Combined Tamiflu and BioR Treatment in Patients with H1N1 Influenza

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Abstract

A comparative study of combined Tamiflu and BioR treatment has been performed in 22 patients with (H1N1) influenza A (the experimental lot) and 17 patients (the control lot) in which only the Tamiflu was administered. The diagnosis of influenza A (H1N1) was confirmed using PCR. The clinical symptomatology varied amongst patients, but the most frequent symptoms were fever, throat pains asthenia, myalgias, hyperemia of the pharyngeal isthmus, dry cough, harsh respiration, chills, and nasal congestion. Tamiflu was administered in a dose of 75 mg orally twice a day, in the morning and in the evening; the average length of treatment was 5 days. BioR was administered to 16 patients as 5.0 mg orally, twice a day, and to 6 patients as1 mg IM, twice a day; average length of treatment was 5 days for all groups. The control group received Tamiflu only, the same dosage as the study group. The average length of treatment was 6.0 days. Comparing the length of the symptoms in the experimental group to that in the control group, we found that duration of symptoms reflecting the influence of the central nervous system in the experimental group was on average 5.0 days as compared to 6.6 days in the control group. Similarly, duration of symptoms affecting the respiratory system in the experimental group was 3.8 days and in the control group 5.3 days. We conclude that the Tamiflu and BioR treatment in patients with influenza A (H1N1) was beneficial and contributed to the decrease of symptom duration as compared to the group of patients treated with Tamiflu alone.

Key words: A (H1N1) influenza, Tamiflu, BioR, treatment.

Комбинированное лечение Тамифлу и БиоР у больных гриппом А (H1N1)

Было изучено эффективность комбинированного лечения Тамифлу и БиоРом у 22 больных гриппом А (H1N1), экспериментальная группа, и 17 больных, контрольная группа, которые получали только Тамифлу. Диагноз гриппа А (H1N1) был установлен биомолекулярным методом (ПЦР). Клиническая симптоматология была многообразная, но самые частые симптомы, которые встречались у обеих групп, были: лихорадка, боли в горле, слабость, боли в мышцах, гиперемия зева, сухой кашель,ознобы и гиперемия лица. Тамифлу был назначен в дозе 75 мг 2 раза в день утром и вечером, длительность лечения в среднем составляло 5,0 дней. БиоР был назначен в дозе 5 мг 2 раза в день перорально у 16 больных, и по 1,0 мг в/м 2 раза в день у 6 больных. Длительность лечения составила 5 дней. В контрольной группе был назначен только Тамифлу в такой же дозировке как в первой группе. Длительность лечения составила 6 дней. При сравнении длительности симптомов в экспериментальной и контрольной группе было отмечено, что симптомы характерные для поражения нервной системы сохранялись в среднем 5,0 дней, а в контрольной группе 6,6 дней, а симптомы поражения верхних дыхательных путей соотвественно – 3,8 и 5,3 дней. Комбинированное лечение Тамифлу и БиоРом в сравнении с лечением только Тамифлу привело к сокращению длительности клинической симптоматики и к уменьшению периода госпитализации больных гриппом и больных бронхопневмонией.

Ключевые слова: Грипп А (H1N1), Тамифлу, БиоР, лечение.

Introduction

In April 2009 cases of contagious, acute respiratory disease in the USA (South California and Texas) were first registered as an influenza A virus of a new type called H1N1. The new virus appeared suddenly and was simultaneously identified in 2 other countries, Mexico and Canada.

The situation with the infection of a new viral influenza A (H1N1) developed rapidly, affecting in a short period of time a great number of people from all continents. These events forced the WHO to raise on 11 June 2009 the level of pandemic alert from place 5 to 6, which meant the beginning of the first influenza pandemia in the 21st century.

Influenza, as well as other respiratory diseases, generates important economical losses every year, with associated costs of medical care, decreased ability to work throughout the duration of infection – either of an affected adult or one taking care of an affected child. The greatest part of expenditures of medical care constitutes the hospitalization costs. About 14.6 billion dollars are spent every year throughout the world to treat influenza and its complications. A single person, in turn, can spend the equivalent of 30-100 Moldovan den on the influenza infection, covering the cost of treatment post influenza complications – which, depending on severity, can easily amount to a cost of $100 American dollars.

