



## Letter to the Editor

## A clinical trial lacking a control group



We are writing to express our concern about an article published in the *International Journal of Infectious Diseases* in 2016 by Rafalsky et al., “Efficacy and safety of Ergoferon versus oseltamivir in adult outpatients with seasonal influenza virus infection: a multicenter, open-label randomized trial” (Rafalsky et al., 2016). In this paper, the authors report various clinical findings in 156 adult patients with antigen-confirmed influenza A or B, who were randomized on entry into the study to receive either Ergoferon or oseltamivir, given orally for 5 days. They observed no statistically significant difference between the two groups in the duration of fever or the time to resolution of other signs and symptoms. They concluded that “Ergoferon and oseltamivir were equally effective and safe in adult outpatients with seasonal influenza A or B virus infection”.

This study is deeply flawed, as it does not include a control group of patients who were randomized to be given a placebo medication or to remain untreated. In the absence of a control group, it is not possible to reach any conclusion as to the efficacy of any medical intervention. Although oseltamivir is approved for the treatment of influenza, there is no way to conclude that patients who received it in this study actually benefited, without comparison to an untreated control group. There is thus no basis for concluding that Ergoferon and oseltamivir were “equally effective”.

We are also surprised that this study of a homeopathic product was published in your journal. In the Methods section, the authors state that the components of Ergoferon (affinity-purified antibodies to interferon gamma, CD4, and histamine), had been diluted by factors of, respectively,  $100^{12}$ ,  $100^{30}$ , and  $100^{50}$  before being incorporated into a tablet. They cite US patent 8,535,664, on which O.I. Epstein, the senior author of this paper, is listed as an inventor, which describes the production of such “homeopathically activated forms of antibodies”. During the past 2 years, four research reports claiming the antiviral activity in vitro or in laboratory animals of Ergoferon or a similar product, Anaferon, have been retracted by three different journals (Tarasov et al., 2019a,b; Gavrilova et al., 2018; Skarnovich et al., 2017; Anon, 2019; Petrova et al., 2019a,b). The wider problem of claims of benefit against a range of diseases for such preparations, diluted beyond the point that any active molecule could possibly remain, was reviewed earlier this year in an article in *BMJ Evidence-Based Medicine* (Panchin et al., 2019).

Both because of the fundamentally flawed design of the study and the nature of Ergoferon as a homeopathic preparation, this article should not have been accepted for publication. We hope that you will take action to see that it is retracted.

## Conflict of interest

We declare no personal or financial conflicts with the subject of this letter that might cause us to reach biased conclusions. We have no relationship with the authors of the 2016 *International Journal of Infectious Diseases* paper that we discuss in the letter.

## Funding source

This is a letter to the editor, no funding was involved in its production.

## Ethical approval

This is a letter to the editor, no experiments in animals or humans were performed by either author.

## References

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Received 16 August 2019