Original article

Efficacy and safety of oral oseltamivir for influenza prophylaxis in transplant recipients

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Background: Haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients are at high risk for severe influenza and its complications, and may not be adequately protected by vaccination.

Methods: Liver, kidney, or liver–kidney transplant or allo-generic HSCT recipients aged ≥1 year were randomized to oseltamivir (75 mg once daily for those ≥13 years or weight-based dosing for children 1–12 years) or placebo for 12 weeks during periods of local influenza circulation. Patients were assessed for influenza infection via daily diary, every-other-week culture and PCR, and baseline and end-of-treatment serology.

Results: A total of 477 subjects were enrolled (239 oseltamivir and 238 placebo); most were adults (96%) and SOT recipients (81%). In the intent-to-treat population, the frequency of laboratory-confirmed clinical influenza (culture positive and/or >4-fold increase in haemagglutinin antibody inhibition [primary end point]) was similar in the oseltamivir and placebo groups (2.1% [5/237] and 2.9% [7/238]). Incidence of laboratory-confirmed influenza was significantly reduced in the oseltamivir group versus placebo when determined by reverse transcriptase-PCR (1.7% [4/237] versus 8.4% [20/238]; 95% CI 2.8, 11.1) or viral culture (<1% [1/237] versus 3.8% [9/238]; 95% CI 0.7, 6.6), giving protective efficacies of 79.9 and 88.8%, respectively. Serious adverse events (oseltamivir 8% and placebo 10%) and adverse events (oseltamivir 55% and placebo 58%) were reported in both arms with a similar frequency. One illness due to oseltamivir-resistant A/H1N1 virus was detected in each group.

Conclusions: Oseltamivir prophylaxis is generally well-tolerated and may reduce culture- or PCR-confirmed influenza incidence in transplant recipients.

Introduction

Influenza is associated with significant morbidity and mortality in haematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients [1]. Seasonal influenza may be responsible for up to 42% of upper respiratory tract infections in HSCT recipients [2,3] and up to 48% of those in SOT recipients during the winter [4–6]. Progression to lower respiratory tract infection is common, with viral pneumonia reported in 29–38% of HSCT patients [2,7] and 47% of SOT patients [8]. Complications of influenza can include bacterial and fungal pneumonia [8] in addition to acute [8–12] or chronic allograft rejection [8,13]. Hospitalization is more frequent in transplant patients, with immunosuppression being recognized as a common underlying factor in patients hospitalized with pandemic (H1N1) 2009 influenza [14,15]. Mortality secondary to influenza is observed in up to 28% of HSCT recipients with influenza and lower respiratory involvement [7] and up to 23% of paediatric SOT recipients with influenza [16].

Vaccination to prevent influenza is recommended for all immunocompromised individuals [15,17,18], but diminished serological responses have been reported in both SOT [19] and HSCT recipients, especially early after transplantation [20–23]. Antiviral prophylaxis could be protective against influenza in these patients. Oseltamivir is effective for prophylaxis [24–27] and is generally well-tolerated in immunocompetent patients [28]. Oseltamivir also has a low potential for clinically relevant pharmacokinetic interactions with...
coadministered medications [29–31], including commonly used immunosuppressive drugs [32]. Two case series of transplant patients suggest that prophylaxis is well-tolerated and associated with a low frequency of influenza infection [33,34]. Antiviral prophylaxis has been recommended by recent guidelines as an alternative to vaccination for the prevention of seasonal or pandemic influenza in immunosuppressed persons [15,17,35]. To address the prolonged periods of potential exposure during community circulation of influenza, we conducted a prospective randomized double-blind placebo-controlled trial to evaluate the efficacy and safety of a 12-week course of oseltamivir prophylaxis in HSCT and SOT recipients.

Methods

Study design

This prospective randomized double-blind placebo-controlled study was conducted between 17 January 2007 and 3 June 2008 at 44 centres in the US, Israel and Europe (see Additional file 1 for a list of all sites). Independent ethics committee approval was obtained for the study protocol and associated materials at all sites.

