Background: The effectiveness of neuraminidase inhibitors to reduce transmission when used as treatment in influenza-infected patients remains debated.

Methods: In a prespecified analysis of a blinded randomized controlled trial on the efficacy of oseltamivir–zanamivir combination therapy versus oseltamivir and zanamivir monotherapy conducted during the 2008–2009 seasonal influenza epidemic, we compared the rate of secondary illness in household contacts of influenza-positive index patients between arms. Secondary illness was defined as occurrence in contacts of fever plus cough within 7 days from randomization of index patients. Analyses were conducted according to the delay between patients’ onset of symptoms and intervention.

Results: A total of 543 household contacts of 267 index patients were included, of which 466 had follow-up assessment. A secondary illness was reported in 58 (12.5%) contacts with no significant difference between arms overall ($P=0.07$). When the analysis was limited to the 232 contacts of 136 index patients with first treatment intake within 24 h of onset of symptoms, a lower rate of secondary illness was reported in the combination therapy arm (2 of 56 [4%]) than in the oseltamivir arm (14 of 81 [17%]; $P=0.014$) and the zanamivir arm (14 of 95 [15%]; $P=0.031$). Multivariate analysis accounting for intra-household correlation confirmed these findings.

Conclusions: Our analysis suggests a greater effectiveness of the combination therapy to reduce transmissibility when given to the index patient within 24 h of onset of symptoms. As the finding was obtained from a subgroup analysis, it should be interpreted with caution.

Short communication

Effect of oseltamivir, zanamivir or oseltamivir–zanamivir combination treatments on transmission of influenza in households

Fabrice Carrat1,2,4, Xavier Duval1,4,5,6, Florence Tubach4,5,7, Anne Mosnier8, Sylvie Van der Werf9,10,11, Annick Tibi12,13, Thierry Blanchon2,3, Catherine Leport4,5,14, Antoine Flahault15,16, France Mentré4,5,7, the BIVIR study group*

1APHP, Hôpital Saint-Antoine, Unité de Santé Publique, Paris, France
2UPMC Université Paris 06, UMR-S 707, Paris, France
3INSERM U707, Paris, France
4INSERM, UMR738, Paris, France
5Université Paris Diderot, Sorbonne Paris Cité, UMR 738, Paris, France
6INSERM CIC 007, Hôpital Bichat, Assistance Publique Hôpitaux de Paris, Paris, France
7AP-HP, Hôpital Bichat, Service de Biostatistique, Paris, France
8Réseau des Groupes Régionaux d’Observation de la Grippe (GROG), Coordination Nationale, Paris, France
9Institut Pasteur, Centre National de Référence des virus influenzae (Région-Nord), Unité de Génétique Moléculaire des Virus à ARN, Paris, France
10CNRS URA3015, Paris, France
11UFR Sciences du Vivant, Université Paris Diderot, Paris, France
12Agence Générale des Equipements et Produits de Santé, Unité Essais Cliniques, Paris, France
13Faculté de Pharmacie, Université Paris Descartes, Paris, France
14Unité de Coordination des Risques Epidémiques et Biologiques, Assistance Publique Hôpitaux de Paris, Paris, France
15Ecole des Hautes Études en Santé Publique, Rennes, France
16UFR de Médecine, Université Paris Descartes, Paris, France

*Corresponding author e-mail: carrat@u707.jussieu.fr

1A list of the members of the BIVIR study group can be found in Additional file 1
Introduction

Prevention of influenza transmission in households is recognized as a means of reducing spread of influenza. Neuraminidase inhibitors (nebulized zanamivir [Relenza®; Glaxo Wellcome] and oral oseltamivir [Tamiflu®; Hoffmann-La Roche]) demonstrated clear efficacy on susceptibility when used as postexposure prophylaxis in household contacts [1]. By contrast, the effectiveness of neuraminidase inhibitors to reduce infectivity and subsequent onward transmission when used as treatment in symptomatic infected patients remains debated [2–5].

