Title: Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection.

Running title: favipiravir in severe influenza

Main point: No data are available on the clinical effectiveness of favipiravir and oseltamivir combination therapy in influenza. Comparing clinical outcomes between combination therapy cohort (n=40) and oseltamivir alone cohort (n=128), combination therapy may accelerate clinical recovery in critically ill patients.

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Abstract

Background: A synergistic effect of combination therapy with favipiravir and oseltamivir has been reported in pre-clinical models of influenza. However, no data are available on the clinical effectiveness of combination therapy in severe influenza.

Methods: Data from two separate prospective studies of influenza adults were used to compare outcomes between combination and oseltamivir monotherapy. Outcomes includes rate of clinical improvement, defined as a decrease of 2 categories on a 7-category ordinal scale, and viral RNA detectability over time. Sub-hazard ratio (sHR) was estimated by Fine and Gray model for competing risks.

Results: In total, 40 patients were treated with combination therapy and 128 with oseltamivir alone. Clinical improvement on Day 14 occurred in the combination group was higher than in monotherapy group (62.5% vs 42.2%, p=0.0247). The adjusted sHR for combination therapy was 2.06 (95%CI: 1.3-3.26). The proportion of undetectable viral RNA at day 10 was higher in the combination group than oseltamivir group (67.5% vs 21.9%, p<0.01). No significant differences were observed in mortality or other outcomes.

Conclusions: Favipiravir and oseltamivir combination therapy may accelerate clinical recovery compared to oseltamivir monotherapy in severe influenza, and this strategy should be formally evaluated in a randomized controlled trial.

Keywords: favipiravir, influenza, critical ill, outcome, oseltamivir.

Introduction

Influenza can result in severe illness and sometimes death, particularly in patients with co-morbidities, advanced age, or pregnancy [1]. Seasonal influenza infection is estimated to cause approximately 300,000–650,000 deaths worldwide annually [1]. Neuraminidase inhibitors (NAIs), specifically oseltamivir, are the only antiviral drugs in widespread use for influenza [2]. Oseltamivir has several limitations, including a short therapeutic time window, a low genetic barrier to resistance, limited antiviral efficacy [3], and, importantly, uncertainty regarding its effectiveness in severe influenza [4,5]. Novel antivirals with different mechanisms of action are therefore needed [6–8], in particular for critically ill influenza patients.

Favipiravir (Toyama Chemical Co, Japan) is a novel inhibitor of influenza RNA dependent RNA polymerase that is active against influenza A, B, and C viruses, including oseltamivir-resistant variants [6,9,10]. In-vitro studies indicate that favipiravir shows synergistic effects with oseltamivir for influenza A viruses [11]. Further, in mice with lethal A(H5N1) influenza infection, combination therapy with oseltamivir and favipiravir is effective late in disease [12,13]. However, no clinical studies have compared the use of favipiravir and oseltamivir combination therapy compared to oseltamivir monotherapy in the treatment of critically ill patients with influenza virus infection. In this study, we analyzed outcomes in critically ill influenza patients treated with favipiravir plus oseltamivir vs oseltamivir monotherapy, using data from two prospective studies in hospitalized influenza patients: one study of favipiravir pharmacokinetics (PK) in combination with oseltamivir (the ‘combination study’) and

the other an observational study of community acquired pneumonia (the 'monotherapy study').

METHODS

Patient Populations

Favipiravir + oseltamivir combination therapy cohort

Data were obtained from adult patients recruited into a phase 2a dose-escalating, multicenter study of favipiravir pharmacokinetics in critically ill influenza patients (NCT03394209). Patients were recruited from 4 tertiary care teaching hospitals between February 2018 and February 2019. Hospitalized patients (aged ≥ 18 years) were eligible if they had: (1) a positive rapid influenza A or B reverse transcriptase-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab (Xpert Xpress Flu/RSV assay, Cepheid, Sunnyvale, CA); AND (2) respiratory failure, defined as having a $PaO_2/FiO_2 \leq 300$ mmHg or receiving mechanical ventilation; AND (3) a time from onset of influenza-like symptoms ≤10 days. Exclusion criteria included pregnancy, breastfeeding, renal replacement therapy at the time of screening, an aspartate aminotransferase > 5 times upper level of normal or Child Pugh score ≥ C. All patients received oseltamivir at a dose of 75mg BD for 10 days and either a favipiravir regimen of 1600mg BD on day 1 followed by 600mg BD on days 2-10 or a favipiravir regimen of 1800mg BD on day 1 followed by 800mg BD on days 2-10. Additional data from 1 patient that received compassionate favipiravir at a dose of 1800mg/800mg was also included. The dose regimens assessed in the combination trial were based on the