Subjects

Recipients of liver, kidney, or liver–kidney transplants or allogeneic HSCT who were ≥1 year old and were receiving ongoing immunosuppression or not otherwise immune reconstituted were enrolled into the study. All subjects had to provide written informed consent (parents or guardians for minors). Females of reproductive potential had to have a negative pregnancy test and agree to effective contraception throughout the study and for one reproductive cycle afterwards. Enrolment began when local surveillance indicated that influenza had begun circulating in the community (no threshold of influenza cases was set for initiation of enrolment) and subjects had to have a negative rapid test for influenza before randomization.

Subjects were excluded if they had symptoms suggestive of influenza-like illness (for example, cough or nasal congestion) or fever (≥37.2°C), transplant rejection or engraftment failure, evidence of veno-occlusive disease, acute or chronic extensive graft-versus-host disease, comorbid conditions that could affect graft function, or severe renal insufficiency (creatinine clearance <10 ml/min in adults or <10 ml/min/1.73 m² in children). Vaccination against influenza was not permitted in the 4 weeks prior to randomization because seroconversion due to the vaccine could not be distinguished from influenza infection. Other exclusion criteria were uncontrolled opportunistic infections, HIV infection, malignancy or uncontrolled vascular, neurologic or pulmonary disease, or gastrointestinal disorders that might interfere with the absorption of oral medications. SOT was not permitted in the 6 months before randomization, and HSCT subjects had to have left hospital following transplantation, so that patients were more likely to be stable and have fewer underlying medical conditions. Influenza antivirals were not permitted in the 2 weeks prior to randomization and the study drug, used as per the protocol, was the only influenza antiviral permitted during the study, that is, there could be no therapeutic use of oseltamivir or zanamivir. Concomitant use of probenecid or investigational drugs was prohibited, and vaccination against influenza was not permitted after randomization during the study.

Interventions and study conduct

Once enrolled, subjects were randomized 1:1 in a blinded fashion to oseltamivir or placebo once daily for 84 days (12 weeks). Children 1–12 years received oseltamivir at the approved weight-based unit doses (30 mg for those ≤15 kg, 45 mg for those >15 kg to 23 kg and 60 mg for those >23 kg to 40 kg) in the form of a suspension once daily. Adults and adolescents ≥13 years received 75 mg doses of oseltamivir in capsule form once daily.

At baseline, subjects were tested for influenza by a rapid antigen test (QuickVue® Influenza A+B; Quidel Corporation, San Diego, CA, USA), by nasal and throat swabs for viral detection (reverse transcriptase [RT]-PCR) and, if possible, by viral culture. A blood sample for determination of haemagglutinin antibody inhibition titre and safety labs was also obtained. Subjects recorded symptoms, oral temperatures (using a study supplied thermometer) and dosing times once daily on diary cards. Subjects made further scheduled visits on days 7, 14, 28, 42, 56, 70, 84 (the final day of dosing) and day 112. During each visit, nasal and throat swabs were collected for viral detection, vital signs and influenza symptoms recorded, diary cards reviewed and subjects questioned about adverse events (AEs) and concomitant medications; additional safety laboratory measures were collected once a month and repeat haemagglutinin antibody inhibition titres were collected at the final visit. Subjects were encouraged to make unscheduled visits if they experienced influenza-like symptoms, during which vital signs were recorded and nasal and throat swabs were collected. At the discretion of the caring physician, any subject who developed symptoms of influenza could be withdrawn from the study and treated. All subjects received routine transplant care at the discretion of their physician.

Laboratory assessments

All samples were tested for the presence of influenza virus by influenza A and B type-specific real-time RT-PCR (TaqMan EZ real-time RT-PCR; Applied
infection [40]. A fourfold rise in influenza-specific anti-
order to limit variation in the preparation and analysis
laboratory followed a standard operating procedure in
haemagglutinin antibody inhibition. All analyses were
available H1N1, H3N2 and B influenza strains in the
ence of antibodies directed against the most recent and
All sera from enrolled subjects were tested for the pres-
amples taken from each patient at baseline, day 56
during prophylaxis, and at the day 112 follow-up visit.
positive samples were further analysed by virus culture
in Madin–Darby canine kidney (MDCK) cells to deter-
multiple infectious virus titre [37]. All samples positive in
influenza A RT-PCR were also subtyped by real-time
PCR using influenza A haemagglutinin H1- or H3-
specific primers and probes [38].

