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Letter to the Editor

Efficacy and safety of Ergoferon versus oseltamivir: Reply to the Letter to the Editor

In a paper published in 2016, we presented the results of a randomized controlled clinical trial conducted during 2011–2014. The study was based on a non-inferiority (NI) design, since the objective was to compare the efficacy and safety of Ergoferon with oseltamivir for the treatment of seasonal influenza in adult outpatients. The study objective as well as the design are very clearly described in the paper, in accordance with current guidelines for NI clinical trials to compare the efficacy of a new drug with an active control (Guidance for Industry, 2016; ICH Harmonised Tripartite Guideline, 2019a,b).

The goal of the study was to show that the difference between the new treatment (Ergoferon) and the active control treatment (oseltamivir) is small enough to allow the known effectiveness of the active control, based on its performance in past studies and the assumed effectiveness of the active control in the current study, to support the conclusion that the new test drug (Ergoferon) is also effective (Guidance for Industry, 2016; ICH Harmonised Tripartite Guideline, 2019a,b). In other words, the goal was to demonstrate that the test drug (Ergoferon) has an effect by showing that its effect is sufficiently close to the effect of an active control (oseltamivir). There was no placebo arm in that study, which is in accordance with NI protocols. In our NI study, the oseltamivir proved effective against seasonal influenza when given within 48 h after the onset of symptoms (Dobson et al., 2015; Jefferson et al., 2009; Treanor et al., 2000; Nicholson et al., 2000). Thus, the design of the study was a NI study in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (ICH Harmonised Tripartite Guideline, 2019a,b).

According to ICH E9 ("Statistical Principles for Clinical Trials" guideline) (ICH Harmonised Tripartite Guideline, 2019b), "only the lower margin is needed for the active control NI trial" and "statistical analysis is generally based on the use of confidence intervals". The NI margin used in the study was 20%. The pre-specified margin was selected to be lower in magnitude than the effect of the control drug over the placebo (ICH Harmonised Tripartite Guideline, 2019a). In the study by Treanor et al. (2000), the effect of oseltamivir versus placebo is stated as follows: "The percentage of subjects with fever at 24 h was 39% in the placebo group, compared with 21% in the 150-mg group (18% difference; 95% CI 6–29%)". Taking into consideration that confidence intervals for proportion differences between arms were presented in the paper (in Table 2), the conclusion about the NI of the studied drug as compared to the control is correct.

So, the statements of the authors of the Letter about "lacking a control group" and "study is deeply flawed" are not correct.

The superiority of Ergoferon over placebo in the treatment of patients with influenza and other acute respiratory viral infections has been shown previously (Anon, 2019a; Verevschikov et al., 2011; Kostinov, 2011; Geppe et al., 2014; Zaplatnikov et al., 2015) and we wrote about this fact in the Introduction section. In the Discussion section, we highlighted the limitations that could be a source of bias, including the open-label trial design and the absence of a placebo group and an untreated group.

The active pharmaceutical ingredients of Ergoferon are released-active forms of the antibodies to interferon gamma (IFN-γ), antibodies to histamine, and antibodies to the CD4 receptor produced on the basis of the patented biotechnological platform. In the Treatment section, we emphasized that Ergoferon is crucially different from homeopathic therapy, so we maintain that Ergoferon is not a homeopathic drug. There is nothing stated in the Guide for Authors for the *International Journal of Infectious Diseases* regarding any possible inappropriate technology that cannot be used for the manufacture or production of the investigational drugs.

