the drug riamilovir, 100 mg capsules, in children aged 12–17 years.

Materials and methods

The multicenter randomized placebo-controlled study included 269 patients with a clinically and laboratory (polymerase chain reaction - PCR) confirmed diagnosis of ARVI (ICD-10 codes: J00, J02, J02.9, J04, J04.0, J04.1, J04.2, J06, J06.0, J06.9). Inclusion in the study occurred after one of the parents/adoptive parents and the patient himself signed an informed consent to participate in the study. The interval between the appearance of the first symptoms of the disease and the inclusion of the patient in the study was no more than 36 hours. The criteria for non-inclusion included a history of vaccination against influenza, SARS-CoV-2, carried out within 12 months before screening, as well as a positive PCR result for viruses influenza and SARS-CoV-2. A total of 132 patients completed the study per protocol, including 97 in Group 1 (patients taking riamilovir) and 35 in Group 2 (patients taking placebo). Randomization was carried out using the envelope method.

In Phase I of the study, 20 patients participating in the PK portion of the study who met the inclusion criteria in the absence of any non-inclusion or exclusion criteria were randomized into 2 groups in a 1:1 ratio:
- group 1 (10 patients) – the drug riamilovir, capsules 100 mg, 1st dose 100 mg (1 capsule), then therapy according to the regimen corresponding to group I (3 times a day, 1 capsule and 2 capsules 1 time at night at within 5 days);
- group 2 (10 patients) - the drug riamilovir, capsules 100 mg, 1st dose 200 mg (2 capsules), then therapy according to the regimen corresponding to group I (3 times a day, 1 capsule and 2 capsules 1 time at night at within 5 days).

At stage II of the study, the remaining patients were randomized into 2 groups:
- group I – riamilovir, capsules 100 mg, 1 capsule 3 times a day and 2 capsules at night (daily dose of the study drug 500 mg, course dose 2500 mg) for 5 days;
- group II – placebo, 1 capsule 3 times a day and 2 capsules at night, for 5 days.

The effectiveness was assessed based on the analysis of primary and secondary endpoints in patients with ARVI (with laboratory-confirmed presence of RNA/DNA virus by PCR method, absence of influenza virus and SARS-CoV-2 markers) who took the drug at least once and met the selection criteria.

The primary end point was the time until the onset of persistent improvement in clinical symptoms on the severity scale for acute respiratory viral infections (less than or equal to 2 points, provided there is no more than 1 point for 1 symptom) with normalization of temperature (less than 37°C); persistent improvement means maintenance symptoms improve for at least 22 hours.

Secondary endpoints:
- area under the curve “score on the scale of severity of the patient’s condition with ARVI - time” during 5 days of therapy;

- time until body temperature normalizes from the moment the first symptoms of the disease appear, measured in hours (normalization means setting the temperature below 37°C without rising above these values in the subsequent period);
- time until the disappearance of all symptoms according to the severity rating scale for ARVI from the moment the first symptoms of the disease appear;
- the proportion of patients with normalization of body temperature below 37°C by 1, 2, 3, 4, 5, 6, 7 and 8 days from the onset of the first symptoms of the disease;
- the proportion of patients with complete disappearance of all symptoms by 1, 2, 3, 4, 5, 6, 7 and 8 days from the onset of the first symptoms of the disease;
-average body temperature at 1, 2, 3, 4, 5, 6, 7 and 8 days from
- time from the moment of appearance to the disappearance of catarrhal-respiratory syndrome, including sore throat, cough, hoarseness, sneezing, runny nose, nasal congestion (according to the ARVI severity scale), in a population of patients who exhibited the corresponding symptoms;

Results

At the screening stage, RNA/DNA of the following viruses was isolated: rhinovirus, adenovirus, respiratory syncytial virus, parainfluenza virus, bocavirus, coronavirus HCoV-229E, human metapneumovirus and their combinations. The detailed distribution of detected viruses is presented.
By the end of therapy, no ARVI virus antigens were detected by PCR.
Between stages I and II, an interim analysis of preliminary safety data and PK of the drug was carried out. After receiving positive findings from the interim analysis, which, in the opinion of the independent clinical trial data monitoring committee, confirmed the feasibility of using the proposed dose and regimen in children, the study moved to phase II. Thus, the hypothesis about the superiority of the drug riamilovir over placebo was confirmed, since the study showed a decrease in the duration of the disease when using the drug riamilovir, 100 mg capsules, compared to placebo by at least 2 days.

Conclusion

As a result of a clinical study, the drug riamilovir was found to be highly effective in treating children aged 12–17 years diagnosed with ARVI. In addition, the safety and good tolerability of the drug riamilovir have been established.
Thus, we can recommend the practical use of the etiotropic antiviral drug riamilovir in the treatment of children aged 12–17 years diagnosed with ARVI due to its high efficiency and safety. The introduction of the drug riamilovir into pediatric practice will significantly expand the arsenal of effective etiotropic antiviral drugs.
In addition, the results obtained allow us to recommend conducting clinical studies in a younger audience of patients (6–11 years old) diagnosed with ARVI.

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