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File: ■ Echinacea (*Echinacea purpurea*, Asteraceae)
■ Influenza
■ Echinaforce® Hotdrink
■ Tamiflu®

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RE: Echinaforce® Hotdrink Is as Effective as Oseltamivir in Early Treatment of Influenza Infections

Rauš K, Pleschka S, Klein P, Schoop R, Fisher P. Echinaforce Hotdrink versus oseltamivir in influenza: A randomized, double-blind, double dummy, multicenter, non-inferiority clinical trial. *Curr Ther Res*. 2015; [epub ahead of print]. doi: 10.1016/j.curtheres.2015.04.001.

Influenza, commonly known as the flu, is a seasonal infectious disease with symptoms such as cough, nasal congestion, headache, myalgia, and fever that affects an estimated 25-50 million people each year in the United States alone. Complications occur frequently and can include life-threatening inflammatory events like encephalitis, myelitis, myocarditis, septic shock, bronchitis, or pneumonia. The recommended medical treatment in early stages of the disease is the administration of neuraminidase inhibitors, e.g. oseltamivir or zanamivir, which has shown a reduction of duration and of complications in clinical trials.

A total of 473 patients were enrolled in this randomized, double-blind, double-dummy, clinical trial carried out for 10 days at 29 general practices in the area of Prague (Czech Republic). Patients had been clinically diagnosed with influenza based on at least 1 respiratory symptom, 1 systemic symptom, and fever ≥ 37.8°C (100.04°F), and had symptoms starting less than 48 hrs before onset of treatment. Inclusion criteria were a negative pregnancy test, body weight > 40 kg, good general health, and signed informed consent. Exclusion criteria included, among others, antibacterial treatment in the past month; influenza vaccination; cardiovascular, liver, kidney, neurological, and endocrinological diseases; and allergies to paracetamol, dextromethorphan, or plants in the family Asteraceae. The mean age of patients was 37 years. Also included in the study were 9 children and adolescents between 12 and 17 years.

A total of 237 patients received Echinaforce® Hotdrink syrup (A. Vogel Bioforce AG; Roggwil, Switzerland; containing 228 mg/ml *Echinacea purpurea* [Asteraceae] herb extract, 12 mg/ml *E. purpurea* root extract, 276.5 mg/ml *Sambucus nigra* [Adoxaceae] berry juice, and excipients) with oseltamivir placebo capsules. Patients in the other

group (n=236) received Echinaforce Hotdrink placebo (containing the same excipients as the Echinaforce Hotdrink verum group plus colorants and flavors) and oseltamivir (Tamiflu®; Hoffmann-La Roche; Basel, Switzerland). Patients in the Echinaforce Hotdrink group received 5 mL syrup 5 times daily on the first 3 days, then 5 mL syrup 3 times daily for the remaining 7 days of the study. At the same time, these patients received oseltamivir placebo capsules twice a day for each of the 10 days. In the oseltamivir verum group, the same regimen was followed with Echinaforce Hotdrink placebo and 1 capsule of oseltamivir twice daily (oseltamivir verum for the first 5 days, followed by oseltamivir placebo capsules for the next 5 days).

Treatment efficacy was evaluated using a symptom diary, in which patients recorded the severity of cough, nasal congestion, sore throat, fatigue, headache, myalgia, feverishness, malaise, sweats, and/or chills according to a scale from 0 to 3 (0=not present, 1=mild, 2=moderate, 3=severe). In addition, the axillary body temperature was measured, and the occurrence of complications was recorded. The cumulative proportion of patients that recovered from influenza after the first, fifth, and tenth day of treatment was chosen as the primary endpoint of the study. Recovery was defined as the first day when symptoms were mild in the evening or altogether absent. Other measured outcomes included body temperature, days without sleep disturbance, duration till return to normal activity, use of rescue medication (paracetamol and dextromethorphan), and additional contacts made to health care professionals. Patients and physicians also evaluated the tolerability and efficacy subjectively on a scale from 1 to 4 (1=very good, 2=good, 3=moderate, 4=poor).

Overall, both treatments were considered efficacious. Recovery was observed after 1, 5, or 10 days in 1.5% and 4.1%, 50.2% and 48.8%, and 90.1% and 84.4% of patients treated with Echinaforce Hotdrink and oseltamivir, respectively. There was no statistical difference in the clinical outcome between the 2 treatments, although the treatment failures after 10 days showed a non-statistically significant trend in favor of the patients receiving Echinaforce Hotdrink. There was also no significant difference in the efficacy judgement by physicians and patients.

The occurrence of complications and adverse side effects was higher in the oseltamivir group compared to the Echinaforce Hotdrink group. In the oseltamivir group, 14 complications were recorded, mainly of respiratory nature (pneumonia [2], sinusitis [4], bronchitis [2], and rhinopharyngitis [1]). The remaining 5 cases were gastrointestinal complications. Complications observed in the Echinaforce group (n=5) were all infections of the respiratory tract. A total of 44 adverse side effects occurred in patients treated with oseltamivir, while 31 adverse side effects were recorded in the Echinaforce Hotdrink group. The higher incidence of adverse side effects was mostly due to the occurrence of nausea and vomiting in the oseltamivir group. The exact nature of the adverse side effects other than gastrointestinal problems was not detailed in the publication, but the authors indicate that no serious adverse events were observed in either of the treatment groups.

No limitations of the clinical study were reported.

In conclusion, the findings of this study suggest that the treatment outcomes of patients suffering from early influenza symptoms who are treated with oseltamivir or Echinaforce Hotdrink are equivalent in patients without concomitant diseases and who are not part of an "at risk" population. The authors suggest that the lower incidence of complications

and adverse side effects with Echinaforce Hotdrink make this an attractive alternative option to the standard treatment with neuraminidase inhibitors, and that the product's availability as a nonprescription medicine makes it a suitable choice for the very early treatment of first symptoms, a central factor in the successful management of influenza infections.

—*Stefan Gafner, PhD*

Note: This study was sponsored by A. Vogel Bioforce AG, manufacturer of Echinaforce Hotdrink. One of the authors (Schoop) is an employee of the company.

Referenced article can be accessed at http://www.currenttherapeuticres.com/article/S0011-393X(15)00005-3/fulltext.