During winter 2008–2009, a large blinded randomized trial comparing the efficacy of oseltamivir–zanamivir combination therapy to oseltamivir monotherapy and zanamivir monotherapy was conducted in France [6]. The trial showed that oseltamivir–zanamivir combination therapy was less effective than oseltamivir monotherapy and not more effective than zanamivir monotherapy for achieving virological and clinical end points. In a prespecified secondary analysis, we compared the rate of secondary illness in household contacts of influenza-positive patients between arms and assessed factors associated with secondary illness.

Methods

A complete description of the trial is described by Duval et al. [6]. Briefly, the trial was conducted in 47 centres in France and included patients 18 years or older who sought medical advice within 36 h of the onset of influenza symptoms and who were tested positive with a rapid influenza test (Clearview® Exact Influenza A & B; Inverness Medical, Cologne, Germany) between 7 January to 15 March 2009. The predominant epidemic strain was A/Brisbane/10/2007 (H3N2)-like influenza virus. At enrolment, a nasal swab was collected and the patient was allocated to one of the three treatment arms: oseltamivir orally 75 mg twice daily plus inhaled placebo (O), zanamivir 10 mg inhaled daily plus oral placebo (Z) and oseltamivir 75 mg orally twice daily plus zanamivir 10 mg inhaled (OZ). The primary end point in the trial was the proportion of patients with reverse transcription (RT)-PCR viral load <200 copies of genome equivalent (cgeq)/µl on a nasal sample collected at day 2 during a nurse visit. Symptoms and other characteristics, including size of the household and presence of any flu-like illness in household members were recorded by the practitioner from the patient at inclusion and at day 7 during a follow-up visit. Patients with negative or missing baseline influenza RT-PCR measurement were excluded from the analyses. A household contact was defined as a subject living in the same house as the randomized patient. Households in which ≥1 contact reported influenza symptoms during the previous 15 days before inclusion of the patient in the trial were excluded. A secondary illness was defined as fever plus cough occurring between inclusion and the follow-up visit in a household contact.

Statistics

The comparison of secondary illness rates between arms was a prespecified analysis. Post hoc subgroup analyses were conducted by taking into account the time between onset of symptoms in the patient and allocation to intervention or by considering only secondary illness that occurred after a minimum time lag after allocation to intervention, as these factors were shown to influence the effectiveness of preventive measures [7,8]. Household contacts with missing follow-up data were discarded from the analyses. The chi² test or the Kruskal–Wallis test was used for global comparisons across the three arms. In case of a significant test, pairwise comparisons were performed. We used an alternating logistic regression model with an exchangeable log odds ratio to test the association between the treatment arm and secondary illness and to identify other factors associated with secondary illness in household contacts [9]. Potential factors were included based on a P-value <0.20 in univariate analysis and were then selected in a multivariate analysis using a backward procedure. For all analyses, a P-value of 0.05 was considered as statistically significant. Analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The analysis set included 267 index patients and 543 household contacts (Figure 1). Characteristics of index patients or household contacts at inclusion (day 0) were well balanced across arms (Table 1). At day 2, the proportion of index patients with a viral load <200 cgeq/µl was lower in the Z arm compared with the OZ arm (33% versus 54%; P=0.007) but did not differ between the O arm and the OZ arm (59% versus 54%; P=0.51).

Follow-up status was available in 466 household contacts, of whom 232 were contacts of 136 index patients with first treatment intake within 24 h of onset of symptoms. A secondary illness was reported in 58 (12.5%) contacts with no significant difference between arms overall (Table 2). When the allocation to intervention occurred within 24 h of the onset of symptoms in the index patient, the rate of secondary illness differed between the three arms (P=0.0499) and pairwise comparisons showed a lower rate in the OZ arm (2 of 56 [4%]) than in the O arm (14 of 81 [17%]; P=0.014) and the Z arm (14 of 95 [15%]; P=0.031). The median time between inclusion and secondary illness onset was 3 days (range 0–7). In total, 14 (25%) secondary
Antiviral Therapy 17.6

Analysis set
Patients with negative RT-PCR or missing measurement or no eligible household contact or households with ≥1 non-eligible household contact

Follow-up data at day 7
Oseltamivir + placebo Patients: 176 Contacts: 330
Zanamivir + placebo Patients: 173 Contacts: 306
Oseltamivir + zanamivir Patients: 192 Contacts: 359