In cases where virus could be detected by culture on
MDCK cells at >1 time point during the dosing period,
neuraminidase activity and inhibitory potency of oseltamivir carboxylate were determined using a
MUNANA substrate-based fluorescent enzyme assay and virus collected from MDCK culture supernatant,
using established methods [39]. Inhibitory potency of
oseltamivir was expressed as 50% inhibitory concentra-
tion (IC50) value and compared with the potency of
hibition for a reference virus strain (influenza A/
Ned/306/00[H1N1] and influenza B/Ned/022/95). Influenza A viruses (H1N1 or unknown subtype) were
studied for the H275Y mutation using mutation spe-
fic primers and probes [38].

Quantitative serology (measurement of the titre of
influenza-specific antibodies) was carried out on serum samples taken from each patient at baseline, day 56
during prophylaxis, and at the day 112 follow-up visit.
All sera from enrolled subjects were tested for the pres-
ance of antibodies directed against the most recent and
available H1N1, H3N2 and B influenza strains in the
haemagglutinin antibody inhibition. All analyses were
performed in batches at the end of the study and the
aboratory followed a standard operating procedure in
order to limit variation in the preparation and analysis
of samples. A fourfold rise in influenza-specific anti-
body titre was considered to be positive for influenza
fection [40].

End points and analysis populations
Efficacy end points were the incidence of laboratory-
confirmed clinical influenza (LCCI) and the incidence of
laboratory-confirmed influenza (LCI). Clinical influenza
was defined as fever ≥37.2°C with cough and/or
usal congestion. Laboratory confirmation of influenza
was established by positive viral culture of samples
lected within 2 days of symptom onset/last dose,
≥4-fold rise in antibody titre at any time during the
trial, a positive RT-PCR test, or a combination of these
actors. Safety was assessed by AE reporting and labo-
atory parameters. Influenza virus isolates were tested
for phenotypic and, where necessary, genotypic resis-
tance to oseltamivir.

The primary end point was the incidence of clinical
influenza that was laboratory confirmed by viral culture
and/or serology in the intent-to-treat (ITT) population,
as defined below. This protocol-specified definition did
not require confirmation of infection by RT-PCR. The
ITT population comprised all randomized subjects who
received >1 dose of study medication and had ≥1 post-
baseline efficacy assessment. The intent-to-treat not
infected at baseline (ITTNAB) population comprised
all subjects in the ITT population who were influenza-
negative at baseline by viral culture and excluded all
subjects who were influenza positive by RT-PCR. The
per protocol (PP) population comprised all ITT subjects
without major protocol violations that had the poten-
tial to impact on efficacy. Safety was assessed in subjects
who received ≥1 dose of study medication and had a
post-baseline safety assessment.

Statistical analyses
Using a two-group, continuity-corrected χ2 test with a
5% two-sided significance level, 470 subjects (235
per group) would provide 80% power to detect a sig-
nificant difference between the oseltamivir and placebo
groups, assuming attack rates of 7.0% for placebo and
1.4% for oseltamivir (estimated from Peters et al. [41]).
The Fisher’s exact test was used for categorical values.
The 95% CIs were calculated using a method combining
Wilson score intervals without continuity correction
for the two proportions being compared [42].

Results
Subject disposition and baseline demographics
A total of 477 subjects were enrolled: 238 were rand-
omized to placebo and 239 to oseltamivir (Figure 1).
Two subjects in the oseltamivir group were excluded
from the ITT population because of a lack of efficacy
data. Seven subjects in the placebo group and five in
the oseltamivir group were positive for influenza by
RT-PCR at baseline, despite a negative rapid antigen
test, and were excluded from the ITTNAB and PP
populations. Of these 12 subjects, 8 were only PCR-
positive for influenza at baseline, three remained posi-
tive at day 7 but were negative at all subsequent visits,
and 1 subject on placebo was positive for influenza A
at baseline and positive for influenza A and B at day
56. Overall, 11 of the 12 subjects completed the study
and one subject on placebo withdrew due to an AE on
day 53. In total, 30 subjects in the placebo arm and 19
in the oseltamivir arm were excluded from the PP
population for having laboratory-confirmed influenza at
baseline or for major protocol violations or deviations
that had the potential to affect efficacy, for example,
six placebo and five oseltamivir subjects who received
immunoglobulin treatment.