For effective results, influenza treatment should be started as soon as possible within 2 days from the first signs of influenza. Tamiflu (oseltamivir) has been shown to be the most efficient, reducing the complications rate by 55%. It acts as a

neuraminidase inhibitor, preventing cleavage of budding viral progeny and instead fixing the virus to the host cell.

The toxic action of the influenza virus includes inhibition of cellular and humoral immunity, resulting in diminished the resistance. The native preparations such as BioR are of a particular interest which have a large spectrum of action: immunomodulatory, immunostimulatory, antiviral, cytoprotector and regenerant.

Due to these aspects we designed a study with BioR to evaluate its role as a therapeutic agent in influenza treatment.

Material and Methods

The study included 22 patients (the study group) from 19 - 68 years of age (the average age was 33.6 ± 0.9) comprised of males – 10 (45.5%), females – 12 (54.5%). There was an equal split between patients residing in urban vs rural areas. Twelve patients were addressed to the family doctor and/or emergency personal and ten presented independently to the admission rooms of CHID- "T. Ciorba". Eight patients were admitted in the first 2 days, eleven on days 3- 5, two on days 7- 8 and one on the 13th day. The length of hospitalization was 5 days for 20 patients, 8 days for 1 and 9 days for 1 patient (the average length was 5.09 ± 0.01 days).

17 patients were enrolled into the control group, they were from 19 - 51 years of age (the mean age was 25.6 ± 1.2), comprised of men - 8 (47.1%), women – 9 (52.9%). Eight were from an urban area (47.1%), and 9 (52.9%) patients were from a rural area ($p > 0.05$). Four patients were initially seen by their family doctor, nine by the emergency medical personal, and five patients came independently to the admission room at "T. Ciorba". 12 patients were seen in the first day of the disease, the other five patients were admitted on the 10th day. The hospitalization length was 5 days for 9 patients, 6 days for 2, 7 days for 4, 9 days for 1 and 10 days for 1 patient (the mean length of hospitalization was 6.1 days). The diagnosis of influenza A (H1N1) was confirmed by PCR in all of the patients included in the study. In the control group, PCR confirmed results were available on the first day of the disease in 1 patient, on the 2nd day in 4 patients, on the 3rd day in 4, on the 7th day in 5, on the 6th day in 2 and on the 9th day in 1 patients. In the experimental group, PCR confirmed H1N1 on the 1st day in 1 patient, on the 2nd day in 4, on the 3rd day in 3, on the 4th day in 5, on the 6th day in 5, on the 7th day in 2 and on the 9th day in 1 patient).

Table 1

Clinical symptomatology in patients of A (H1N1) influenza the study lot and control lot

Symptoms	The study group 22 patients			The control group 17 patients			χ^2	p
	Abs.	P1±Es1	The length of symptoms	Abs.	P2±Es2	The length of symptoms		
Cephalagia	18	81,8±8,2	4,5	11	64,7±11,6	6,4	4,53	**
Ocular pains	6	27,3±9,5	3,7	3	17,6±9,2	4,2	5,25	**
Myalgias	13	59,1±10,5	5,0	7	41,2±11,9	5,6	7,79	***
Arthralgias	8	36,4±10,3	4,2	4	23,5±10,3	4,8	7,00	***
Asthenia	10	45,5±10,6	6,8	14	82,4±9,2	7,7	16,53	****
Chills	8	36,4±10,3	3,4	5	29,4±11,1	3,2	1,64	*
Fever < 38°C	9	40,9±10,5	7,6	6	35,3±11,6	7,5	0,89	*
Fever > 38°C	13	59,1±10,5	5,0	11	64,7±11,6	6,2	0,49	*
Nasal congestion with choriza	3	13,6±7,3	4,3	8	47,1±12,1	5,2	23,74	****
Throat pain	16	72,7±9,5	4,2	12	70,6±11,1	4,8	0,06	*
Fascies tumefied	1	4,5±4,4	1,0	5	29,4±11,1	4,8	21,02	****
Fascies congested	8	36,4±10,3	3,2	7	41,2±11,9	4,0	0,56	*
Injected scleare	2	9,1±6,1	4,5	5	29,4±11,1	4,8	14,04	****
Lacrimations	2	9,1±6,1	3,5	6	35,3±11,6	4,6	19,45	****
Hyperemia of the pharynx	20	90,9±6,1	5,9	17	100,0±0,0	6,2	0,83	*
Chest pains	10	45,5±10,6	3,0	2	11,8±7,8	4,0	96,48	****
Dyspnoea	3	13,6±7,3	6,2	17	100,0±0,0	8,6	74,59	****
Dry rales	6	27,3±9,5	4,2	5	29,4±11,1	6,8	0,16	*
Moist rales	4	18,2±8,2	8,0	2	11,8±7,8	8,0	3,50	*
Crepitant rales	3	13,6±7,3	3,3	1	5,9±5,7	6,0	10,22	***
Harsh breathing	17	77,3±8,9	5,7	10	58,8±11,9	6,6	5,79	**
Attenuated breathing	3	13,6±7,3	3,0	1	5,9±5,7	4,0	10,22	***
Nausea	4	18,2±8,2	2,5	5	29,4±11,1	2,6	4,29	**
Vomiting	5	22,7±8,9	2,0	4	23,5±10,3	2,7	0,03	*
Watery diarrhea	1	4,5±4,4	1,0	3	17,6±9,2	1,5	9,73	***
Tachycardia	5	22,7±8,9	3,5	3	17,6±9,2	4,3	1,46	*
Bronchopneumonia	5	22,7±8,9	6,2	5	29,4±11,1	6,6	1,52	*
Bronchitis	18	81,8±8,2	-	4	23,5±10,3	-	144,40	****
Changes of the ECG	4	18,2±8,2	-	1	5,9±5,7	-	25,72	****

