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The Possibility of Optimizing the Therapy of Influenza and Other Acute Respiratory Viral Infections in Pediatric Practice

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Received: 03.02.2012, accepted for publication: 01.03.2012

This article covers the results of studies on safety and clinical efficacy of interferon inducer during influenza and other acute respiratory viral infections in children aged 7-14 years. It is shown that the antiviral immunostimulatory agent shortens the main symptoms of the disease, prevents the development of complications and can be recommended for use in pediatric patients for the treatment of influenza and other viral infections

Key words: *inducer of interferon, influenza, SARS, treatment, children.*

Acute respiratory infections are the most common human pathologies, and their growth is recorded in many countries around the world, regardless of climatic zones and levels of socio-economic development [1]. Consistently high incidence of influenza and other acute respiratory viral infections (ARI) is preserved among all age groups, while children get sick more frequently [2, 3]. Of particular risk are often ill children (OIC), who often undergo repeated and severe acute respiratory viral infection that may adversely affect the health, lead to the exclusion of basic functional systems of the body, contribute to the formation of chronic foci of infection, prevent carrying out of vaccination, overburden premorbid background, and delay physical and psychomotor development [4, 5].

It is known that resistance to infection depends on the genetically determined activity of immunocompetent cells (ICC) to develop human interferon (IFN). Development of infectious process with acute respiratory infections has place in case of an existing deficit of synthesis of interferon and other cytokines, which are products of humoral ICC. The immune

system of children is characterized by high proliferative activity of lymphocytes with predominance of the fraction of undifferentiated, "naive" lymphocytes, reduced cytotoxic and IFN-producing activity of IKK [6, 7].

At present time, the study of cytokines role, especially of IFN in the pathogenesis of SARS, is fundamental to understanding the causes of their severe and complicated course, as well as to establish the reasons for the formation of a special group of FIC [8]. Initially, a weak immune response in children with severe deficiency of interferon determine the severity and nature of the disease, promotes the development of bronchopulmonary complications, and requires optimization of therapy with SARS drugs with antiviral and immunomodulatory properties [9, 10].

In recent years, clinicians included into their arsenal some new drugs for treatment and prevention of influenza and other viral respiratory infections - interferon inducers. It is known that IFN themselves are mediators of immunity, having a universally broad spectrum of biological activity, including antiviral and immunomodulatory effects. Development of IFN is the first line of cell defense against viral infection, which significantly outcomes the synthesis of specific antibodies and other immune factors. Unlike antibodies, IFN inhibits the intracellular stages of virus reproduction in infected cells and provide immunity to viruses surrounding healthy cells [11]. These facts have led to the use of IFN preparations in the treatment and prevention of influenza and SARS, and further for use of interferon inducers [3, 9, 10].

Action mechanisms and activity spectrum of interferons and interferon inducers are similar, but the latter have several advantages over exogenous IFN. IFN inducers include drugs that increase the ability of cells to the synthesis of endogenous interferon, which have not only anti-virus, but immunocorrective effect that can be attributed to a new generation of drugs is universal, broad-spectrum [11-13].

Clinical efficacy of interferon inducers in children having influenza and other viral respiratory infections is shown in several studies [14-17]. The choice of a particular drug from the group of inducers of IFN to treat SARS in children is determined by child's age and individual tolerance.

The first oral inducer of endogenous IFN α, β, γ is tilorona (Amiksin, JSC "Pharmstandard-Tomskhimfarm", Russia. Registration number LSR-000175/08, 1/24/08).

Tilorona was developed over 30 years ago and still is the best-studied drug among those available in the pharmaceutical market of IFN inducers with well-known safety profile and efficacy for a wide range of diseases having infectious and noninfectious origin. To date, there were published over 450 research papers in which safety and efficiency of tilorona was experimentally and clinically proved in various diseases in children and adults.