Baseline demographics for the ITT population were
well balanced between the two arms (Table 1). Most
subjects were male (66%), adult (96%) and SOT recipi-
ents (81%); 40% were vaccinated. Immunosuppressive
drug use within 12 months of the baseline assessment

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was reported with a similar frequency in both groups. Most subjects (454 [95.6%]), were ≥80% compliant with the prophylaxis regimen. Influenza A (H1), A (H3) and B were all detected as breakthrough infections at baseline (Table 1). These three subtypes cocirculated worldwide during the study period; influenza A (H1) predominated in the US in 2006–2007 and in Europe in 2007–2008, while influenza A (H3) was most commonly reported in Europe in 2006–2007 and in the USA in 2007–2008 [43,44].

**Figure 1. Flow of participants through the study**

- **USA, n=140**
- **Europe, n=337**
- **Total recruitment, n=477**
- **Randomized to placebo, n=238**
- **Randomized to oseltamivir, n=239**
- **ITT, n=238**
- **ITT, n=237**
- **PCR-positive at baseline, n=7**
- **PCR-positive at baseline, n=5**
- **ITTNAB, n=231**
- **ITTNAB, n=232**
- **Per protocol, n=208**
- **Per protocol, n=220**
- **Safety population enrolled as treated, n=237**
- **Safety population enrolled as treated, n=238**
- **35 Patients withdrawn, 14 due to AEs**
- **18 Patients withdrawn, 7 due to AEs**

Subjects are summarized in the group to which they were randomized. One subject was randomized to placebo and received oseltamivir; that subject was analyzed in the oseltamivir treatment group for the safety population analysis. *Patients with major violations/deviations confounding efficacy. AE, adverse event; ITT, intent-to-treat; ITTNAB, intent-to-treat not infected at baseline.*
Efficacy
Regarding the primary end point, LCCI by viral culture and/or serology in the ITT population, very few subjects (12 in total) had LCCI: 7 (2.9%) in the placebo group (5 SOT and 2 HSCT recipients) and 5 (2.1%) in the oseltamivir group (3 SOT and 2 HSCT recipients; Table 2). The difference in proportions between the groups was not statistically significant (95% CI -2.3, 4.1). The only significant difference in LCCI was detected by RT-PCR alone in the ITTNAB population, where an 85.8% treatment effect of oseltamivir was observed compared with placebo (95% CI 0.1, 5.7; Table 2). All other analyses based on this end point, including LCCI by viral culture alone and RT-PCR alone, showed no significant difference between the study groups. For the LCI end point (ITT population),

Table 1. Baseline demographics and clinical characteristics in the intent-to-treat population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=238)</th>
<th>Oseltamivir (n=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>48.9 (1–74)</td>
<td>49.4 (1–76)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>152 (64)</td>
<td>163 (69)</td>
</tr>
<tr>
<td>Transplant type</td>
<td></td>
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</tr>
<tr>
<td>SOT, n (%)</td>
<td>195 (82)</td>
<td>193 (81)</td>
</tr>
<tr>
<td>HSCT, n (%)</td>
<td>43 (18)</td>
<td>44 (19)</td>
</tr>
<tr>
<td>Median time post-SOT transplant, days (range)</td>
<td>1,104.5 (110–10,011)</td>
<td>1,379.0 (188–9,589)</td>
</tr>
<tr>
<td>Median time post-HSCT transplant, days (range)</td>
<td>424.0 (49–3,204)</td>
<td>367.0 (40–5,486)</td>
</tr>
<tr>
<td>Vaccinated, n (%)</td>
<td>98 (41)</td>
<td>93 (39)</td>
</tr>
</tbody>
</table>