approved favipiravir regimen in Japan (two 1600 mg oral loading doses on day 1, followed by 600 mg twice daily (BID) on days 2–5) and on the higher one (1800 mg BID on day 1 followed by 800 mg BID thereafter) tested in randomized, placebo-controlled phase 3 treatment trials outside of Japan. The latter two trials showed significant although modest antiviral effects and variable clinical efficacy in uncomplicated influenza outpatients (4^{th} and 5^{th} isirvAVG meeting report [14,15]). The dose regimens were not weight-based. The single patient given compassionate favipiravir and oseltamivir received the same higher dose regimen as those enrolled in the formal trial.

Oseltamivir monotherapy cohort

We used a cohort of adult patients with community acquired pneumonia (CAP) and laboratory-confirmed influenza A or B virus infection who received oseltamivir monotherapy as the comparator group. These were patients who had been recruited into the CAP-China study between October 2016 and February 2019, a prospective multicenter observational study of CAP in 34 hospitals from 10 provinces of mainland China (NCT02492425) [14]. The study recruited 2336 patients, of whom 796 patients were admitted to the China-Japan Friendship Hospital (CJFH). In order to ensure baseline comparability of the combination and monotherapy cohorts, we applied the same inclusion and exclusion criteria used in the combination study to the 796 CJFH patients enrolled in the monotherapy study. i.e. laboratory confirmed influenza infection, $PaO_2/FiO_2 \leq 300$ mmHg or receiving mechanical ventilation, and a time from onset of influenza-like symptoms ≤10 days. Of 796 cases, 128 patients at CJFH met

these eligibility criteria.

Study design and outcomes

Both studies were approved by the Institutional Review Board (IRB) of CJFH and other sites.All enrolled patients in the combination therapy cohort were managed according to a standardized protocol and data collection practices across the four participating hospitals. In the combination therapy protocol, adjunctive therapies such as corticosteroids were prohibited. Of note, the 3 other hospitals participating in the combination trial did not participate in the observational study. The enrolled patients in the monotherapy group at CJFH were managed according to physician discretion.

The primary clinical outcome was the time to clinical improvement after starting therapy, right censored at 28 days. Clinical improvement (the event) was defined as either a decline of two categories on the modified seven-category ordinal scale of clinical status or hospital discharge, whichever came first [16]. The seven-category ordinal scale [17, 18] consists of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalization, not requiring supplemental oxygen; 4, hospitalization, requiring supplemental oxygen; 5, hospitalization, requiring nasal high-flow oxygen therapy and/or non-invasive mechanical ventilation; 6, hospitalization, requiring ECMO and/or invasive mechanical ventilation; 7, death. Other clinical outcomes included: clinical status assessed by 7-category ordinal scale on day 7 and 14, 28-day mortality, in-hospital mortality, duration (days) of mechanical ventilation, duration (days) of hospitalization in patients who survived, and time (days) from treatment

initiation to death.

The primary virological endpoints were the proportions of patients with a negative nasopharyngeal swab for influenza qRT-PCR on days 2, 5, 7 and 10 after starting treatment. The virologic studies were performed on upper respiratory tract samples from both studies at a central laboratory (CJFH) as described previously [16,19].

Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]), and categorical variables as number (proportion). Two-group comparisons (favipiravir/oseltamivir combination vs oseltamivir) were conducted by the Mann-Whitney U test or χ^2/ Fisher's exact test, where appropriate. Differences between rates of clinical improvement were portrayed by Kaplan-Meier curves to track the improvement over time for two groups and tested by log-rank test.