$p > 0.05$; **$p < 0.05$; ***$p < 0.01$; ****$p < 0.001$.

Results and discussions

This study evaluated a wide range of clinical symptomatology in the enrolled patients, presented in tab. 1.

Analysing table 1, we can see multiple clinical symptoms in both groups, affecting the central nervous system, respiratory and cardiovascular systems. The most frequent symptoms were fever(100% in the first lot and 100% in the second one), throat pains (72,7% and 70,6%), asthenia (45,5 % and 82,4%) myalgias (59,1% and 41,2%), hyperemia of the pharyngeal isthmus (90,9 % and 100 %), harsh breathing (77,3 % and 58,8%), chills (36,4 % and 29,4%), fascies congested (36,4% and 41,2%).

When comparing the length of clinical symtoms in the study group and the control group we come to the conclusion that the length of the symptoms reflecting the affected central nervous system in the study group was on average 5,0 days, while in the control the average was of 6,6 days. With respect to the symptoms affecting the respiratory system, duration was 3,8 days in the experimental grouo and 5,3 in the control group.

Bronchopneumonia occurred at the same frequency in both groups in 5 patients. The length of hospitalization with bronhopneumonia in the experimental group was on average 5,2 days and in the control group 7,0 days.

The changes in leukogram are listed in table 2.

According to the data from table 2, leukocytosis is not characteristic for viral infections and leukopenia was revealed only in 5 patients from the experimental group and in one patient from the control group. Normocytosis was revealed more frequently (77.3 % and 94.1 %), left deviation (95.4 % and 76.7%) and monocytosis (45.4 % and 47.1%).

Treatment

Treatment of patients from the study group was an antiviral, Tamiflu, combined with an immunomodulatory BioR. Treatment for the control group was with Tamiflu and placebo.

Tamiflu was administered in a dose of 75 mg orally twice a day, in the morning and in the evening after meals. The duration of treatment was 5 days in 15 patients, 6 days in 5 patients, 9 in 1 patients and 10 days for 3 patients. The average length of treatment was 5 days.

BioR was administered in a dose of 5 mg orally twice a day in the morning and in the evening in 16 patients and 1 ml. IM twice a day for 5 days in 6 patients. The patients from control group were given the Tamiflu only in a dose of 75 mg orally twice a day in the morning and in the evening. The duration of treatment was 5 days for 9 patients, 6 days for 4 patients, 7 days for 2 and 10 days for 1 patients the average being 6 days.

Taking into account that the toxic action of influenza virus inhibits both cellular and humoral immunity, leading to attenuation of local resistance and increased susceptibility to infection with bacterial foci in trachea, bronchi and lungs, an antibiotic treatment was administrated as shown in tab. 3.