Immunosuppression
Calcineurin inhibitor (CyA, FK506), n (%) 151 (64) 143 (60)
Sirolimus, n (%) 29 (12) 27 (11)
Mycophenolate mofetil, n (%) 109 (46) 114 (48)
Corticosteroids, n (%) 103 (43) 92 (39)
Influenza type of breakthrough infections:
A/H1N1, n (%) 6 (2.5) 11 (4.6)
A/H3N2, n (%) 9 (3.8) 9 (3.8)
B, n (%) 16 (6.7) 10 (4.2)

Table 2. Summary of outcomes for laboratory-confirmed clinical influenza by analysis population and method of laboratory confirmation

<table>
<thead>
<tr>
<th>Method of laboratory confirmation and population</th>
<th>Placebo, n(total n (%)</th>
<th>Oseltamivir, n(total n (%)</th>
<th>Treatment effect, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral culture and/or serology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT†</td>
<td>7/238 (2.9)</td>
<td>5/237 (2.1)</td>
<td>28.3</td>
<td>-2.3, 4.1</td>
</tr>
<tr>
<td>ITTNAB</td>
<td>7/231 (3.0)</td>
<td>4/232 (1.7)</td>
<td>43.1</td>
<td>-1.7, 4.6</td>
</tr>
<tr>
<td>PP</td>
<td>6/208 (2.9)</td>
<td>4/220 (1.8)</td>
<td>37.0</td>
<td>-2.1, 4.5</td>
</tr>
<tr>
<td>Viral culture and/or serology and/or RT-PCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT†</td>
<td>8/238 (2.4)</td>
<td>5/237 (2.1)</td>
<td>37.2</td>
<td>-1.9, 4.6</td>
</tr>
<tr>
<td>ITTNAB</td>
<td>8/231 (3.5)</td>
<td>4/232 (1.7)</td>
<td>50.2</td>
<td>-1.4, 5.1</td>
</tr>
<tr>
<td>RT-PCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT†</td>
<td>7/238 (2.9)</td>
<td>2/237 (&lt;1.0)</td>
<td>71.3</td>
<td>-0.6, 5.2</td>
</tr>
<tr>
<td>ITTNAB</td>
<td>7/231 (3.0)</td>
<td>1/232 (&lt;1.0)</td>
<td>85.8</td>
<td>0.1, 5.7</td>
</tr>
<tr>
<td>Viral culture</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ITT†</td>
<td>4/238 (1.7)</td>
<td>1/237 (&lt;1.0)</td>
<td>74.9</td>
<td>-0.9, 3.8</td>
</tr>
<tr>
<td>ITTNAB</td>
<td>4/231 (1.7)</td>
<td>1/232 (&lt;1.0)</td>
<td>75.1</td>
<td>-0.9, 4.0</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ITT†</td>
<td>3/238 (1.3)</td>
<td>5/237 (2.1)</td>
<td>–</td>
<td>-3.7, 1.8</td>
</tr>
<tr>
<td>ITTNAB</td>
<td>3/231 (1.3)</td>
<td>4/232 (1.7)</td>
<td>–</td>
<td>-3.2, 2.2</td>
</tr>
</tbody>
</table>

†The primary end point was intent-to-treat (ITT). ITTNAB, intent-to-treat not infected at baseline; PP, per protocol; RT, reverse transcriptase.
significantly fewer subjects in the oseltamivir group were influenza-positive by viral culture alone or RT-PCR alone than in the placebo group (Table 3); the associated relative reductions in the risk of LCI with oseltamivir prophylaxis were 88.8% and 79.9%, respectively.

Of the 39 illness visits, only eight placebo subjects and none of the oseltamivir subjects were positive for influenza. Influenza-like symptoms caused by other viruses circulating during the influenza season were therefore responsible for the majority of illness visits. In addition, among those who were positive for influenza by serology (at any time point) most had only mild influenza symptoms, but four placebo and six oseltamivir subjects were asymptomatic throughout the study.

