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BRIEF REPORT

Pharmacokinetics and Pharmacodynamics of Conventional-Dose vs Triple-Dose Oseltamivir in Severely Immunocompromised Children With Influenza

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This randomized phase 1b study evaluated the pharmacokinetics/pharmacodynamics of conventional-dose (30–75 mg twice daily [BID]) vs triple-dose (90–225 mg BID; weight-adjusted) oseltamivir for treatment of influenza in severely immunocompromised children <13 years. Oseltamivir carboxylate (OC) C_{max} and $AUC_{0\text{-}12h}$ were ~2-fold higher with triple-dose vs conventional-dose oseltamivir. Increased dose/exposure of oseltamivir/OC did not improve virological outcomes or reduce viral resistance. Median time to cessation of viral shedding was similar with triple-dose and conventional-dose oseltamivir (150.7 vs 157.1 hours, respectively); median time to alleviation of baseline fever was longer with conventional-dose oseltamivir (28.4 vs 11.3 hours). No new safety signals were identified.

Keywords. children; clinical trial; immunocompromised; influenza; oseltamivir.

Influenza infection can be associated with substantial morbidity and mortality in children, the elderly, and immunocompromised (IC) populations [1, 2]. Oseltamivir is a potent and selective inhibitor of influenza A and B neuraminidase enzymes, which is approved in Europe and the United States for the treatment of influenza in adults and children. In a meta-analysis of 2561 pediatric patients aged <18 years with influenza, oseltamivir reduced the duration of illness by around 18 hours compared with placebo [3].

Concerns exist about the emergence of resistance with conventional doses of oseltamivir in IC populations [4], as prolonged viral replication and reduced immune-mediated viral clearance are associated with a higher incidence of drug-resistant viruses during treatment [5, 6]. Although a dose of 75 mg twice daily (BID) or equivalent was shown to be adequate for otherwise healthy patients, IC patients exhibit longer viral shedding [7], and therefore a higher dose and/or longer dosing period may be of utility. In a randomized, double-blind phase 3b study evaluating conventional- and double-dose oseltamivir in mostly IC adult and some pediatric patients aged <18 years with influenza (NCT00545532), oseltamivir was well tolerated, with a trend toward better tolerability with the conventional dose over an extended 10-day dosing period [8].

Very few pharmacokinetic (PK) and pharmacodynamic (PD) data are available on the use of oseltamivir in IC patients. This randomized phase 1b study (NV25719 [NCT01715909]) evaluated the PK and PD of conventional-dose vs triple-dose oseltamivir for the treatment of influenza in severely IC pediatric patients.

METHODS

Study Design

This was an open-label, multicenter, parallel-group study in IC patients aged <13 years with centrally confirmed influenza (by reverse transcriptase polymerase chain reaction [RT-PCR]). An open-label design was considered appropriate, as the key end points were the objective laboratory measurements for PK in blood and PD from nasal swabs. Patients were receiving induction, consolidation, or re-intensification chemotherapy for hematologic malignancy or undergoing a conditioning regimen before or <6 months after hematopoietic stem cell transplantation. Additional inclusion criteria included symptoms or signs suggestive of influenza-like illness and ≤96 hours between onset of such symptoms and administration of the first dose of study drug. Key exclusion criteria were significant renal impairment (creatinine clearance [CrCl] <60 mL/min/1.73 m^2 in children >1 year) or antiviral treatment with activity against influenza or probenecid medication within 2 weeks prerandomization. Patients may have received seasonal flu vaccine.

Treatment

Patients were randomized 1:1 to receive oral conventional-dose (based on the approved dosing regimen) or triple-dose

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oseltamivir at an age- and weight-adjusted dose ranging from 30 to 225 mg BID for ≥5 to ≤20 days, dependent on the duration of viral shedding (Supplementary Table 1). Dosing continued until the absence of viral shedding, demonstrated by a negative RT-PCR result. The first dose of study treatment and doses around the sparse PK sampling were given in the clinic; other doses could be administered at home.

The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board or independent ethics committee at each participating center. All patients or their legal guardians provided written informed consent.

