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Research Article

Effectiveness of Interferon Gamma for the Treatment of Moderate and Severe Influenza by Neuraminidase Inhibitors: The Results of an Open-Label Randomized Controlled Clinical Trial (Season 2018-2019)

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Summary Box

What is already known on this subject?

Antiviral drugs recommended by the WHO significantly reduce the duration of influenza symptoms and decreases the risk of complications. Vaccination presents a valuable measure, however influenza still remains one of the most widespread infectious diseases. Interferons possessing a wide range of antiviral activity are also effective against influenza viruses.

What this study adds?

Recombinant interferon gamma for intranasal administration could provide benefits in the complex treatment of moderate-to-severe influenza. Interferon gamma shows the best clinical effectiveness in combination with zanamivir. Either combined with zanamivir, or with oseltamivir, interferon gamma reduces the length of hospital stay of patients with moderate influenza and can be recommended for the treatment of influenza in patients receiving specialized inpatient care.

Abstract

Background: Interferon gamma for intranasal administration has been approved for the prevention and treatment of influenza in complex therapy. Its effectiveness and safety was proved in randomized controlled clinical trials. This open-label comparative clinical trial aimed to evaluate the effectiveness and safety of interferon gamma in therapy of influenza.

Methods: 300 patients were included. The main inclusion criterion was diagnosis of moderate or severe influenza that required hospitalization. The patients were randomly allocated to one of three groups (1:1:1/2).

— Group A: interferon gamma + zanamivir + symptomatic treatment.

— Group B: interferon gamma + oseltamivir + symptomatic treatment.

— Group C (control): zanamivir or oseltamivir (1:1) + symptomatic treatment.

The patients were observed daily throughout the hospitalization period. All patients underwent scheduled clinical examinations including body temperature measurement, registration of complaints and clinical parameters, blood count, biochemical blood test, urinalysis. In case of clinical signs of pneumonia, patients received chest radiography. If this complication was confirmed, the patient would have received antibacterial therapy.

Results and Conclusion: We noted a trend towards earlier disappearance of the symptoms of intoxication in patients treated with interferon gamma. The study showed that interferon gamma influences the hospitalization length in patients with moderate influenza; compared to the control group, there was a statistically significant reduction of the duration of hospital stay in patients, who received interferon gamma. Good tolerance to interferon gamma was demonstrated. Further studies are needed to evaluate the effectiveness of interferon gamma for the treatment of complicated influenza.

Background

Influenza is one of the most widespread infectious diseases, and it puts a significant social and economic burden on health care systems worldwide. The morbidity with influenza in 2018 in Russia was 26.33 per 100,000 persons (24.5% lower compared to 34.86 per 100,000 in 2017); 113.90 per 100,000 children age 1-2; and 93.91 per 100,000 children age 3-6 according to Rospotrebnadzor. The WHO estimates that influenza epidemics account for 3-5 million severe cases of the disease and 250,000—500,000 deaths from respiratory diseases annually. Lethal cases of influenza in industrialized countries most often occur after 65 years of age. Complications of influenza may also develop in young and healthy persons, who are not a risk group and therefore are not covered by mandatory annual vaccination against influenza.

Drugs of choice for the treatment of influenza are neuraminidase inhibitors (zanamivir and oseltamivir). Interferons are also effective against this disease and are recommended as a part of a combined treatment. The results of this study confirm the effectiveness and safety of interferon gamma in a combined hospital treatment of patients with moderate-to-severe and severe influenza.

Keywords: Influenza, Interferon gamma, Moderate-to severe and severe influenza, Hospitalization

Introduction

Despite the ready availability of vaccines and various effective antiviral drugs, influenza remains one of the most widespread infectious diseases [1-3] and puts a significant social and economic burden on the health care system worldwide.

Economic losses caused by influenza depend on the age of patients and on the duration of temporary disability or hospitalization in complicated cases. Official data provided by Rospotrebnadzor [1] show that the economic burden of influenza was more than 1,096,935,000 RUB in 2018-2019 epidemic season. Drug treatment recommended by the WHO significantly reduces the duration of the disease and decreases the risk of complications [4]. It is especially important in patients with moderate and severe influenza, who often require specialized inpatient care [5,6].

