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Letter to the Editor

Baloxavir for influenza: Enrichment obscured lack of effect in North-American adults

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The FDA recently approved the use of baloxavir marboxil (baloxavir) in patients aged 12–64 years with uncomplicated influenza [1]. The effectiveness of baloxavir had been tested in one phase III trial named CAPSTONE-1 [2]. It consisted of two subtrials: one subtrial compared baloxavir (40 mg once) with placebo and oseltamivir in adult patients, and the other baloxavir with placebo in adolescent patients (total n = 1436). The trial was performed in Japan, the United States, and Canada. In the reported primary efficacy analysis, baloxavir reduced the time to alleviation of flu symptoms with 26.5 hours compared to placebo. However, an enriched study population has obscured baloxavir's lack of effect in North-American adult patients.

The goal of enrichment is to select a study population that is likely to show a favourable response to treatment in terms of high efficacy and low risk of side effects [3]. Selection of such responders can be accomplished with restrictive eligibility criteria, information about response to similar treatments in the past or in the run-in period of the trial, and an analysis based on the outcomes of patients that did not drop-out during the trial. As a result of (de)selection, patients that contributed to the trial results do not represent average patients in daily practice. Efficacy may be overestimated and risk of side effects underestimated.

The CAPSTONE-1 population has been enriched in numerous ways. Firstly, the trial enrolled more Japanese (60%) than North-American patients (40%). A review of the PMDA, the Japanese counterpart of the FDA, reported that the reduction in time to symptom alleviation was 27.2 h among Japanese adults, and 2.1 h among American adults [4]. Although this seems a post-hoc analysis, a population pharmacokinetic analysis of phase I and II studies had already shown that baloxavir exposure was approximately 35% lower in non-Asians than Asians [4, 5]. The ratio of Japanese versus North-American patients was even more skewed in the primary efficacy analysis that was performed among influenza-confirmed cases (78% respectively 22%). Of the randomised Japanese patients, 97% had confirmed influenza compared to 42% of the randomised North-American patients. Inclusion of Japanese patients was based on clinical symptoms and a positive rapid influenza diagnostic test [1]. North-American patients, on the other hand, were primarily screened for clinical symptoms.

Secondly, CAPSTONE-1 participants weighed on average much less (mean BMI 25.0 kg/m^2) than the general adult American (28.8) and Canadian population (27.2) [6]. Weight is an important factor in the pharmacokinetics of baloxavir [1]. The FDA review showed that baloxavir reduced the time to alleviation of flu symptoms in patients weighing less than 80 kg with 28 h and in patients weighing more than 80 kg with 18 h, even though the latter received a dose of 80 mg instead of 40 mg [1]. Only 23% of the baloxavir-treated participants weighed 80 kg or more, while in the American population more than half of the adults weighs more than 80 kg [1, 2].

Thirdly, the treatment effects of baloxavir in the subtrial among adults (n = 569) were pooled with those of the subtrial in adolescents (n = 118) to obtain the reported effect. The latter subtrial showed a larger effect of baloxavir. In influenza-confirmed cases, time to symptom alleviation was 40.6 h in Japanese adolescents and 58.6 h in the American adolescents for baloxavir compared to placebo [4]. The rather large effect in the American adolescents might be explained by the enrolment of other types of patients, because the time to symptom alleviation in the placebo group was almost twice as long in the American adolescents (166.1 h) compared to the Japanese adolescents (86.1). The latter was much closer to the placebo response in the American adults (82.1) and Japanese adults (74.0) [4].

Finally, the primary result presented in the article has been calculated in the influenza-positive patients (74% of the randomised patients). These patients do no represent the patients with and without confirmed influenza that are prescribed anti-viral agents in clinical practice, i.e. the intention-to-treat (ITT) population. The effect was 23.2 h in the ITT population of all randomised patients [2].

In conclusion, enrolment of an enriched population of primarily Japanese adults and patients weighing less than 80 kg, and pooling the results from the adult and adolescent subtrials have masked the lack of effect of baloxavir in North-American adults. By presenting the results in a non-ITT population the validity of the results has been limited even further.

Declarations of interest

None.

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