Resistance
Viral samples from 22 subjects (11 in each study group) with LCI at >1 time point (any method) or infection with influenza A (H1N1 or unknown subtype) were tested for resistance mutations. Two subjects, both receiving placebo, had positive viral cultures at >1 time point during the dosing period. Case 1 tested positive for influenza A/H1N1 by viral culture and RT-PCR on days 7 and 14 and by RT-PCR alone on day 28, and case 2 tested positive for influenza B by viral culture and RT-PCR on days 7 and 14 and by RT-PCR alone on day 28, and for influenza A/H1N1 by viral culture and RT-PCR on days 42 and 56. Phenotypic analysis of the viruses from these two cases indicated that all virus samples tested were sensitive to inhibition by oseltamivir carboxylate. One additional subject in the placebo group and another in the oseltamivir group had a breakthrough infection with an A/H1N1 with an H275Y mutation; A/H1N1 with the H275Y mutation was circulating during the period of study. Case 1 was a 16-year-old male in the oseltamivir group who was 1-year post-HSCT for acute myeloid leukaemia. A nasopharyngeal sample collected on day 7 tested PCR- and culture-positive for influenza A/H1N1. A second sample collected on day 14 tested PCR-positive for influenza A subtype indeterminate. All other nasopharyngeal samples (including the baseline sample) tested PCR-negative. Upper respiratory tract infection was reported on day 5 and abdominal pain and diarrhoea (lasting for 2 days only) were reported on day 7. All symptoms were mild, resolved without treatment or complication and were absent by day 30. Case 2 was a 39-year-old male in the placebo group who was almost 9 years post-HSCT for chronic myeloid leukaemia. A nasopharyngeal sample collected on day 38 tested PCR- and culture-positive for influenza A/H1N1. All other samples (including the baseline sample) tested PCR-negative. Upper respiratory tract infection was

<table>
<thead>
<tr>
<th>Method of laboratory confirmation</th>
<th>Placebo (n=238), n (%)</th>
<th>Oseltamivir (n=237), n (%)</th>
<th>Treatment effect, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-PCR</td>
<td></td>
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<tr>
<td>Overall*</td>
<td>20 (8.4)</td>
<td>4 (1.7)</td>
<td>79.9</td>
<td>2.8, 11.1</td>
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<tr>
<td>Clinical case</td>
<td>7 (2.9)</td>
<td>2 (&lt;1.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infection with fever</td>
<td>2 (&lt;1.0)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infection with symptoms</td>
<td>4 (1.7)</td>
<td>1 (&lt;1.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>7 (2.9)</td>
<td>1 (&lt;1.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of samples from routine visit</td>
<td>14</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Viral culture</td>
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</tr>
<tr>
<td>Overall*</td>
<td>9 (3.8)</td>
<td>1 (&lt;1.0)</td>
<td>88.8</td>
<td>0.7, 6.6</td>
</tr>
<tr>
<td>Clinical case</td>
<td>4 (1.7)</td>
<td>1 (&lt;1.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infection with fever</td>
<td>2 (&lt;1.0)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infection with symptoms</td>
<td>1 (&lt;1.0)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (&lt;1.0)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of samples from routine visit</td>
<td>5</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Serology</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall*</td>
<td>20 (8.4)</td>
<td>29 (12.2)</td>
<td>–</td>
<td>-9.4, 1.7</td>
</tr>
<tr>
<td>Clinical case</td>
<td>3 (1.3)</td>
<td>5 (2.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infection with fever</td>
<td>5 (2.1)</td>
<td>7 (3.0)</td>
<td>–</td>
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<tr>
<td>Infection with symptoms</td>
<td>7 (2.9)</td>
<td>6 (2.5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>5 (2.1)</td>
<td>11 (4.6)</td>
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<td>–</td>
</tr>
<tr>
<td>Number of samples from routine visit</td>
<td>20</td>
<td>29</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>36 (15.1)</td>
<td>30 (12.7)</td>
<td>16.3</td>
<td>-3.8, 8.7</td>
</tr>
</tbody>
</table>

*Breakthrough infections in the intent-to-treat not infected at baseline (ITTNAB) population by reverse transcriptase (RT)-PCR (placebo, 13 solid organ transplant [SOT] and 4 haematopoietic stem-cell transplant [HSCT]; oseltamivir, 2 SOT and 1 HSCT), viral culture (placebo, 5 SOT and 2 HSCT; oseltamivir, 0 SOT and 1 HSCT) and serology (placebo, 9 SOT and 7 HSCT; oseltamivir, 22 SOT and 6 HSCT).
reported on day 31 and a 5-day course of ciprofloxacin was initiated. Symptoms resolved without complication and were absent on day 38. Both subjects were from the same investigative site and both completed the study.