Given all involved patients were critically ill, we used a Fine and Gray model for competing risks analysis in Cox proportional hazard model [20]. The cumulative incidence function (CIF) of clinical improvement was calculated, which describes the cumulative probability of a decrease of 2 categories or discharge alive. Then unadjusted and adjusted sub-hazard ratios (sHRs) and 95% confidence intervals (95% CIs) were estimated. In multi-regression analysis, only variables with a p value < 0.05 in univariate analysis or a presumptive association with the event were included to minimize bias. Additionally, to compare outcomes between groups throughout the study period, proportional-odds model analyses based on the 7-category clinical status were conducted from day 1 (antiviral treatment start) through to day 28.

A two sided alpha of < 0.05 was considered statistically significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc.), unless otherwise indicated.

Because we detected baseline differences in clinical characteristics between the combination and monotherapy groups, we undertook post hoc analyses of the subset of patients who did not receive systemic corticosteroids and also of the subset of patients enrolled in the two studies only at CJFH.

Results

Study Populations and circulating influenza virus subtypes

A total of 40 patients who received favipiravir and oseltamivir combination therapy and 128 patients that received oseltamivir monotherapy were included. The reasons for exclusion among the 796 patients with laboratory-confirmed influenza admitted to CJFH were: age less than 18 years (n = 40), missing clinical data (n = 131), a PaO_2/FiO_2 ≥ 300 at admission to hospital (n=446), days of initial antiviral treatment from symptom onset >10 (n=50), or death within 24 hours at admission (n = 1). The flow chart is shown in Figure 1. In 2016-17 and 2018-19 influenza seasons, influenza A(H1N1)pdm09 virus was the most commonly circulating subtype nationally (70-80%), and influenza A(H3N2) virus was the second most commonly detected subtype (15-30%). However, approximately equal proportions of influenza A(H1N1)pdm09 and B/Victoria viruses were observed in 2017-18 influenza season. Detailed data can be found on the Chinese National Influenza Center website [21].

Clinical characteristics

The baseline characteristics of patients in the two groups were comparable in terms of: demographic characteristics, comorbidities, influenza type/subtype, and clinical features including the median 7-category-scale score at admission, median PaO_2/FiO_2, Charlson comorbidity index score, APACHE II score, and SOFA score. The median day of admission from symptom onset for the two groups was similar [5 days (3-7) vs 6 day (4-8), p=0.3245]. The time between symptom onset and starting antivirals was non-significantly shorter in the oseltamivir monotherapy group (median, 5.0 [IQR 3 – 7]) compared to the combination group (6.0 [IQR 4 – 8] days, p = 0.1237), and the proportion treated within 2 days of symptom onset somewhat larger (57.5% vs 43.0%). Higher proportions of patients in the oseltamivir monotherapy group had elevated serum creatinine and creatine kinase concentrations, but other routine laboratory measures were similar.

A much higher proportion in the monotherapy cohort received systemic corticosteroids within the first 24 hours of admission (53.1% vs 0, p < 0.0001). Of the 128 patients in the oseltamivir only group, 68 cases (53%) were administrated corticosteroids (Supplementary Table 2). Among the patients who received corticosteroids, the median maximum dose of corticosteroid administered was equivalent to 40 mg methylprednisolone (IQR, 26.7-40 mg). The median duration of treatment with corticosteroids was 3 days (IQR, 1.0–5.0 d). The baseline characteristics of the subset of patients without systemic corticosteroid administration indicated that the two groups were comparable (Supplementary Table 1), although the combination group had a

significantly higher APACHE score than the monotherapy group at enrolment (median APACHE II Score, 14 vs 9, p = 0.0241) (Table 1).

Clinical Outcomes in univariate analysis

Univariate analysis showed that patients treated with combination therapy had the same median time to clinical improvement (12 [IQR 9.5 – 15] days vs 12 [IQR 8 - 19] days, log-rank test p = 0.0477), but significantly different cumulative incidences of clinical improvement compared with those receiving oseltamivir monotherapy (Table 2, Figure 2). Significantly lower proportions of patients with severe outcomes (categories 5 – 7) were observed according to the 7-category ordinal scale at day 7 (60.0% vs 63.3%, p = 0.0257) and day 14 (30.0% vs 48.5%, p = 0.0069) in the combination therapy cohort. The median ICU length of stay was non-significantly longer in patients that received combination therapy (12.0 [7.0, 20.5] vs 10.5 [5.7 to 19.4]) (p = 0.1811). There was no significant difference in in-hospital mortality, day 28 mortality, length of hospital stay, days from treatment initiation to discharge or death, or the rate of clinical improvement at day 7 and day 28 (Table 2). The distribution of patients falling into the seven-category ordinal scale from baseline (day1) to 28 days are shown in Figure 3.