Antiviral treatment is the most important component of combined therapies of influenza; the drugs of choice are neuramini-

dase inhibitors (zanamivir and oseltamivir) [1,2,7,8]. Interferons are also effective against influenza [9-15] and are recommended as a part of a combined therapy [7].

There are three types of interferon (alpha, beta, and gamma) with different characteristics and range of antiviral activity [16].

Recombinant interferon gamma for intranasal administration was approved for the prevention and treatment of influenza in a combined therapy. Its effectiveness was demonstrated in several randomized controlled clinical trials [9-15]. One flask of the studied drug contained 100,000 ME of lyophilized recombinant interferon gamma, which should be diluted before use [17]. Interferon gamma is effective against A and B subtypes of influenza virus, as well as against H5N1 influenza [9-15].

Methods

This post-authorization clinical trial was aimed to evaluate the effectiveness and safety of recombinant interferon gamma for intranasal administration in a combined therapy of adult patients hospitalized in a specialized facility due to clinical indications of influenza. The study was open-label and comparative. All pharmaceuticals were used exclusively for the registered indications and in standard therapeutic doses recommended for the treatment of this disease. All therapeutic procedures were conducted according to the current Russian clinical guidelines on the treatment if influenza [7] and the rules of good clinical practice [18,19]. All selected patients provided their written informed consent prior to the study enrollment according to the Declaration of Helsinki. Two copies of the explanation sheet with the informed consent were signed and dated by the patient and by the researcher. The patient received one copy, and the other copy was retained by the research center.

Influenza was diagnosed clinically by a physician. In the first 24h after randomization, the administration of drugs did not depend on laboratory diagnosis of the infection.

The main criterion of the inclusion into the study was clinical and/or laboratory diagnosis of moderate-to-severe or severe influenza, which required hospitalization due to clinical indications. Male and female patients in the age of 18-65 were included.

After the informed consent and the evaluation of inclusion/exclusion criteria, patients were assigned to one of the following study groups in the proportion of 1:1:1/2 using adaptive randomization:

— Group A (experimental group): interferon gamma + zanamivir + symptomatic treatment for at least 5 days.

— Group B (experimental group): interferon gamma + oseltamivir + symptomatic treatment for at least 5 days.

— Group C (control group): zanamivir or oseltamivir (1:1) + symptomatic treatment for at least 5 days.

All drugs were administered in accordance with instructions and standard recommended doses.

Lyophilized recombinant interferon gamma for the preparation of the solution for intranasal administration was diluted with 5 ml of water for injections and administered intranasally as approved for medical use. The participants received the drug for 5 consecutive days, 2 drops 5 times a day into each nasal passage previously washed according to the instruction.

Zanamivir and oseltamivir were administered in standard recommended doses according to the instructions on their medical use:

— zanamivir: 2 inhalations (2 × 5 mg) 2 times a day for 5 days, total daily dose 20 mg.

— oseltamivir: 75 mg 2 times a day per os for 5 days, total daily dose 150 mg.

Symptomatic treatment was applied at the discretion of the researcher according to the Federal Clinical Recommendations 'Influenza in adults' (Moscow, 2017) by the International Infection Association. [7] The recommendations allowed the following drugs:

— nonsteroidal anti-inflammatory drugs in case of body temperature over 38°C:

1. ibuprofen 200-400 mg per os 3-4 times a day for 3-10 days.
2. paracetamol 500-1000 mg up to 4 times a day.

— expectorants:

1. acetylcysteine 200 mg per os 2-3 times a day after meals
2. guaifenesin 200-400 mg (10-20 ml) per os 3-4 times a day after meals
3. bromhexine 8 mg (1-2 pills) per os 3-4 times a day
4. ambroxol 30 mg per os 3 times a day

— antitussives in patients with dry nonproductive cough:

1. dextromethorphan (included into multicomponent drugs)
2. butamirate (syrup) 15 ml per os 4 times a day.

Throughout the period of hospital stay, the participants were observed daily.