According to the information in table 3, cephalosporins, macrolides, B-lactams and fluoroquinolones were used in the treatment of patients with the influenza virus. Only one patient

Table 2

The changes in leukogram in patients of A (H1N1) influenza, the study lot and control lot

The leukogram	The study lot			Control lot			χ^2	p
	Abs.	P1 ± Es1	Media	Abs.	P2 ± Es2	Media		
Leukopenia	5	22,7 ± 8,9	3,1	1	5,9 ± 5,7	3,9	48,24	****
Leukocytosis	0	0,0	0	0	0,0	0	-	-
Normocytosis	17	77,3 ± 8,9	5,9	16	94,1 ± 5,7	5,6	3,01	*
Left deviation	21	95,5 ± 4,4	22,0	13	76,5 ± 10,3	19,6	4,71	**
Lymphocytosis	5	22,7 ± 8,9	42,5	5	29,4 ± 11,1	56,8	1,52	*
Lymphopenia	5	22,7 ± 8,9	11,5	0	0,0	0	-	-
Monocytosis	10	45,5 ± 10,6	16,1	8	47,1 ± 12,1	17,3	0,05	*
VSH increased	7	31,8 ± 9,9	30,4	7	41,2 ± 11,9	24,2	2,13	*

$p > 0.05$ **$p < 0,05$ **** $p < 0.001$.

Table 3

Antibiotic treatment in the study and control groups for patients with A (H1N1) influenza

Antibiotics	The study lot			Control lot		
	No of patients	Dose	Duration of treatment	No of patients	Dose	Duration of treatment
Cephalosin	4	1,0x2 td	3,5 days	3	1,0x3 td	5,6 zile
Ceptriaxin	4	1,0x3 td i.m.	7,5 days	1	0,25x2 td	2,0
Cephexim	1	1,0x2 td	4,0 days	-	-	-
Cepin	2	1,0x2 td	4,5 days	-	-	-
Azitromycin	4	500,0x1 td	3,0 days	-	-	-
Ampicillin	3	1,0x3 td	6,0 days	1	150mgx3 td	4,0
Amoxicillin	5	1,0x2 td	4,5 days	10	1,0x3 td	4,0
Augumentin	2	1,2x2 td	4,5 days	-	-	-
Ciprinol	1	400mgx2 td	4,0 days	-	-	-
Oxacyllin	-	-	-	1	0,4x4 td i.m.	5.0

from the control group was not administered antibiotic treatment. The length of antibiotic treatment in the study group was 4.0 while in the control group it was 4.5 days.

Pathogenic and symptomatic treatment

Both groups received some maintenance therapy. In 9 patients this included glucose 5%, physiological serum 0.9%, haemodesia and arginine in 1 patient, antipyretics in 15 patients, vitamins (ascorutin) in 29 patients, desensitizers in 15 patients, expectorants in 6 patients, broncholytics in 7, antitussives in 8, respiratory analeptics in 6, vasoconstrictive decongestants in 8, diuretics and corticosteroids in one patient for a day.

Conclusions

Treatment with Tamiflu and BioR in patients with A (H1N1) influenza was beneficial and contributed to:

- Reduction by an average of one day in the length of symptoms that affected the central nervous system, and particularly those reflecting the action of the sympathetic nervous system,
- Reduction of symptoms affecting the respiratory system (3.8 days in the experimental group and 5.3 days in the control one).
- Decreased hospitalization length in patients with influenza A (H1N1) (5.09 days in the experimental group and 6.1 in the control group).
- Decreased hospitalization length of patients with bronchopneumonia in the experimental group (5.2 days vs 7 days)

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Stem Cells in the Future of Dental Care

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Abstract

Tooth loss compromises human oral health. Although several prosthetic methods (such as artificial denture and dental implants) are clinical therapies to tooth loss problems, they are thought to have safety and usage-time issues. Recently, tooth tissue engineering has attracted more and more attention. Stem cell based tissue engineering is thought to be a promising way to replace the missing tooth. Mesenchymal stem cells (MSC) are multipotent stem cells which can differentiate into a variety of cell types. The potential MSC for tooth regeneration mainly include stem cells from human exfoliated deciduous teeth, adult dental pulp stem cells, stem cells from the apical part of the papilla, stem cells from the dental follicle, periodontal ligament stem cells and bone marrow-derived mesenchymal stem cells. This review outlines the recent progress in mesenchymal stem cell research and its use in tooth regeneration and oral and craniofacial applications.

Key words: mesenchymal stem cell, tooth engineering, dental pulp stem cell.