A Randomized Open Label Study Comparing the Safety, Tolerability and Pharmacokinetics (PK) of Amantadine Hydrochloride and Ribavirin with Oseltamivir Phosphate (TCAD) Administered Orally Versus Oseltamivir alone Administered Orally to Influenza A Virus Infected Hospitalized Immunocompromised Patients

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Primary: To determine the safety and tolerability of TCAD administered orally to immunocompromised patients diagnosed with influenza ASecondary: To assess the antiviral effect, the speed of symptom resolution, and the influenza complication rate of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON32938

Source
ToetsingOnline

Brief title
TOMI trial: Triple Or Monotherapy in Influenza

Condition

- Immune disorders NEC
- Respiratory tract infections

Synonym
Influenza A in immucompromised patients

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Adamas ,Adamas pharmaceuticals

Intervention

Keyword: Immuncompromised, Influenza A, Oseltamivir

Outcome measures

Primary outcome

Descriptive statistics of adverse events (AEs), drug specific AEs, and AEs

resulting in treatment interruption (CTC grading scale)

Secondary outcome

1. Viral load as a function of time as measured by qPCR and culture (TCID50 or

PFU/ml)

2. Proportion of patients not shedding replicating virus at days 5 +/-1 and 10

+/-1 (defined as negative virus culture).

3. Proportion of patients not shedding viral nucleic acids at days 5 +/-1 and

10 +/-1 (defined as having RNA copies below detection limit of 1,000 copies per

ml by RTPCR).

4. Viral resistance as a function of drug exposure, as measured by sequencing

and in vitro susceptibility testing

5. Duration of symptoms as defined in symptom survey

6. Frequency of confirmed pneumonia (radiographically with or without

laboratory/microbiological testing)

7. Duration of hospitalization

8. Days on O2/supplemental needs as measured by O2 saturation

9. Number of ICU admissions and duration

10. Days on ventilation

11. Number of deaths

12. PK of TCAD in influenza A infected immunocompromised patients

Study description

Background summary

Influenza causes annual epidemics of acute respiratory illness. In the Netherlands, both influenza A H1N1 and H3N2 subtypes circulate. Although the incidence of influenza in transplant recipients has not been assessed prospectively, large retrospective cohort studies have clearly demonstrated that transplant recipients have more prolonged shedding of influenza and have a higher rate of complications, including death, than immunocompetent patients; mortality rates have been documented to be as high as 23%. The prolonged shedding predisposes to the emergence of neuraminidase inhibitor resistant variants. Available evidence suggests that antiviral therapy is associated with reduced morbidity and mortality attributable to influenza in both stem cell and solid organ transplant patients.
Available antivirals with activity against influenza include M2 inhibitors (amantadine and rimantadine), neuraminidase inhibitors (oseltamivir and zanamivir), and ribavirin. Among immunocompetent patients, both the M2 inhibitors and neuraminidase inhibitors reduce the severity of illness, duration of fever, time to return to normal activity, quantity of viral shedding, duration of impaired activity, and complications leading to antibiotic use, particularly bronchitis.

Influenza virus resistance has been described for both the M2 inhibitors and the neuraminidase inhibitors (NAI). Resistance to the M2 inhibitor is mediated by mutations in the M2 ion channel and results in cross-resistance among all

drugs in the class. M2 inhibitor resistance developes rapidly during treatment and appears to be stable and persistent.
These features have contributed to the rapid and widespread emergence of influenza A/H3 virus resistant to M2 inhibitors that currently limits the effectiveness of this class of drugs. On the other hand, neuraminidase inhibitor resistance can occur as the result of mutations in either the NA or HA gene, does not always result in cross-resistance among all neuraminidase inhibitors, and may be more transient.

The use of combinations of antivirals has been studied in non-immunocompromised patients with the goal of minimizing emergence of resistant variants and potentiating effects on viral replication and clinical recovery (Hayden 1996).
One study prospectively studied rimantadine versus rimantadine plus nebulized zanamivir (Ison, Gnann et al. 2003). Although this study underrecruited subjects and was therefore underpowered to detect a difference between the two arms, there was a trend toward more rapid resolution of symptoms. Additionally, the two detected resistant variants to emerge on therapy were recovered from patients in the monotherapy arm.

An additional problem is the high rates (>90%) of oseltamivir resistance among circulating H1N1 viruses, current US CDC recommendations include combination treatment with oseltamivir and rimantadine as an acceptable alternative for treating H1N1 and unknown genotypes. However, given the known rapid development of amantadine and rimantadine resistance during monotherapy with these agents , this regimen carries a substantial risk of generating dual resistant viruses if used for treatment of current oseltamivir-resistant H1N1 viruses.
Adamas Pharmaceuticals Inc. has reported that the triple combination therapy (amantadine, oseltamivir, and ribavirin) is highly synergistic over specific and physiologically-relevant concentration ranges in the in vitro models (MDCK cells), and reduces the EC50 of the drugs significantly when compared to monotherapy and dual therapy.

Study objective

Primary: To determine the safety and tolerability of TCAD administered orally to immunocompromised patients diagnosed with influenza A

Secondary: To assess the antiviral effect, the speed of symptom resolution, and the influenza complication rate of combination antiviral therapy as compared to oseltamivir monotherapy, and to evaluate its pharmacokinetics.