Safety and tolerability
Overall, the incidence of AEs was comparable between the oseltamivir and placebo arms (55% versus 58%, respectively; Table 4). The most common AEs were gastrointestinal disorders (21% and 22%, respectively), infections and infestations other than influenza (18% and 19%, respectively), and general disorders (12% and 11%, respectively). Serious adverse events (SAEs) occurred with a comparable frequency in the two arms (8% and 10%, respectively; Table 5). Two placebo recipients died while off study drug: a 58-year-old female HSCT recipient, who discontinued study medication on day 55, died on day 83 due to recurrent acute myeloid leukaemia and a 47-year-old female liver transplant recipient, who discontinued study medication on day 15, died on day 65 due to septic shock. Both deaths were considered unrelated to the study medication. No deaths occurred in oseltamivir recipients during the study.

A total of 7 (2.9%) and 14 (5.9%) subjects in the oseltamivir and placebo groups, respectively, withdrew for safety reasons, all due to AEs. In total, 11 (4.6%) oseltamivir recipients and 21 (8.9%) placebo recipients withdrew for non-safety reasons, typically due to refusal of treatment (7 oseltamivir and 9 placebo recipients), failure to return (5 placebo recipients) or development of influenza-like illness (1 oseltamivir and 2 placebo recipients). No subjects in the oseltamivir group suffered transplant rejection, compared with 4 (1.7%) in the placebo group. Of these, one occurred off treatment, 5 days after the last dose. Graft-versus-host disease was reported in 4 (1.7%) oseltamivir recipients (three new events, one worsening of a baseline condition; all subjects completed the study) and 4 (1.7%) placebo recipients (three of which were considered to be SAEs). Mean values for laboratory parameters were generally within normal ranges, with little variation over time. Five subjects (two placebo and three oseltamivir) had grade 3 or 4 shifts from baseline (mostly transient shifts in alanine aminotransferase, aspartate aminotransferase or haemoglobin), of whom three had laboratory-confirmed influenza (data not shown).

Discussion
In the current study, the difference in the frequency of LCCI confirmed by viral culture and/or serology in the ITT population (primary end point) was not statistically significant between the oseltamivir prophylaxis

<table>
<thead>
<tr>
<th>Table 4. Adverse events of all grades with ≥5% incidence in either arm in the safety population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td>All body systems</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Infections and infestations</td>
</tr>
<tr>
<td>General disorders</td>
</tr>
<tr>
<td>Respiratory disorders</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
</tr>
<tr>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Investigations</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
</tr>
</tbody>
</table>

Data are n (%).

<table>
<thead>
<tr>
<th>Table 5. Serious adverse events with ≥1% incidence in either arm in the safety population</th>
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</thead>
<tbody>
<tr>
<td><strong>Serious adverse event</strong></td>
</tr>
<tr>
<td>All body systems</td>
</tr>
<tr>
<td>Infections and infestations</td>
</tr>
<tr>
<td>Musculoskeletal disorders</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>Respiratory disorders</td>
</tr>
<tr>
<td>Deaths</td>
</tr>
</tbody>
</table>

Data are n (%). A 58-year-old female on study day 83 (off-treatment), secondary to recurrent acute myeloid leukaemia and 47-year-old female on study day 65 (off-treatment), secondary to septic shock.
treated with oseltamivir and acquired infection during the naturally resistant virus. The second subject was received placebo and likely acquired infection during periods when the naturally-resistant seasonal A/...an H275Y resistance mutation. In the current study, breakthrough infections in infection, thereby reducing the risk of resistance emergence. In the current study, breakthrough infections with viruses containing the H275Y resistance mutation were identified in two subjects. Both were enrolled during periods when the naturally-resistant seasonal A/H1N1-H275Y virus was circulating. The first subject received placebo and likely acquired infection with the naturally resistant virus. The second subject was treated with oseltamivir and acquired infection during the treatment period. In this case, the development of drug resistance cannot be entirely ruled out. However, as infection was acquired during a period when the naturally resistant A/H1N1-H275Y virus was circulating and sequence analysis showed similarities, the likelihood of drug selection appears low. Both subjects cleared the virus infection, and nasopharyngeal samples collected at later time points tested influenza-virus-negative by RT-PCR and culture.