541 Randomized patients
Index patients: 78 Contacts: 161
Index patients: 84 Contacts: 164
Index patients: 77 Contacts: 141
Index patients: 89 Contacts: 188
Index patients: 90 Contacts: 177
Index patients: 90 Contacts: 178
Index patients: 102 Contacts: 181

Figure 1. Participant flow chart

Table 1. Characteristics of 267 treated index patients and their 543 household contacts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Oseltamivir + zanamivir</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>87</td>
<td>90</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.56</td>
</tr>
<tr>
<td>18–44 years, n (%)</td>
<td>63 (72)</td>
<td>57 (63)</td>
<td>60 (67)</td>
<td>-</td>
</tr>
<tr>
<td>45–64 years, n (%)</td>
<td>19 (22)</td>
<td>29 (32)</td>
<td>26 (29)</td>
<td>-</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>5 (6)</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>42 (48)</td>
<td>48 (53)</td>
<td>43 (48)*</td>
<td>0.74</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>10 (11)</td>
<td>11 (12)</td>
<td>8 (9)*</td>
<td>0.77</td>
</tr>
<tr>
<td>Timeframe ≤24 h, n (%)</td>
<td>43 (49)</td>
<td>54 (60)</td>
<td>39 (43)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean symptom score at day 0, n (%)</td>
<td>15.3 (2.9)</td>
<td>15.3 (3.2)</td>
<td>15.3 (2.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Severe cough at day 0, n (%)</td>
<td>27 (31)</td>
<td>23 (26)</td>
<td>28 (31)</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean log₁₀ viral load at day 0, cgeq/µl</td>
<td>4.61 (1.33)</td>
<td>4.41 (1.47)</td>
<td>4.16 (1.43)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean number of contacts (so)</td>
<td>2.16 (1.04)</td>
<td>1.97 (1.00)</td>
<td>1.98 (1.03)</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean log₁₀ viral load at day 2, cgeq/µl</td>
<td>2.15 (1.25)</td>
<td>2.72 (1.31)</td>
<td>2.17 (1.13)</td>
<td>0.002</td>
</tr>
<tr>
<td>Viral load &lt;200 cgeq/µl at day 2, n (%)</td>
<td>48 (59)</td>
<td>29 (33)</td>
<td>45 (54)</td>
<td>0.002</td>
</tr>
<tr>
<td>Observance (100%) at day 2, n (%)</td>
<td>76 (87)</td>
<td>75 (83)</td>
<td>75 (83)</td>
<td>0.69</td>
</tr>
<tr>
<td>Eligible household contacts, n</td>
<td>188</td>
<td>177</td>
<td>178</td>
<td>-</td>
</tr>
<tr>
<td>Age of eligible household contacts</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.16</td>
</tr>
<tr>
<td>0–4 years, n (%)</td>
<td>18 (10)</td>
<td>19 (11)</td>
<td>25 (14)</td>
<td>-</td>
</tr>
<tr>
<td>5–17 years, n (%)</td>
<td>50 (27)</td>
<td>55 (31)</td>
<td>41 (23)</td>
<td>-</td>
</tr>
<tr>
<td>18–44 years, n (%)</td>
<td>53 (28)</td>
<td>60 (34)</td>
<td>65 (37)</td>
<td>-</td>
</tr>
<tr>
<td>45–64 years, n (%)</td>
<td>50 (27)</td>
<td>35 (20)</td>
<td>37 (21)</td>
<td>-</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>9 (5)</td>
<td>7 (4)</td>
<td>7 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>8 (4)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Vaccinated eligible household contacts, n (%)</td>
<td>18 (8)</td>
<td>11 (5)</td>
<td>14 (7)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*One missing. **Timeframe between onset of symptoms to intervention. *Patient self-report at day 0, defined as the ratio of the sum of the severity (0= none, 1= mild, 2= moderate and 3= severe) of seven influenza symptoms to a maximum of 21. Cough with patient self-report severity of 3. The number of participants missing data in oseltamivir: 6, zanamivir: 6 and oseltamivir–zanamivir combination: 7. The number of participants missing data in oseltamivir: 9, zanamivir: 16 and oseltamivir–zanamivir combination: 8.**
illnesses occurred the day of or the day after inclusion. No difference between the treatment arms was revealed when these illnesses were excluded.