The mechanism of antiviral action of the drug is associated with inhibition of virus-specific proteins transition into infected cells, resulting in suppressed reproduction of the virus [9, 12, 18]. Despite the diversity of the genetic material of viruses, tilorona (as well as IFN) inhibits the replication of universal processes, which is almost all viruses containing RNA or DNA are sensitive to immunostimulating. Tilorona induces the synthesis of all interferons classes, including IFN γ. Its important feature is ability to maintain long-term therapeutic IFN levels in serum. When one dose of drug is administered into the serum, IFN titers reaches maximum values in 24 h, while duration of IFN circulation in the blood is 4-5 days, indicating its prolonged effect.

Tilorona goes well together with other antivirals, immunomodulators, and antibiotics (additive effect). These properties of the drug were nrcessary for its application in children.

So, the study of therapeutic efficacy and safety of tilorona for treatment of flu and SARS in 180 children over the age of 7 years, in a multicentered randomized and placebo-controlled study, demonstrated this drug's effect on the rate of resolution of the main clinical symptoms of the disease, rapid elimination of the pathogen, significant improvement in interferon status [19].

The aim of this work is the definition of safety and clinical efficacy of tilorona for treatment of flu and other viral respiratory infections in children aged 7-14 years.

Patients and observation methods

The work was conducted in a pediatric polyclinical complex MBUZ GDKB #1 in Krasnoyarsk in two last months of 2010. This study refers to the open and controlled observational studies.

Patients were selected for the study by following criteria:

— the presence of SARS with severe clinical symptoms (body temperature on the day of drug assignment ≥ 37,5 ° C, weakness, headache, dizziness, catarrhal symptoms);

— initiation of treatment within 48 hours after illness occured;

— age of the patients is 7 - 14 years (inclusive);

— obtaining of informed consent for participation in the study from the patient's parents

Exclusion criteria were the following:

— participation of the patient in another study;

— patients having hypersensitivity to any component of the study drug;

— patients having chronic renal, endocrine, onco-hematological, neurological, cardiovascular or other diseases, which, according to the doctor, can affect the results of the study;

— children receiving treatment with other immunomodulatory agents within 28 days preceding the first day of the study;

— rejection of parents or the patient to participate in the study

The study involved 60 children aged 7-14 years diagnosed with influenza or other viral respiratory infections in the first 48 hours after the disease initiated.

Patients were randomized into 2 groups:

I — main group (n = 30), who received tilorona;

II - control group (n = 30), who received standard therapy without the use of immunotrophical drugs during the study. Groups of patients had no gender differences.

For children of the main group there was administered Amiksin of 60 mg (1 tablet) once daily after a meal in the 1st, 2nd and 4th days; course dose was 180 mg. In case of slow reverse dynamics on the background of the therapy, the main group used the drug for 1, 2, 4, 6 th days of starting treatment; course dose was 240 mg.

Range of other medications that were prescribed in the acute phase to the patients in both groups, was traditional and included antipyretics, decongestants, saline solutions for nasal lavage, mucolytics, or expectorants, and antisense drugs. Antibiotic therapy was administered only upon special decision.

Observation and treatment of children were carried out in accordance with the condition under which each patient was inspected by pediatrician at least 4 times.

Effectiveness of therapy was evaluated on terms of normalization of temperature, the disappearance of intoxication sympthoms (headache, weakness, lethargy, loss of appetite), a decrease of catarrhal symptoms (runny nose, cough, inflammatory changes in the oropharynx). At the same time possibility of adverse reactions was taken into account.

Complete term of observations on each patient was at least 7 days, and in case of slow inverse dynamics it was prolonged up to a full recovery.

Statistical analysis of the material was carried out using analysis of variance and determination of the arithmetic mean (M), the average error of the arithmetic mean (m), followed by the establishment of significant differences between the averages in the groups (p).

Results of the research

Comparative assessment of the effectiveness of therapy tilorona was performed for 60 children, among them there were 31 boys and 29 girls. In the study group the average age of patients was 11,3 ± 2,7 years, and - 12,6 ± 1,4 years in the control group. There were established no significant differences in age structure in the observed group of patients.

