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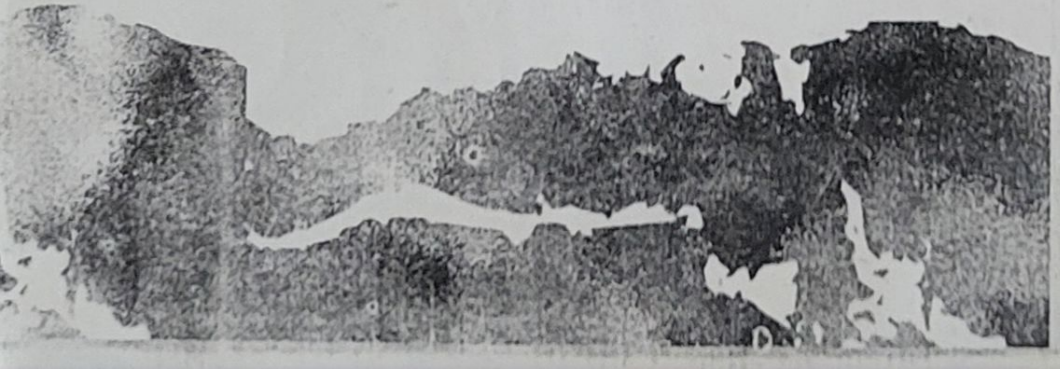

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CLINICAL EXPERIENCE IN THE TREATMENT OF FLU PATIENTS WITH OSELTAMIVIR DURING THE INTERPANDEMIC PERIOD

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SUMMARY

The influenza epidemics are very important health and economics issues. That explain why defining the methods for proper treatment and prophylaxis of influenza has become so important over the past few years. The study included people with present influenza symptoms throughout the last influenza season / December/ 2001-April/2002 / confirmed by IIF, ELISA-IgM, isolation of the virus and with clear clinical symptoms. The goal of the study was on the basis randomized, double-blind study to evaluate the therapeutic effects of oselatamivir concerning the duration of the illness and symptoms. The study shows that the therapy with oselatinivir resulted in reduction of symptoms in febrile as well as in non febrile patients, smaller administration of symptomatic therapy, less complications as a secondary bacterial infections, lower administration of antibiotics. The drug oselatamivir is very well tolerated and only 5,9% of the treated patients noted intolerance with vomiting. From the present study the authors conclude that treatment of influenza with oselatamivir causes significant shortening of illness period as well as of clinical expression and symptoms of influenza.

Key words: influenza epidemics, oseltamivir, influenza virus A and B

In regions having a temperate climate, influenza epidemics occur annually. They occur predominately during the winter months, and are usually associated with increased mortality among the higher risk population (namely, the elderly and persons with chronic diseases). Likewise, the general population's morbidity rate also increases, very dramatically in some years. The effect of influenza epidemics is here attested by significant work or school absenteeism, and decreased level of worker productivity. These effects are prolonged, in many cases, as symptoms of the illness can last for up to seven days. For illustration, in 1997 influenza and pneumonia were ranked sixth among the leading causes of mortality in USA. Over the past 25 years, an average of 20,000 Americans a year have died from these disease. It is estimated that the annual economic loss due to influenza stands at $3-5 billion. These factors explain why defining the methods for proper treatment and prophylaxis of influenza has become so important over the past few years. While vaccination remains the standard form of prophylaxis, an increasing number of studies have begun to investigate the prophylactic potential of certain chemotherapeutics. Despite everything the illness continues to appear, especially among the children and young adults, the groups with the highest risk for morbidity. Antiviral agents remain a complementary treatment, and in no way substitute for extensive and efficient vaccine programs. Antiviral agents administered early during the infection can reduce the duration of the illness and lessen the degree of symptom expression (intensiveness, severity), and with all that also to reduce the general impact of influenza.

The first antiviral agents used to treat influenza infections were amantadine and rimantadine, but their use was limited only to a few regions worldwide. With time, questions were raised regarding their true role in the treatment of influenza, their side effects, and most importantly, their potential in selection of resistant viral strains.