Because corticosteroid use is an important potential confounding factor and because all patients who received corticosteroids were in the oseltamivir monotherapy group, we conducted a sensitivity analysis including only patients in the oseltamivir monotherapy group who did not receive corticosteroids (N = 60). The detailed clinical outcomes are listed in Supplementary Table 3. A similar pattern between cohorts was observed, with most clinical outcomes being similar other than length of ICU stay.

Virologic Outcomes

The proportion of patients with undetectable viral RNA was significantly higher in the favipiravir plus oseltamivir group compared to the oseltamivir monotherapy group (10% vs 0.8% at day 2, 30 % vs 5.5% at day 5, 45.0% vs 15.6% at day 7, 67.5% 21.9% at day 10, all $p < 0.01$) (Table 2). After exclusion of those patients receiving systemic corticosteroids, the proportion of patients with undetectable viral RNA remained significantly higher in the combination therapy group compared to the oseltamivir monotherapy group (30 % vs 10% at day 5, 45.0% vs 16.7% at day 7, 67.5% vs 21.7% at day 10, all $p < 0.05$) (Supplementary Table 2). In the patients in the combination therapy group, no isolated influenza virus variant showed phenotypic resistance to favipiravir. One patient developed the emergence of the NA H275Y mutation related to resistance of oseltamivir. We did not monitor the development of resistance of oseltamivir in the monotherapy group,

Competing risk analysis

To evaluate the risk magnitude of relevant factors associated with clinical improvement, univariate and multivariate Fine and Gray regression models for competing risks were performed, and the results are shown in Table 3, Figure 2 and Supplementary Figure 1. Combination treatment was independently associated with clinical improvement, whereas APACHE II Score, Charlson comorbidity index, and lactate dehydrogenase (LDH) > 245U/L were also independent risk factors for a worse clinical outcome after a stepwise selection. In the multivariate Fine and Gray model, combination therapy was found to be an independent factor associated with clinical improvement vs oseltamivir

monotherapy (adjusted sHR 2.06, 95% CI 1.30-3.26; p = 0.0021), after adjustment for APACHE II score, Charlson comorbidity score, LDH > 245U/L and days from illness onset to starting antiviral treatments (Table 3). In addition, after 10 days of antiviral therapy, the proportional-odds model indicated that combination therapy was significantly associated with a lower proportion of severe outcomes compared to oseltamivir alone at each study day after adjusting for influenza type, Charlson comorbidity index, LDH, days from illness onset to starting antiviral treatments and APACHE II score compared with oseltamivir monotherapy (Figure 4).

In the sensitivity analysis, which included only patients who did not receive corticosteroids (n=60), combination therapy was not significantly associated with clinical improvement after adjusting for APACHE II Score (adjusted sHR 1.54, 95% CI 0.88-2.69; p = 0.1322) (Table 3). Another sensitivity analysis was conducted after removal of the influenza B cases altogether from both groups. A similar trend was observed. The adjusted sHR for combination therapy was 1.99 (95%CI: 1.3-3.23) (Supplementary Table 4).

A post hoc analysis of only those patients enrolled in the two studies at our hospital (CFJH) found a similar trend for the difference in clinical improvement observed in the whole cohorts. The adjusted sHR for combination therapy was 2.02 (95% CI: 1.09-3.72) in those patients from our hospital (Supplementary Table 5). A sensitivity analysis was conducted between oseltamivir only group excluding patients with corticosteroids (n=60) and combination therapy group only at CFJH (20). There were no factors associated with clinical improvement (Supplementary Table 6).

Safety

The combination of favipiravir and oseltamivir appeared to be generally tolerated well, but we did not include have placebo control group in the combination study. No SAEs were thought to be related to favipiravir, though 3 patients had reversible increases in serum alanine aminotransferase.