Etiology of infection was established by polymerase chain reaction (PCR) in 81.6% (49) children, for whom in 59.2% (29 people) there was detected monoinfection, while in 40.8% (20) there was detected mixed infection. In 18.4% (11) of patients etiology of SARS for various reasons has not been established. We observed predominant influenza in 77.5% of patients and monoinfection in 34.7% of patients (17), in association with other infections in 42.8% (21). Etiological structures of acute respiratory viral infections in both groups were quite comparable (Table 1).

In all observed cases the disease started acutely with the increase in temperature to 38 ° C (63.3%) and 38,5-39 ° C (43.3%). Febrile fever over 39 ° C occurred only in 13% children from the main group with influenza. 40% of children receiving tilorona, and 46.7% of children in the control group complained on fatigue, malaise, loss of appetite. Headache occurred in 30 and 23.3% of children, respectively. Copious mucous discharge from the nose was observed in 46.6% of the main group patients and 50% of control group; nasal congestion with poor discharge was observed in 30 and 26.6% of children, respectively. Cough was observed in 83.3% of the children of the main group and 90% of those of the comparison group. Conjunctivitis evidences (5 persons) were characterized by mixed-variants of influenza and adenovirus infection (Table 2). Taking into consideration all abovementioned sympthoms, all patients were diagnosed with a form of moderate SARS.

Thus, the groups of observed patients were comparable by sex and age composition, the etiological structure, the severity of the disease, the composition of the basic treatment.

Having analyzed the duration of the main symptoms of the disease on the background of the therapy in the two groups it could be noted that in all 30 children receiving tilorona, symptoms of intoxication and fever stopped by the 5th day of therapy. At the same time 76.7% (23) patients of the main group had temperature reaction docked in the first 3 days of illness (of whom 36.7% - in the first 2 days), and only in 23.3% (7) duration of temperature was 4-5 days. Average duration of thermal reactions in children receiving tilorona, was 2,8 ± 0,4 days (Table 3).

In group II patients who received only conventional therapy, no child had their temperature normalized in the first two days of the disease; in 53.3% (16) drop in temperature occurred at the end of the third day, and 40% (12) - only by the 5th day, with 6.7% (2) - remained longer than 5 days. The average duration of fever in this group was 3,7 ± 0,6 days, which was significantly higher, comparing with children of the main group, $p < 0.001$ (see Table. 3).

Along with a decrease in temperature in 80% (24) of patients receiving treatment of IFN inductor, in the first three days other symptoms of intoxication (headache, dizziness, weakness, poor appetite) disappeared for these patients, while only in 20% of patients (6) they were present for 4 days and the average duration of symptoms of intoxication was 2,8 ± 0,8 days (Table 4). In the control group that was receiving standard therapy, 70% (21) of patients had their symptoms of intoxication persisting up to 5 days, and 30% (9) - for more than 5 days with an average duration of up to 4,2 ± 1,2 days, which was significantly higher than the corresponding values in the study group, $p < 0.005$ (see Table 4).

The duration of catarrhal symptoms was also significantly shorter in the main group compared with patients receiving conventional therapy, that on average was 2,1 ± 1,1 vs. 5,2 ± 0,4 days, respectively, $p < 0.01$ (Table . 5).

In 76.7% (23) patients of the group by the end of the week there were cropped major clinical manifestations of the disease, which was regarded as a clinical cure. Only in 23.3% (7) of children, illness was complicated by the development of sinusitis (3), bronchitis (2), otitis media (2) (Table 6). Among children with SARS who received only conventional therapy, disappearance of clinical evidences of SARS on the 7th day was observed only in

46.7% (14) of cases, while in 53.3% (16) patients the disease was accompanied by the development of bronchitis (7), otitis media (4), sinusitis (5) (see Table. 6).

Having an authentic major reduction of the sympthoms relief period, there significantly decreased duration of treatment of patients with SARS. So, the average duration of illness in patients with uncomplicated course in main group was 3,2 ± 0,2 days, while in control group it was 5,6 ± 1,2 days ($p < 0.01$); if the disease course was complicated - 6.8 ± 0,8 and 8,2 ± 1,3 days, respectively, $p < 0.05$ (Table 7).