In the multivariate analysis of the 466 contacts, secondary illness was associated with severe cough in the index patient (OR versus not severe 2.08 [95% CI 1.06, 4.08]; \( P = 0.03 \)) and no other covariate was significant. When the analysis was restricted to the 232 household contacts of index patients allocated to intervention within 24 h of onset of symptoms, secondary illness was associated with younger age in the index patient (OR per year increase 0.95 [95% CI 0.91, 0.98]; \( P = 0.005 \)), and was increased in case of monotherapy by comparison with combination therapy (O arm versus OZ arm OR 5.29 [95% CI 1.08, 25.9]; \( P = 0.04 \) and Z arm versus OZ arm OR 4.60 [95% CI 0.97, 21.7]; \( P = 0.05 \)).

### Discussion

When the index patient was treated within 36 h of onset of symptoms, no significant difference was shown between oseltamivir, zanamivir or oseltamivir plus zanamivir concerning the secondary illness rates in patients’ household contacts. However, when the analysis was restricted to treatment initiated <24 h from the onset of symptoms, the combination of oseltamivir plus zanamivir was found to be associated with a lower secondary illness rate than oseltamivir or zanamivir monotherapy.

This finding was surprising, as the trial found superior virological and clinical effectiveness with oseltamivir [6] – and, consequently, a decrease of secondary illness in the O arm compared to the two other arms was expected. A selection bias was unlikely since we did not find any difference regarding various virological end points between influenza-positive patients selected in the household contact analysis and those not selected (Additional file 2).

Among other explanations for our findings, a false-positive finding by inflation of statistical type I error in a post hoc subgroup analysis cannot be eliminated. However, the fact that we observed significant differences when the intervention could be applied quickly in the presumably first influenza-infected patient is in favour of a lack of a false-positive result. Indeed, studies of antiviral treatment to limit influenza transmission within the household suggested that effectiveness could be obtained only when the intervention was applied within 1 day of first symptoms in the index patient [4]. Based on these findings, we hypothesize that the combination therapy might have a different kinetic pattern with faster antiviral activity than each standalone monotherapy, leading to a more rapid decline in viral load and acting on transmission when it can be prevented, that is, during the first 24 h of symptoms. This hypothesis does not contradict with the trial findings, but is not supported by direct data, thus highlighting the need for pharmacodynamic studies of combined neuraminidase inhibitor therapy.

Our secondary analysis has other limitations. First, secondary illness in household contacts was not virologically confirmed and was simply reported without any objective measurement of fever by the patient during a medical follow-up visit, and therefore may have been subject to lack of specificity and recall bias. Second, our study did not capture non-febrile respiratory illnesses or asymptomatic influenza infections. Therefore, the rate of febrile secondary illness underestimated the rate of secondary influenza infections. However, assuming that the proportion of febrile illnesses among all influenza infections was comparable across the study arms, the differences in secondary influenza infection rates between the combination and monotherapy arms would be higher than those reported for febrile illnesses. Third, some household contacts with febrile illnesses may have been infected from sources outside the household; this proportion has been estimated at 23% during the H1N1-2009 pandemic [10]. Fourth, 77 (14%) household contacts were lost to follow-up and a bias caused by unequal distribution of unmeasured confounders between arms