Study design

This open label randomized study will investigate the safety, tolerability and virologic benefit of amantadine hydrochloride and ribavirin with oseltamivir

phosphate (TCAD) versus neuraminidase inhibitor monotherapy for the treatment of influenza A in up to 40 immunocompromised patients infected with influenza A (H3N2) viruses. Patients infected with influenza A (H1N1) viruses (up to 30 patients) will be treated with open-label TCAD. Reason for the distinction between H3N2 and H1N1 viruses is that nearly 100% of currently circulating H1N1 viruses are oseltamivir-resistant. Current influenza H3N2 viruses are all susceptible to oseltamivir.
Eligible immunocompromised patients diagnosed with influenza A (H3N2) virus infection, as assessed by subtype specific PCR, will be randomized to receive either TCAD (amantadine/ribavirin with oseltamivir phosphate) or oseltamivir alone for a minimum of 10 days.
Patients diagnosed with influenza A(H1N1) virus infection will receive open-label TCAD for a minimum of 10 days.
In all patients, the duration of study treatment may be extended for one additional 10 day dosing period depending on duration of symptoms, continued viral shedding (Positive Rapid Antigen or DFA), and clinician judgment.
Patients may receive study drug in the hospital or on an outpatient basis. Outpatients will return to the Clinical Study Unit at each designated outpatient study visit for study evaluations as outlined in the schedule of events (Appendix A).
Assessment of viral shedding and genotypic and phenotypic drug resistance will be performed. Nasopharyngeal swabs (or washes) and blood samples will be taken and efficacy, resistance, and safety evaluations made at intervals during the study. Peripheral venous blood samples for pharmacokinetic (PK) analysis of amantadine, ribavirin and oseltamivir carboxylate will be collected on Day 3 (or Day 4 or 5 if Day 3 is not practical) at pre-dose (trough) and at 1, 2, 4, and 8 hours following the morning dose of study drug.

Routine safety monitoring (including AE reporting, clinical laboratory tests, vital signs, and O2 levels) will be conducted during and after dosing in all patients. A final safety assessment will occur approximately 30 days after the final dose of study drug. A Data Safety Monitoring Board (DSMB) will monitor patient safety throughout the duration of the study.

Intervention

- Nasopharyngeal swabs (or washes)
- Peripheral venous blood samples will be drawn from indwelling catheters or by direct venipuncture into collection tubes
- TCAD (Amantadine 75 mg q8h orally, Ribavirin 200 mg q8h orally en Oseltamivir 50 mg q8h orally) versus Oseltamivir alone 50 mg q8h orally.

Study burden and risks

The nonclinical and clinical pharmacology, pharmacokinetics, and safety of amantadine HCl, oseltamivir phosphate, and ribavirin have been well studied.

There do not appear to be overlapping or synergistic toxicities between the drugs, and therefore there is no expectation that the drugs given together should have increased safety concerns compared to the drugs given alone.

Several studies describe the safety and/or the pharmacokinetics of double-combination therapy for the treatment of viral infections: ribavirin with amantadine (Adinolfi, Utili et al. 2003; Engler, Flechtenmacher et al. 2004; Thuluvath, Maheshwari et al. 2004; Oguz, Cicek et al. 2005; Younossi, McCullough et al. 2005), amantadine with oseltamivir (Morrison, Roy et al. 2007), and oseltamivir with ribavirin (Poutanen, Low et al. 2003). These studies revealed little evidence of a clinically significant safety issues posed by multiple administrations of this triple combination using labeled doses of each drug product.
An open-label, single dose, parallel-group crossover study to evaluate the safety and pharmacokinetics of single doses of amantadine 100 mg, oseltamivir 75 mg and ribavirin 600 mg and the combination of amantadine/oseltamivir/ribavirin was conducted in 42 healthy volunteers (Adamas Pharmaceuticals, personal communication). The study treatments in this trial were safe and well tolerated. There were no significant treatment-emergent adverse events, deaths, or serious adverse events. The results of this study indicated that the single dose pharmacokinetics of amantadine, oseltamivir, oseltamivir carboxylate, and ribavirin are not altered when the three drugs are administered together.
From understanding the metabolism of the individual components, an acceptable PK and safety profile is predicted with simultaneous administration of all three drugs.
13 times Venepuncture and 13 times nasopharyngeal swab will be done. The complications of this type interventies are minimal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age *18 years, male or female.
2. Able to provide informed consent
3. Immunocompromised.
4. Positive influenza subtype-specific PCR test for influenza A H3N2 or H1N1 virus.
5. Female patients must be surgically sterile or clinically post-menopausal for at least 2 years, or, if of child-bearing potential or perimenopausal who use any sort of contraceptives

Exclusion criteria

1. Nausea
2. Use of antiviral influenza medications within 10 days.
3. Creatinine clearance less than 30 ml/min.
4. Current clinical evidence of a recognized or suspected uncontrolled non-influenza infectious illness with onset prior to screening.
5. Known hypersensitivity to amantadine, ribavirin, oseltamivir.
6. Women who are pregnant (positive serum or urine pregnancy test), who are attempting to become pregnant, or who are breast-feeding.
7. Psychiatric or cognitive illness or recreational drug/alcohol use.
8. Seizure disorder or history of seizure activity within 12 months prior to study participation.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	70
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rebetol
Generic name:	Ribavirin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Symmetrel
Generic name:	Amantadine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tamiflu
Generic name:	Oseltamivir
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-009985-15-NL
CCMO	NL26809.018.09