Previously, a consensus had been reached regarding the need for prompt treatment of influenza. The rationale was that even the most uncomplicated bout of influenza is a long-lasting illness which significantly limits daily activities. However, this consensus changed after several additional considerations were taken into account. The risk of side effects, especially during the amantadine therapy, the possibility for appearance of resistant types, and the need for reassurance that the illness treated is in fact caused by the Influenza A virus. The efficiency of these drugs is documented only against influenza virus type A. Therefore, their administration becomes insufficient in years when mixed influenza epidemics occur. Thus the need for an efficient antiviral agent with broader activity spectra and with better characteristics regarding the safety profile. First in the new class of antiviral agents which actively inhibit the influenza-neuraminidase, the enzyme which is essential for viral replication in vitro, was zanamavir. Its efficiency, proven in vitro on experiment model with animals and young adults, covers both influenza A and B infections. The clinical effectiveness of locally administered (through oral inhalation) zanamavir against natural influenza infection in humans has been documented in large placebo-controlled studies. But the very use of the inhaler for its application means that patients need to be taught how to use an inhaler. In patients with asthma or chronic obstructive pulmonary disease (COPD), Zanamavir can induce bronchospasm and reduced pulmonary function- such patients, therefore, should avoid using zanamavir. In addition, zanamavir has certain, albeit rare, side effects; most prominent are irritation of the nose and throat, coughing and headaches. Unlike zanamavir, the newer neuraminidase inhibitor, oseltamivir, is administered orally (75 mg tablets) and is a "prodrug". This means it must be converted, with the activity of hepatic esterase, into its active form, oseltamivir carboxilate. Oseltamivir carboxilate is not further metabolized and as such is completely eliminated through renal excretion. Its only registered side effects are nausea and vomiting, which can be lessened by taking the drug together with food. Compared with other antiviral agents, this drug has a very small potential for selection of resistant strains/variants of the virus. With all of these considerations in mind, we sought to define the clinical efficiency and safety of oseltamivir on the general population, with our own material. Furthermore, this study involved persons at high risk for developing complications associated with influenza infection. This randomized, double-blind study evaluated the therapeutic effects concerning the duration of the illness and symptoms relief in function of defining the indicators for the severity of the illness.

MATERIAL AND METHODS

This study included people aged 18 or older with present influenza symptoms, of a duration of 48 hours or less throughout the last influenza season (December/2001-April/2002). Primarily, these were patients treated during the last two months of the season. Influenza symptoms are defined by fever, chills and the presence of two or more of the following: myalgia, headache, cough or sore throat. The probability of proving influenza infection in the patients that were included was high, considering the fact that this study was undertaken during the period in which there was high percent of 85% of serologically proven (by the IIF method) influenza cases. In addition, this study also included patients over 65 years of age, as well as patients with chronic diseases (cardiovascular, respiratory, endocrinal, diseases of the metabolism, excluding those patients having an unstable disease); this category of patients is marked as a high risk group for developing complications or more severe or prolonged forms of the illness. In the study, oseltamivir was administered in an oral dosage of 2x75 mg/daily, for a period of 5 days. The study was completed with successive gathering of the planned 50 (20 with, and 30 without oseltamivir) patients, based on the principle of coincidence and according to their daily arrival at the Clinic for Infectious Diseases in Skopje. We randomly analyzed the patients in a 1:1/1:2 relation to those patients who did not

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ABBREVIATIONS USED IN THIS PAPER:
COPD - chronic obstructive pulmonary disease