At the screening stage, patients received unique ID numbers, which were then indicated in their original medical records and in case report forms (CRFs). If a patient was discharged from hospital before the next scheduled visit, this fact was noted in the original medical record and CRF along with the cause of such early discharge (recovery / protocol violations / transfer to another hospital.

All patients in the experimental and control groups received scheduled clinical examinations that included body temperature measurement, and the registration of complaints and clinical parameters (fever over 37°C; symptoms of intoxication, i.e. aches, nausea, vomiting, weakness; and difficulty in breathing). At least two clinical signs of intoxication were required, because all patients complained about weakness during the entire period of observation. Signs of respiratory insufficiency (RI) and shortness of breath were noted separately. Catarrhal signs and cough were not evaluated.

To assess the safety of the therapy all patients in the experimental and control groups underwent blood count, biochemical blood test, and urinalysis before and after the treatment. Laboratory diagnosis of influenza was not an inclusion/exclusion criterion and was left to the discretion of the investigator.

All adverse events (AEs) were noted in a special form. Researchers were required to assess the level (severity) of all AEs, their connection to the studied drug, measures taken, and the outcome of such events. The study included 300 patients.

The experimental group A included 100 adult patients, 93 with moderate influenza and 7 with severe influenza. The group received interferon gamma in a combined therapy with zanamivir according to the regimen described above.

The experimental group B included 100 adult patients, 94 with moderate influenza and 6 with severe influenza. The group received interferon gamma in a combined therapy with oseltamivir according to the regimen described above.

The control group (group C) included 100 adult patients, 97 with moderate influenza and 3 with severe influenza. 50 patients in the control group received oseltamivir, and 50 received zanamivir.

In the groups A and B, symptomatic therapy could be administered by the researchers according to the Federal Clinical Recommendations 'Influenza in adults' (Moscow, 2017) by the International Infection Association [7].

Statistical analysis of the homogeneity of the sample and the significance of differences of main parameters of the study was conducted using t-test function; differences were considered significant if $p \leq 0.005$.

The demographic characteristics of the participants are shown in Table 1.

Table 2 shows the distribution of participants by diagnosis and severity of the disease.

Results

The results of a dynamic control of the signs of the influenza are shown in Table 3.

At the screening stage, all patients had signs of fever and symptoms of intoxication. Only 5-11% of patients had signs of respiratory insufficiency, and 93% of such patients suffered from a severe form of influenza. On the third day of treatment, about a half (46-56%) of the participants in the experimental groups had no signs of fever, while fever was present in 71% patients in the control group. On the forth day of treatment, symptoms of intoxication were two times more frequent in the group C compared to the groups A and B. This positive trend in respect of the relief of main symptoms was noted before the fourth day of observation, which supports the inclusion of interferon gamma into the therapy.

A separate comparative analysis of the average length of hospitalization in three groups was conducted. Table 4 presents the data on hospital stay in all study groups.

The average length of hospital stay was 16.5% lower in the experimental groups, which received interferon gamma, compared to the control group. The differences between the groups A and B and the group C were statistically significant in this regard (p=0.0001). At the same time, no significant differences were found in the length of hospitalization between the groups A and B (p=0.44). It was therefore demonstrated that the use of interferon gamma in a combined therapy of moderate influenza reduces the period of hospital stay in routine clinical practice.

Adverse effects of therapy with interferon gamma were assessed during the entire period of observation. No adverse events were registered in groups A and B, which received this drug. Doses rec-

ommended in the instruction on medical use of interferon gamma did not cause adverse events in the observed population and was well-tolerated.

Discussion

This study was carried out in accordance with the rules of the Russian Federation for the organization and conduct of clinical trials, which are harmonized with the international rules of good clinical practice. The study was conducted in a routine clinical practice on a non-commercial basis, so the spectrum of the analyzed parameters was minimal, which, of course, limits the possibilities for a detailed assessment of the effect of the addition of interferon gamma on numerous symptoms of intoxication with influenza. The main target of the study was to determine how justified the use of intranasal interferon gamma in a hospital setting is, how safe its use is and whether it shortens the period of illness, therefore, only the most frequent symptoms of intoxication - fever (above 37°C), pain, weakness, nausea, vomiting - was analyzed. The study design did not provide for any additional laboratory tests to assess the effect of interferon gamma on blood parameters, such as leukocytosis, etc. Immunogenicity was also not specifically evaluated, because the intranasal form of interferon gamma is officially registered in the Russian Federation for the treatment and prevention of influenza, in this study the drug was used strictly according to registered indications within of the approved instructions for medical use, so there was no need to assess its immunogenicity. The safety of interferon gamma in intranasal form, including immunogenicity, has been evaluated in previous studies [9-12]. It should be noted that the Russian Federation is the only country where interferon gamma in intranasal form is officially approved for the treatment and prevention of influenza.