In the course of therapy all patients tolerated tilorona well, and adverse reactions to the drug were not observed.

Conclusion

The results of the cuurent observations suggest the clinical efficacy of interferon inducer Amiksin in the treatment of influenza and other viral respiratory infections. Taking into consideration the drug therapy for children aged 7-14 years, the total duration of illness, duration of symptoms of intoxication, fever, catarrhal symptoms in the nasopharynx and oropharynx were significantly reduced regardless of the etiology and clinical manifestations of the disease. In addition, antiviral therapy with immunomodulatory drugs reduced the risk of non-smooth course of the disease. No side effects were reported for children who used tilorona. The interferon inducer may be recommended for use in pediatric practice for the treatment of influenza and SARS both at home and in the hospital.

Table 1. Nosological forms of SARS

Nosological form	**Main group (n=23)**		**Control group (n=26)**	
	total	**%**	**total**	**%**
SARS monoform	12	52,2	14	53,8
Unfluenza viruses H3N2 H1N1 H1N1swine	 5 1 2		 3 3 3	
Parainfluenza	3		3	
Respiratory syncytial virus	1		2	

Mixed forms of SARS	11	47,8	12	46,2
Influenza virus A (H3N2) +B	3		2	
Ingluenza virus B + parainfluenza	4		3	
Adenovirus + Influenza virus A (H1N1)	2		3	
Influenza virus A (H1N1)+parainfluenza	2		2	
RS-virus + parainfluenza	-		2	

Table 2. Clinical symptoms observed in patients with SARS

Sympthoms	**Main group (n=30)**		**Control group (n=30)**	
	total	**%**	**total**	**%**
Temperature rise	30	100	30	30
Lethargy, malaise	12	40	14	46,7
Rhynorea	14	46,6	15	50
Cough	25	83,3	27	90
Tickling in the throat	12	40	8	26,7
Nasal congestion	9	30	8	26,7
Headache	9	30	7	23,3
Rash	-	-	1	3,3

Table 3. The duration of the temperature of the reaction observed in patients with SARS

Duration in days	**Main group (n=30)**		**Comparison group (n=30)**	
1−2	11	36,7	-	-
3 days	12	40,0	16	53,3
4−5 days	7	23,3	12	40,0
>5 days	-	-	2	6,7
Average duration	2,8±0,4		3,7±0,6*	

Note * — p<0,001.

Table 4. The duration of symptoms of intoxication observed in patients with SARS

Duration in days	**Main group (n=30)**		**Control group (n=30)**	
	total	**%**	**total**	**%**
1−2	11	36,7	-	-
3	13	43,3	-	-
4−5	5	16,7	21	70
>5	1	3,3	9	30
Average duration	2,8±0,8		4,2±1,2*	

Note. * — p<0,005

Table 5. The duration of catarrhal symptoms in patients with SARS observed

Duration in days	**Main group, n=30**		**Control group, n=30**	
	total	**%**	**total**	**%**
1−2	16	53,3	1	3,3
3	12	40,0	9	30,0
4−5	2	6,7	7	23,3
>5	-	-	13	43,3
Average duration	2,1±1,1		5,2±0,4*	

Note. * — p<0,01.

Table 6. The nature of the disease courseflow observed in SARS patients

Disease courseflow	**Main group, n=30**		**Control group, n=30**	
	total	**%**	**total**	**%**

Uncomplicated	23	76,7	14	46,7*
Complicated with:	7	23,3	16	53,3*
bronchitis	2		7	
maxillary sinusitis	3		5	
otitis	2		4	

Note. * **—** p<0,05.

Table 7. The duration of the disease in the observed patients (in days)

Disease courseflow	**Main group (n=30)**	**Control group (n=30)**	***p***
Uncomplicated	3,2±0,2	5,6±1,2	p<0,01
Complicated	6,8±0,8	8,2±1,3	p<0,05

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