Regarding the concern itself, it is highly important to note that Ergoferon is registered in the country of origin (i.e., the Russian Federation) as the conventional drug (registration number ЛСР-007362/10 dated July 29, 2010). All of the manufacturing and quality control steps for Ergoferon have been validated and approved by the Ministry of Health of the Russian Federation (regulatory agency). The primary substances of the drug are rabbit polyclonal antibodies produced in the UK (Pentlands Science Park, Bush Loan, Penicuik, Midlothian, EH26 0PZ, UK) in accordance with GMP requirements. The active pharmaceutical ingredients (released-active dilutions of antibodies) are produced by GMP manufacturing facilities in Russia. Clinical studies on Ergoferon (Anon, 2019b,c; Sel'kova et al., 2019; Geppe et al., 2019; Kondyurina et al., 2016a,b), as well as other released-active drugs (Anon, 2019d,e), have been conducted in accordance with GCP and they are controlled by the Ministry of Health of the Russian Federation. Detailed information about the drug Ergoferon is available on the official website of the Ministry of Health (Anon, 2019f).

The fact that the drugs based on released-active antibodies are not homeopathic was supported by experts from the US Food and Drug Administration (FDA) during the Critical Path Innovation Meeting (CPIM) on July 8, 2016 (Anon, 2019g). The participants at the meeting were FDA experts from the following offices of the Center for Drug Evaluation and Research: Office of the Center Director, Professional Affairs and Stakeholder Engagement Staff, Office of Translational Sciences (OTS) Immediate Office, OTS Office of Clinical Pharmacology, Office of Regulatory Policy, Office of Pediatric Therapeutics, Office of Pharmaceutical Quality, Office of Policy for Pharmaceutical Quality. As a result of the CPIM, the FDA experts concluded that Materia Medica drugs should be proceeded for registration using a standard regulatory approach with some modifications in the relevant divisions (Division of Antiviral

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Products; Division of Neurology Products; Division of Metabolism and Endocrinology Products).

Moreover, this unambiguous conclusion was also supported earlier by the Biological Medicines Section experts of the Medicines and Healthcare Products Regulatory Agency (MHRA) (Anon, 2019h) at the Scientific Advice Meeting in 2015. The experts were provided with a dossier on Anaferon (another drug produced using the same technology as was used for Ergoferon, but only antibodies to IFN-γ were used as the starting substance). After careful considering of the dossier, the MHRA experts came to the following conclusion (cited from document Ref. 1029/Anaferon dated September 28, 2015): "Anaferon is considered to be a biological drug product and eligible for a full Marketing Authorization. As it is an antiviral drug product, the Centralized procedure is the only regulatory route available for Anaferon".

Thus, experts from the competent regulatory agencies have confirmed that the drug is non-homeopathic. We quote the conclusions of the FDA (Memorandum of the CPIM in July 8, 2016) and MHRA experts because these documents are not publicly available. It is a well-known fact that a drug-maker receives these documents during the research and development stage of a new drug.

The drug is a biotechnological product, unlike homeopathic remedies. Unlike homeopathy, the efficacy and mechanism of action of our drugs have been proved in preclinical studies conducted in contract research organizations and public research institutions in Russia, France, the UK, Belgium, Germany, the Netherlands, Norway, the USA, etc., under the supervision of globally recognized scientific opinion leaders (Kheyfets et al., 2011; Gorbunov et al., 2015a,b; Ganina et al., 2016; Emelianova et al., 2016; Khakimova et al., 2016; Emel'yanova et al., 2017; Kanareikina et al., 2019).

The effect of released-active antibodies has been shown to be strictly specific, while the trigger mechanism of their effect lies in the modification of conformational characteristics of the target molecule. For instance, investigations of released-active antibodies to IFN-γ using nuclear magnetic resonance spectroscopy demonstrated their modifying effect on the conformational characteristics of the IFN-γ molecule, causing a shift in the equilibrium between the monomer and dimer forms of this cytokine (transformation from inactive into the active form of the protein). Conformational changes were observed in amino acid residues of the C-terminal fragment of the IFN-γ molecule and amino acid residues involved in the formation of this cytokine dimer (Epstein, 2013, 2018). Consequently, the modified nature of the ligand–receptor interaction of the IFN-γ with its receptor was observed as being the trigger mechanism of the effect of released-active antibodies to IFN-γ.

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Ethical approval

Not required.

Conflict of interest

Elena Andrianova and Mikhail Putilovskiy are employees of the OOO "NPF "MATERIA MEDICA HOLDING".

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