Assessments

Blood samples for the characterization of oseltamivir PK, and its active metabolite oseltamivir carboxylase (OC), were collected on day 3 or day 4 within 30 minutes predose and at 1.5 ± 0.5, 4 ± 1, and 8 ± 1.5 hours postdose. Plasma concentrations of oseltamivir and OC were measured using a validated liquid chromatography–tandem mass spectrometry method (calibration range: 1–500 ng/mL for oseltamivir, 10–5000 ng/mL for OC). Nasal swabs for PD assessment were taken at baseline, on day 4, and at least every other day from day 5 onwards. Time to cessation of viral shedding and evaluation of viral load were determined from nasal swabs using RT-PCR and viral culture. Viral resistance (genotypic/phenotypic) was investigated using aliquots of the samples taken for PD assessments. Safety was assessed by the incidence of adverse events (AEs), coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 21.1). Efficacy was measured by the time to alleviation (TTA) of baseline fever and all influenza symptoms using the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) [9].

Statistical Analysis

The study aimed to enroll ≥20 influenza-infected patients (≥10 per dose cohort). No formal sample size calculations were performed. The intent-to-treat (ITT) population comprised all patients who received at least 1 dose of oseltamivir. The ITT influenza-infected population (ITTi) were patients in the ITT population with central laboratory RT-PCR-positive influenza infection from any swab sample collected at baseline or during the study. Patients in the ITT population who had at least 1 postdose drug concentration measurement at a scheduled time point formed the PK-evaluable population (PKEP). The safety population was the same as the ITT population, but patients were classified according to actual treatment received.

A population PK model was used to determine key exposure parameters; analyses were conducted via nonlinear mixed effects modeling using NONMEM software, version 7.4.3 (Icon Development Solutions, Ellicott City, MD, USA). Exposure–response relationships were evaluated between independent variables of exposure and dependent variables including continuous, binary, and time-to-event exposure–response analyses. TTA of fever and all influenza symptoms were summarized across dose cohorts by the median of the Kaplan-Meier curve and associated 95% confidence interval (CI).

RESULTS

Patients

Sixty-six patients were screened between January 2014 and July 2018, of whom 30 from sites across Colombia, Germany, Greece, Israel, Italy, Mexico, Poland, and Spain were randomized to treatment (15 per dose cohort) (Figure 1). The ITT and safety populations included all randomized patients. The ITTi population included 20 patients (n = 11 conventional-dose cohort, n = 9 triple-dose cohort) with central laboratory–confirmed influenza infection. Twenty-seven patients completed the study; 1 patient in the conventional-dose cohort discontinued due to noncompliance, and 2 in the triple-dose cohort chose to withdraw. Ten patients were excluded from the ITTi population: 8 had no evidence of baseline RT-PCR-confirmed influenza infection at the central laboratory, and 2 had malignancies that did not meet eligibility criteria.

Twenty-one (70%) children were male, and 9 (30%) were female. The median age (range) was 5 (1–12) years; there were no infants <12 months. All patients had hematologic malignancies, mostly acute lymphoid leukemia (n = 20, 66.7%) or acute myeloid leukemia (n = 4, 13.3%). Compared with the conventional-dose cohort, patients in the triple-dose cohort were younger, and a higher proportion had influenza A infection at baseline (Table 1). Median time from onset of symptoms to start of treatment was similar in both cohorts (~44 hours). There were no differences between the cohorts with respect to medical history or prior treatment.

PK Analysis

The PKEP included 26 patients (n = 14 conventional-dose cohort, n = 12 triple-dose cohort). Two patients were excluded from the PKEP due to lack of postdose drug concentration measurements, and a further 2 due to the presence of malignancies not eligible for study entry. After administration of multiple oral doses of oseltamivir at steady state (day 3 or 4), mean oseltamivir concentrations were 1.5 to 3.5 times higher in the triple-dose vs the conventional-dose cohort, and mean OC concentrations were 1.7 to 2.0 times higher (Figure 2A). Model-predicted steady-state mean exposure metrics for oseltamivir (C_{max} and $AUC_{0\text{-}12h}$) were 2.1 to 2.5 times higher in the triple-dose cohort than in the conventional-dose cohort, and steady-state mean exposure metrics (C_{max}, C_{min}, and $AUC_{0\text{-}12h}$) for OC were 1.9 to 2.0 times higher (Supplementary Table 2).