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take Oseltamivir. All of them were outpatients and they were given a questionnaire in which, on a twice daily basis, morning and evening, over the next ten days, they marked their temperature and the severity of symptoms (clinical manifestation). The clinical manifestation of symptoms we marked on a 6 degree scale, on which 0 corresponds with a total absence of symptoms, and 5 with the highest intensity of presence of symptoms. On the same questionnaire the patients noted any sleeping disorders, their capability for completing daily normal activities, and their overall health condition. The further analysis of the study included only patients with confirmed influenza infection (IIF, ELISA-IgM, isolation of the virus from samples taken from the upper respiratory tract, on the very first day the patients arrived at the Clinic). Of 41 patients (82%, 41/50), it was found later that 17 (85%, 17/20) had taken oseltamivir, and 24 (80%, 24/30) had not. Our primary clinical goal was to determine the duration of the illness until any lessening could be noted in clinically significant symptoms, defined with the absence of chills, fever of lower than 37.5°C, and a mark "0" (absence) or "1" (mild) for any other major symptoms (for example headache, mialgia, sore throat or cough) remaining during the next 24 hours. The time needed for relief of symptoms was determined on the basis on half day from starting of the treatment (day one), with the morning parameters from day one of the treatment that correspond with "0" day. The time period from the morning measurements until the evening ones represents half day. In addition, we sought to determine the middle score of symptoms, sleep disruption, duration of symptoms before normalization of daily activities, as well as the usage of acetaminophen and cough-relieving drugs. The degree of clinical expression of the five symptoms (chills, headache, mialgia, cough, and sore throat) was summarized for each patient by calculating the middle score of symptoms, used as a measure for the overall severity of clinical symptoms. The middle score of the symptoms is determined with varians analysis.

RESULTS AND DISCUSSION

In the group of patients treated with oseltamivir, the final point, alleviation of major symptoms, was achieved around the fourth day. In the group of patients who were not treated with oseltamivir, alleviation occurred only on the sixth day. This difference was more obvious in patients who arrived at the Clinic and began their treatment during the first 24 hours of symptoms appearance, (for 2-3 days). The difference was also most notable among those patients who were febrile or belonged to the high risk group at the time when put under therapy. In patients who had their treatment started within 24 hours of symptomatic appearance, therapy with oseltamivir shortened the illness period to 0.5-1 day. Therapy with oseltamivir resulted in a reduction of symptomatic duration in febrile, as well as non febrile patients (at the time of inclusion in the study), though the effects were more evident in the former group. The middle duration of symptoms in the high risk group of patients was longer compared with the entire treated group (6.56 contrary to 6.0 days), which documents the trend for faster relief of symptoms in patients with high risk. Therapy with oseltamivir also resulted with smaller administration of symptomatic therapy, e.g. the same was associated with reduction of the usage of acetaminophen and antitusics. During the first three days, administration of acetaminophen was decreased for 38%, and for cough-relieving drugs 29%. In this study we also analyzed the incidence of secondary diseases (otitis media, pneumonia, etc), as well as the incidence of hospitalizations. Complications were rare in the group treated with oseltatmivir, meaning, a reduction of patients with otitis media as a complication has been achieved from 12.5% (3/24) to 5.9% (1/17) as well as with pneumonia from 20.8% (5/24) to 11.8% (92/17), and generally speaking with all this a dramatic reduction of hospitalizations has been managed, from 29.2% (7/24) to 11.8% (2/17). Administration of antibiotics was significantly lower in the group of patients treated with oseltamivir. Patients treated with oseltamivir tolerated the medicine very well, and only in one patient is noted intolerance with vomiting (5.9%). It took many years for consensus on use of amantadine and rimantadine to be reached in North America. This was partly due to the fact that the studies, especially those involving treatment, were small and differed in design, making assessment of the precise therapeutic benefit difficult. The development of neuraminidase inhibitors provides an alternative antiviral therapy for the management of influenza infection. This agents have convincing efficacy against influenza caused by different types of influenza viruses, as is shown in many studies. In contrast to older antiviral drugs, studies with the neuraminidase inhibitors have used the same well-defined end point and similar design. The benefits of them appear to be greatest where the illness is most severe, as would be expected from the natural history of influnza infection, and when treatment is given early. There are also benefits on patient quality of life and functioning. The results of all studies with oseltamivir indicate that it is well tolerated, with a reported side-effect profile comparable to placebo. In this study this was evident in both otherwise healthy persons and in those at high risk of complications. The fact that oseltamivir can be used to treat all strains of influenza A and B viruses and that resistance has not been detected during acute therapy, also suggests that it has definite advantages over the older antiviral agents. From the presented results we can conclude that treatment of influenza with oseltamivir causes significant shortening of illness period as well as of clinical expression and symptoms of ifluenza. Thus, there seems to be a clear role for oseltamivir in the treatment of type A and B influenza infections.

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