Discussion

This retrospective study is the first to explore the comparative effectiveness of combined favipiravir and oseltamivir treatment in severe influenza. Previous randomized controlled trials have shown that favipiravir monotherapy inhibits viral replication but variably reduces symptom duration in uncomplicated influenza infection relative to placebo using the same higher dose regimen (1800mg/800mg) that we tested in hospitalized patients [16,17]. Our findings suggest that favipiravir and oseltamivir combination therapy may be associated with greater antiviral effects and faster clinical improvement in severe influenza.

To date, no antiviral randomized controlled trials (RCTs) have established a treatment regimen superior to oseltamivir monotherapy in hospitalized patients with influenza due to susceptible strains [22,23]. Of concern is the relatively high frequency of emergence of oseltamivir-resistant variants in critically ill patients and their association with poor outcomes [24]. Recent RCTs of antibody based therapies given in combination with standard of care NAIs have yielded disappointing results [25–27]. However, pivotal studies of the polymerase inhibitors pimodivir and baloxavir in combination with NAIs are currently in progress for treatment of severe influenza in

hospitalized patients (NCT03376321, NCT03684044), and other agents with putative anti-influenza activity (e.g., arbidol, diltiazem) are also being trialed (NCT03212716, NCT03787459). Various adjunctive therapies have been proposed for severe influenza [28], and several RCTs are planned (NCT03238612, NCT03901001, NCT03900988). To the best of our knowledge, no RCT of favipiravir therapy in hospitalized patients with influenza is currently planned.

Since this is a retrospective comparison and treatment was not randomly assigned, potential bias and unmeasured confounders may exist. Of note, the oseltamivir monotherapy group was from one hospital (CJFH), whereas the favipiravir and oseltamivir patients were recruited from three additional hospitals involved in the favipiravir PK study but not in the oseltamivir monotherapy one. However, all data were prospectively collected in the context of protocolized clinical studies. Most baseline characteristics were comparable between groups, and baseline risk factors, except for corticosteroid use, were adjusted for in the regression model. Overall 24.4% (41/168) of patients died before clinical improvement at day 28, and these patients with fatal outcome would be excluded if the traditional Cox proportional hazard models and Kaplan-Meier analyses were performed. Considering the existence of such competing events, the competing risk analysis, the Fine and Gray model, is more appropriate rather than omitting the data.

There are several other limitations in our study. Firstly, several studies have shown that corticosteroid use is associated with worse outcomes in patients with severe influenza [28–33]. In this study, systemic corticosteroids were administered in 53% of patients in

the oseltamivir monotherapy group but in none of those in the combination therapy group. Since the use of corticosteroids only in oseltamivir group could not be adjusted in the Fine and Gray model, we conducted a sensitivity analysis in the subset of patients who did not receive corticosteroids. While the results were in the same direction, the adjusted hazard ratio was no longer statistically significant, although the differences in virologic outcomes on days 5, 7 and 10 remained significant. Secondly, we did not assess quantitative virology or the emergence of variant viruses with reduced susceptibility during treatment. As recently reported [24], critically ill A(H1N1)pdm09 influenza patients have frequent emergence of oseltamivir resistant virus during persistent virus detection on monotherapy, and emergence is associated with high mortality. A further limitation was the small number of patients in both groups, particularly in the favipiravir and oseltamivir combination group, which may have resulted in insufficient power. In addition, the effect of combination therapy for influenza B should be interpreted cautiously because of the relative lack of information on influenza B. Since the study periods between two groups differed, though notwithstanding overlapped, the oseltamivir monotherapy cohort serves primarily as a historical control. Finally, preliminary analysis of the plasma favipiravir concentrations from the PK study indicate that the levels of exposure were lower than expected in these severely ill patients, as previously reported in favipiravir-treated Ebola patients [34]. Consequently, we may not have used an optimal favipiravir dose.

In summary, our findings suggest that oseltamivir and favipiravir combination therapy may be superior to oseltamivir monotherapy in the treatment of severe influenza

patients. However, a double blinded, randomized controlled trial is needed to establish the efficacy and safety of favipiravir and oseltamivir combination therapy compared to oseltamivir monotherapy.

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Conflicts of interest

The authors have no conflict of interest or financial relationships to disclose. No form of payment was given to anyone to produce the manuscript. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Author Contributions:

Dr. Bin Cao and Dr. Yeming Wang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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