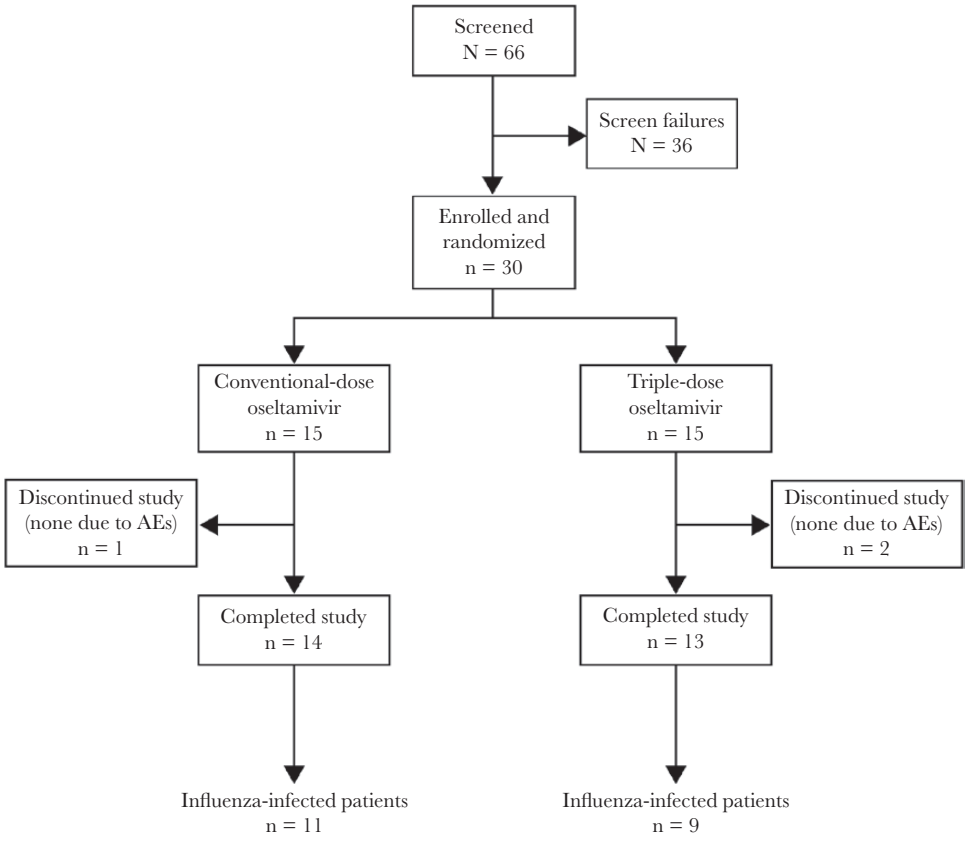

Figure 1. Patient disposition. Abbreviation: AE, adverse event.

PD and Exposure–PD Analysis

None of the patients had baseline oseltamivir viral resistance. Three patients developed treatment-emergent viral resistance: 1 (9.1%) in the conventional-dose cohort and 2 (22.2%) in the triple-dose cohort. All of these patients had influenza A infection (2 with the H1N1 subtype and 1 with the H3N2 subtype) and prolonged viral shedding. When excluding patients with postbaseline resistance, median time to cessation of viral shedding (by RT-PCR) was similar in the 2 dose cohorts (150.7 hours [95% CI, 60.4–302.2] triple-dose vs 157.1 hours

Table 1. Baseline Demographic and Disease Characteristics of the ITT and Safety Population

Characteristic	Conventional-Dose Oseltamivir (n = 15)	Triple-Dose Oseltamivir (n = 15)
Median age (range), y	6 (1–12)	3 (2–8)
Mean weight (SD), kg	26.7 (11.9)	18.9 (7.8)
Male, No. (%)	10 (66.7)	11 (73.3)
Influenza strain and type, No. (%)	(n = 11)[a]	(n = 9)
A–H1N1 2009	2 (18.2)	4 (44.4)
A–H3N2	2 (18.2)	4 (44.4)
B	7 (63.6)	1 (11.1)
Immunocompromised condition, No. (%)		
Hematopoietic stem cell transplant	2 (13.3)	0
Acute lymphoid leukemia	8 (53.3)	12 (80.0)
Acute myeloid leukemia	4 (26.7)	0
Non-Hodgkin lymphoma	1 (6.7)	1 (6.7)
Other	0	2 (13.3)[b]
Median time from onset of symptoms to start of treatment (range), h	44.5 (20–95)	44.0 (20–80)

Abbreviation: ITT, intent to treat.

[a]Only 11 patients in the conventional-dose cohort and 9 patients in the triple-dose cohort had centrally confirmed influenza infection.

[b]These 2 patients did not have hematologic malignancies and therefore did not meet the study inclusion criteria.