Despite the small number of resistant virus detected in the current study, it is noteworthy that the increased duration of viral shedding observed in immunocompromised hosts may encourage the selection of drug-resistant viruses and that such variants have been isolated in clinical practice from patients receiving neuraminidase inhibitors both as treatment and prophylaxis, including those infected with pandemic (H1N1) 2009 [47,52]. It is therefore essential to monitor viral samples from these patients for resistance and to encourage individuals who are receiving antiviral prophylaxis to contact their health provider if symptoms develop while on prophylaxis.

Oseltamivir prophylaxis was well-tolerated in this trial, with a comparable overall incidence of AEs (55% versus 58%) and SAEs (8% versus 10%) to placebo. The majority of events were gastrointestinal disorders (21% oseltamivir and 22% placebo) and rarely resulted in the discontinuation of therapy. This tolerability profile is consistent with other published experience with oseltamivir prophylaxis of up to 19 weeks duration in immunocompetent adults [24,26,53] and children [27], in immunocompromised subjects [33,34]. As may be expected in an immunocompromised population, the incidence of infections in our study was relatively high (18% overall, of which 4% were serious events), although there was no difference in frequency between the two groups. Overall, the rate of study withdrawal due to AEs in the oseltamivir group was low (2.9%), and was approximately half that of placebo (5.9%).

This study enrolled transplant recipients who were stable and mostly beyond the period of peak lymphopenia, but did not enrol other immunocompromised patient types. Since patients earlier post-transplant are less likely to respond to the influenza vaccine, this study provides insight that implementing antiviral prophylaxis, when patients may not be protected by available vaccines, is both a safe and potentially effective alternative. The risk of antiviral resistant viruses circulating in the community and emerging after prophylaxis is of concern, particularly with regard to the emergence of H275Y mutants that are resistant to oseltamivir. If prophylaxis is used, it should be implemented, as it was in this trial, in patients proven not to be infected with influenza at the time of initiation. Furthermore, patients with signs or symptoms of influenza should immediately contact their health provider.
seek care and be treated, potentially with alternative regimens until susceptibility can be confirmed. In this study of influenza prevention in HSCT and SOT recipients, no protective advantage of oseltamivir over placebo against LCCI could be shown, although significant reductions in the relative risk of LCI were observed. Prophylaxis was safe and well-tolerated in this vulnerable population, with a similar AE profile to placebo. Breakthrough infections with viruses containing the H275Y resistance mutation were detected in two subjects only, both of whom likely acquired infection with the naturally-resistant A/H1N1-H275Y virus that was circulating during the study period.

Acknowledgements

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Disclosure statement

MGI has undertaken unremunerated consultation for Biota, Cellex, Clarassance, GlaxoSmithKline, NexBio, Roche, Toyama and T2 Diagnostics, remunerated consultation for Abbott, Abbott Molecular, Astellas, Biogen Idec, Crucell and ViraCor, and has received research support, paid to Northwestern University (Chicago, IL, USA), from ADMA, Adamas, BioCryst, Chimerix, GlaxoSmithKline, Roche and ViraCor; he is also a paid member of the data and safety monitoring boards for Chimerix and NexBio. He has been a paid speaker for Abbott Molecular. MYS has undertaken consultancy for Astellas and has received research support, paid to Hadassah-Hebrew University Medical Center (Jerusalem, Israel), from Rafa, Genzyme and Fresenius. He has been a paid speaker for Genzyme. AN and RD are employees of Hoffman-La Roche, Inc. All other authors declare no competing interests.

Additional file

Additional file 1: A list of principal investigators who enrolled patients in this study can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-OA-2183_Ison_Add_file1.pdf.

References