### Table 2. Comparison of secondary illness rates in 466 household contacts with follow-up data across arms

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Household contacts, n</th>
<th>Oseartamivir, n/total (%)</th>
<th>Zanamivir, n/total (%)</th>
<th>Oseltamivir plus zanamivir, n/total (%)</th>
<th>( P )-value (overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subgroups</td>
<td>466</td>
<td>23/161 (14)</td>
<td>25/164 (15)</td>
<td>10/141 (7)</td>
<td>0.0676</td>
</tr>
<tr>
<td>Time to intervention ≤24 h</td>
<td>232</td>
<td>14/81 (17)</td>
<td>14/95 (15)</td>
<td>2/56 (4)</td>
<td>0.0499</td>
</tr>
<tr>
<td>Excluding secondary illness the day of inclusion(^a)</td>
<td>228</td>
<td>13/80 (16)</td>
<td>11/92 (12)</td>
<td>2/56 (4)</td>
<td>0.0711</td>
</tr>
<tr>
<td>Excluding secondary illness the day of inclusion and the day after inclusion(^a)</td>
<td>226</td>
<td>12/79 (15)</td>
<td>10/91 (11)</td>
<td>2/56 (4)</td>
<td>0.0962</td>
</tr>
<tr>
<td>Time to intervention &gt;24 h</td>
<td>234</td>
<td>9/80 (11)</td>
<td>11/69 (16)</td>
<td>8/85 (9)</td>
<td>0.4491</td>
</tr>
<tr>
<td>Excluding secondary illness the day of inclusion</td>
<td>233</td>
<td>8/79 (10)</td>
<td>11/69 (16)</td>
<td>8/85 (9)</td>
<td>0.3996</td>
</tr>
<tr>
<td>Excluding secondary illness the day of inclusion and the day after inclusion</td>
<td>225</td>
<td>7/78 (9)</td>
<td>6/64 (9)</td>
<td>6/83 (7)</td>
<td>0.8787</td>
</tr>
</tbody>
</table>

\(^a\) Also excludes one secondary illness in the oseltamivir arm without information on the delay between inclusion and onset of symptoms.
cannot be excluded. Fifth, the trial did not include an untreated placebo–placebo arm, therefore does not allow assessment of the absolute decrease of secondary illness rates using neuraminidase inhibitors.

It is worthy of note, however, that the rates of febrile secondary illnesses reported in the O or Z monotherapy arms (9–17%) were similar to those reported in a non-pharmaceutical intervention study conducted in the same setting and during the same influenza season (16%) [11]. Secondary, febrile illness rates were also in the range of values reported in the literature during seasonal epidemics [3,4] and the risk reduction of household transmission was of similar magnitude to the reduction reported with early zanamivir treatment in a retrospective survey during the H1N1-2009 pandemic [5]. Finally, the strength of our analysis was that data was collected during a blinded randomized trial, and was therefore less subject to differential bias across arms.

Considering all household contacts, we found that the severity of cough in the index patient was associated with an increased risk of secondary illness in household contacts, which may be associated with a greater amount of infectious droplets generated during intense coughing [12]. We also found that younger age in the index patient was associated with more transmission, which is consistent with findings from other household studies [5,13,14].

Our analysis suggests a greater effectiveness of the combination therapy to reduce transmissibility when given to the index patient within 24 h of onset of symptoms. As the finding was obtained from a subgroup analysis, it should be interpreted with caution and warrants further study on the topic.

Acknowledgements

We are grateful to the members of the independent data monitoring committee for their helpful advice, to Marc Guerrier for his fruitful support in the ethical aspects of the research, to Philippe Ravaud for stimulating discussion and to Roche and GSK laboratories for providing oseltamivir, zanamivir and corresponding placebos.

We thank all members of the different teams and contributors who collaborated in the trial for their excellent support and all investigators and patients for their active participation in the study.

Disclosure statement

FC is member of the French Ministry of Health advisory board on influenza and the National Public Health Council, and participated in scientific boards for Novartis and GSK. XD has received funds for travel for scientific conference from GSK and Roche, and lecture fees from Roche and Gilead. AM has membership in the French Ministry of Health advisory board on influenza, involvement in some epidemiological studies partially or fully funded by Roche and GSK, has received funds for travel for participation in scientific meetings from Roche and is member of the scientific committee of the Groupe d’Expertise et d’Information sur la Grippe (GEIG). TB has received funds for travel for a scientific conference from Roche, and is a member of the scientific committee of the GEIG. FM received funds from Roche, Preclinical Pharmacokinetic Department, for a course on MONOLIX in December 2008. CL is an associated expert to the National Public Health Council. All other authors declare no competing interests.

Additional files

Additional file 1: A list of the members of the BIVIR study group can be found at http://www.intmedpress.com/uploads/documents/AVT-11-SC-2282_Carrat_Add_file1.pdf

Additional file 2: Supplementary table 1, which displays a comparison of baseline characteristics between the 267 index patients selected in the study and 274 patients not selected but included in the trial, can be found at http://www.intmedpress.com/uploads/documents/AVT-11-SC-2282_Carrat_Add_file2.pdf

References