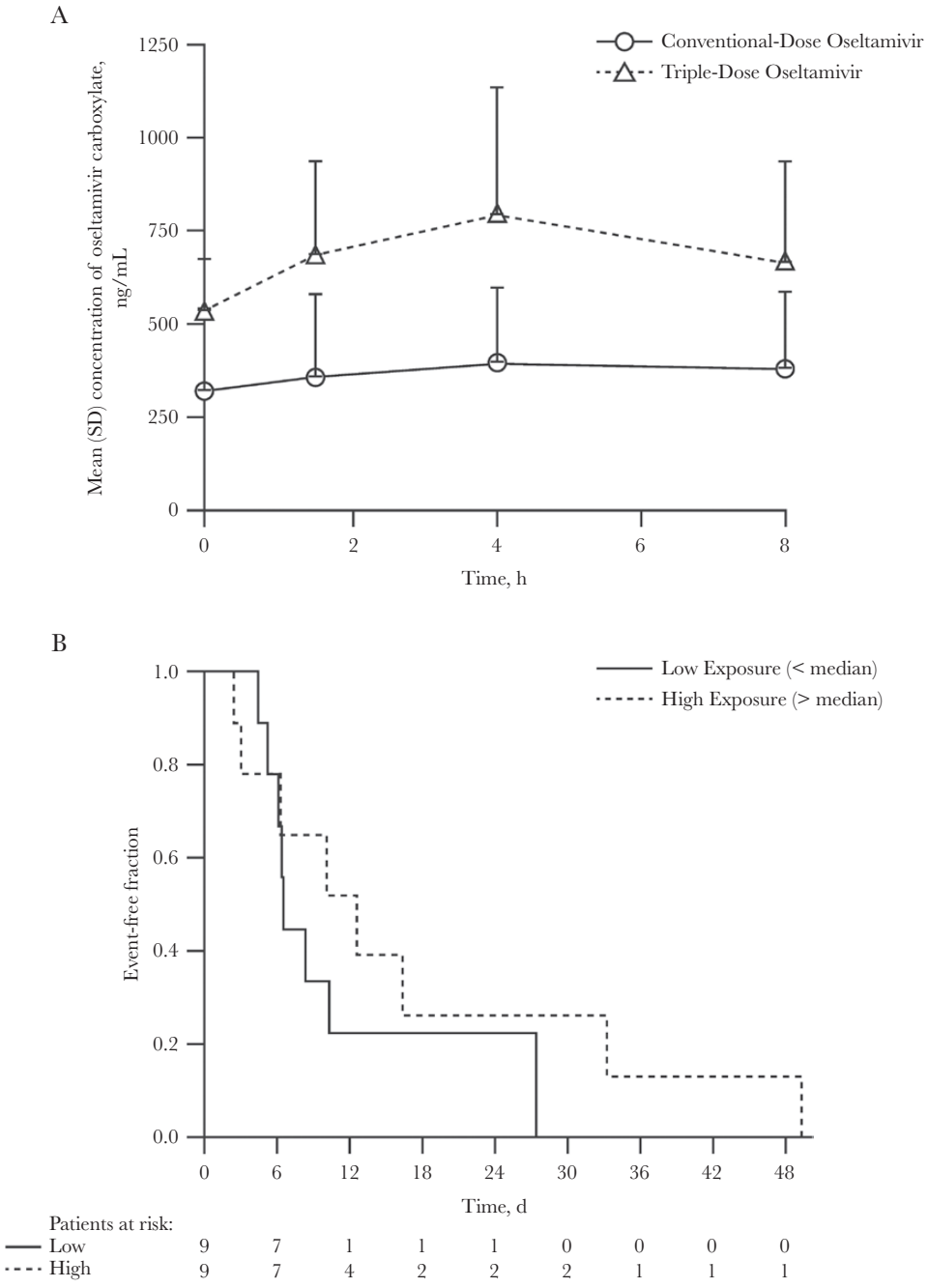

Figure 2. Pharmacokinetic and pharmacodynamic analysis: (A) mean concentration–time profiles of oseltamivir carboxylate (OC) at steady state (day 3 or 4) after administration of multiple oral doses of oseltamivir; (B) Kaplan-Meier plot of time to cessation of viral shedding by OC exposure group, defined by the median of the predicted OC steady-state C_{min} (<median = low exposure, >median = high exposure). Time to cessation of viral shedding was similar between the groups for the first part of the curve (including patients with postbaseline resistance) but shorter in the low-exposure group vs the high-exposure group during the second part of the curve. However, this part of the curve is mostly driven by patients with treatment-emergent resistance and the intervals between assessments.

[95% CI, 106.2–248.1] conventional-dose oseltamivir). There were no observed exposure–PD relationships for virological outcomes, such as time to cessation of viral shedding (Figure 2B) or treatment-emergent resistance. Exposures of OC from both oseltamivir doses exceeded inhibitory concentrations (IC_{95} values) of all in vitro tested sensitive influenza strains over the entire dosing period.