Vaccination against influenza is considered an effective measure for the prevention of epidemics. However, vaccinated persons still can be vulnerable to the disease, e.g. because of the unavailability of quadrivalent influenza vaccines in Russia, violation of vaccination procedures, and mismatching between circulating strains and vaccine strains of the virus in a given epidemic season. New strains and combinations of strains of influenza virus appear every year, and this greatly complicates the development of active vaccines [20-22].

Based on the previous findings [9-12] and the results of this clinical study, we could conclude that interferon gamma provides benefits in the treatment of moderate-to-severe influenza. Statistical analysis was not conducted in the subgroup of patients with severe

Table 1: Distribution of the patients by study groups, sex, and age.

Parameter	Group A	Group B	Group C
Mean age, years	36.6	36	35.9
Men, %	48	55	49
Women, %	52	45	51
n	100	100	100

Table 2: Distribution by diagnosis and severity level.

Diagnosis and severity	Group A	Group B	Group C
Moderate influenza, %	93	94	97
Severe influenza, %	7	6	3

Table 3: The dynamics of clinical symptoms in the main and control groups.

Group	Symptoms	Period of observation				
		Day 1	Day 2	Day 3	Day 4	Day 5
A	Fever, %	100	72	46	11	6
	Intoxication, %	100	71	37	9	4
	Respiratory insufficiency, %	8	7	1	1	0
B	Fever, %	100	81	56	14	2
	Intoxication, %	100	64	43	14	2
	Respiratory insufficiency, %	5	1	0	0	0
C	Fever, %	100	84	71	25	1
	Intoxication, %	100	73	42	23	1
	Respiratory insufficiency, %	11	3	2	1	0

Table 4: Length of hospital stay of patients with moderate influenza in the study groups.

Group	A (interferon gamma+ zanamivir)	B (interferon gamma + oseltamivir)	C (zanamivir or oseltamivir)
Days in hospital	6.27	6.36	7.56
p-value (comparison to the control group)	0.0001	0.0001	
p-value (comparison between the experimental groups)	0.44		
Average hospital stay in days (A + B)	6.31		
p-value (comparison to the control group)	0.0001		
Reduction of hospitalization, days Δ (A+B) vs (C), days, (%)	1.25 (16.5%)		

influenza due to the limited sample.

The best results of treatment were achieved in the group A (zanamivir + interferon gamma); elimination of intoxication symptoms and fever in this group was faster (day 3). No statistical differences in the length hospital stay were found between groups A and B, so both regimens of combined therapy (interferon gamma + zanamivir, and interferon gamma + oseltamivir) can be recommended for the treatment of moderate influenza.

Conclusion

The conducted open-label comparative study of the effectiveness and safety of intranasal form of interferon gamma in patients with moderate-to-severe and severe influenza, who required hospitalization, demonstrated good effectiveness of the drug, which manifested itself in a lower duration of fever and other symptoms of intoxication including signs of respiratory insufficiency. This confirms findings of other authors [9-12] on the effectiveness and safety of interferon gamma in a combined therapy of influenza. The influence of interferon gamma on the length of hospital stay deserves special attention; a statistically significant reduction of hospital stay for almost 1.5 days was found in patients, who received this drug, compared to the control group. Good tolerance and a trend towards earlier disappearance of symptoms of intoxication in the experimental groups were also noted. Therefore, the use of interferon gamma in a combined therapy of influenza can be advised for the hospital treatment of moderate forms of the disease. Further studies are required to assess the influence of the drug on complicated influenza.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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