Safety

The mean treatment duration was 9 days with both conventional-dose and triple-dose oseltamivir. The proportion of patients with at least 1 AE was similar in the 2 dose cohorts (Supplementary Table 3). On-treatment AEs (73.3% conventional dose vs 86.7% triple dose) were most commonly vomiting (33.3% in each group), anemia (26.7% vs 6.7%), and diarrhea (20.0% vs 6.7%).

AEs considered related to oseltamivir occurred in 1 patient (6.7%) receiving conventional-dose (vomiting) and 3 patients (20.0%) receiving triple-dose oseltamivir (nausea, vomiting, and abdominal pain; dysgeusia; and erythematous rash). There were no deaths, serious AEs, or AEs leading to treatment withdrawal or oseltamivir dose modification/interruption.

Efficacy

The median TTA of baseline fever was longer with conventional-dose vs triple-dose oseltamivir (28.4 hours [95% CI, 0.0–88.2] vs 11.3 hours [95% CI, 0.0–not evaluable {NE}], respectively). The median TTA of all influenza symptoms was also longer in the conventional-dose cohort (179.4 hours [95% CI, 24.7–NE] vs 34.5 hours [95% CI, 0.0–84.9] with triple-dose oseltamivir). However, this study was designed to investigate PK/PD, not efficacy, so the results should be interpreted with caution due to the small sample size.

DISCUSSION

We report data from a phase 1b study conducted to determine the population–PK and PK/PD relationships of 2 doses of oseltamivir for the treatment of influenza in severely IC children aged <13 years. Despite previous studies demonstrating linear PK of oseltamivir and OC, we observed an approximately 2-fold higher OC exposure with triple-dose vs conventional-dose oseltamivir. This apparent nonlinearity may relate to an imbalance in baseline covariates in the dose cohorts, such as age, weight, or CrCl. Interestingly, treatment-emergent resistance rates (22.2% triple-dose cohort) were similar to those reported for otherwise healthy infants <12 months enrolled in clinical studies (18.3%) [10]. An increase in dose or exposure of oseltamivir or OC did not lead to improved virological outcomes or a reduction in viral resistance. This was not unexpected, as exposures from both of the doses investigated were considered at, or close to, the plateau of the exposure–response curve.

The nature and severity of AEs were consistent with the established safety profile of oseltamivir and typical of those seen in IC pediatric patients with influenza. Imbalances in AEs between dose cohorts were not clinically meaningful, and no increased incidence of AEs was evident with higher drug exposure. There were no deaths during the study.

The median TTA of baseline fever was longer with conventional-dose vs triple-dose oseltamivir, but only 8 patients had baseline fever, and there were no restrictions on the use of antipyretics during the study. This limits data interpretation. The median TTA of all influenza symptoms was also considerably longer with conventional-dose vs triple-dose oseltamivir, whereas the median time to cessation of viral shedding was similar between the dose groups. However, as the CARIFS score has been validated in otherwise healthy children, symptom evaluation may have been confounded by hematologic illnesses, concomitant chemotherapy, and possible reporter bias in this open-label study. The median treatment duration was 9 days in both dose cohorts, which supports the use of an extended treatment period in IC pediatric populations beyond the approved 5 days. The median time from symptom onset to start of treatment was <48 hours in both cohorts, thereby excluding late treatment initiation as a potential difference between the dose cohorts.

There are some limitations to consider. As a phase Ib study in a narrow, young patient population, the sample size was small. Patients were recruited over several influenza seasons and were potentially exposed to different influenza strains with varying disease severity. The open-label study and adaptive dosing design (treatment adapted by the objective measure of viral clearance) was considered the best treatment approach for patients, but this limited the ability to discern between the effects due to dose or treatment duration.

In summary, no additional meaningful benefit on virological end points was seen with oseltamivir exposures higher than those achieved with the conventional dose in this pediatric IC population, and the incidence of viral resistance was similar with both doses. Despite the limitations outlined, these results contribute to a better understanding of oseltamivir use in IC children with influenza infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. F.B. has acted as an advisory board member for Amgen, Bayer, and EusaPharma, has received honoraria for speaking at/attending symposia from Amgen, EusaPharma, and Jazz Pharmaceuticals, and his institution has received honoraria from Roche as part of the submitted work. M.B.'s institution received honoraria from Roche as part of the submitted work. J.S.-L. received personal fees from Roche during the conduct of the study. E.L.-M. received a grant from Roche during the conduct of the study; C.N.-M., J.H.-S., and S.S. are Roche employees. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Data sharing. Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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