Establishing a Controlled Human Infection Model (CHIM) with a Rhinovirus challenge agent in healthy volunteers

Published: 27-10-2023
Last updated: 07-04-2024

To validate a rhinovirus controlled human infection model, investigating the time course of infectious and immunological parameters after inoculation with an RV16 inoculum and to compare the response of volunteers without (part A) and with (part B)...

Ethical review	Approved WMO
Status	Pending
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON56012

Source
ToetsingOnline

Brief title
Rhinovirus CHIM validation study

Condition

- Viral infectious disorders

Synonym
respiratory tract infections, Viral infections

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Centre for Human Drug Research;Leids Universitair Medisch Centrum

Intervention

Keyword: CHIM, Respiratory tract infections, Rhinovirus

Outcome measures

Primary outcome

To identify the inoculation dose needed to induce rhinovirus infection in 80% of exposed healthy adult volunteers without pre-existing immunity to RV16.

Primary endpoints for the primary objective:

• Infection rate (number and frequency of subjects with rhinovirus infection as assessed by PCR) for each inoculation dose in subjects seronegative for RV16 (part A)

Secondary outcome

• To investigate the safety and tolerability of controlled infection after inoculation with RV16

• To identify the inoculation dose needed to induce symptomatic rhinovirus infection in exposed healthy adult volunteers without pre-existing immunity to RV16.

• To assess the rhinovirus kinetics in nasal wash, nasal swab and saliva

• To assess the effect of background immunity on rhinovirus kinetics in nasal wash, swab and saliva (part B)

• To characterize the disease severity and duration of RV16 challenge in healthy adult volunteers

• To assess the effect of background immunity on disease severity and duration (part B)

Secondary endpoints for the secondary objectives:

• Nature, frequency and severity of (serious) adverse events

• Self-reported symptoms (assessed by the Jackson score and WURSS-21

questionnaire) that are classified as severe.

• Clinical laboratory test

• Vital signs

• Physical examination, symptom directed and on indication

• Concomitant medication

• Self-reported nasal pain assessed by a visual analogue scale (VAS)

• Attack rate (proportion of subjects with a symptomatic rhinovirus infection)

for each inoculation dose in subjects seronegative for RV16 at baseline (part A)

• Rhinovirus viral load onset, peak and duration as determined by serospecific

qPCR

• Self-reported symptoms assessed by the Jackson score and

WURSS-21questionnaire. These symptoms will not be reported as adverse events.

• Infection rate for each inoculation dose in subjects seropositive for RV16

(part B)

• Attack rate for each inoculation dose in subjects seropositive for RV16 (part

B)

Study description

Background summary

Human Rhinovirus (HRV) is a single strand, positive sense RNA-virus, and the etiological agent responsible for 60% of upper respiratory tract infections

(URTIs). HRV transmission occurs primarily through direct contact or aerosols, achieving infection mainly by intranasal or conjunctival inoculation. Over 150 strains of Rhinovirus have been identified, divided over three species, HRV-A, -B and -C.
URTIs caused by HRV occur throughout the year; in temperate regions, peaks occur in early fall and late spring. In the general population, HRV infection may occur more than once per year: on average, people experience 2 to 3 URTIs yearly. Symptoms of HRV infection are generally referred to as *the common cold*, including nasal congestion, rhinorrhea, sore throat, coughing or headache. Though infections are generally self-limiting, symptoms can significantly impair quality of life and productivity. In addition, HRV can induce more serious complications, such as pneumonia and otitis media, in vulnerable individuals, such as young children and immunocompromised patients. Moreover, HRV is the primary trigger for asthma exacerbations and plays a major role in exacerbations of COPD. This way, HRV amounts to a significant economic burden; given this substantial impact on vulnerable patients and society in general, extensive efforts have been undertaken do develop effective therapeutic interventions. Regrettably, despite these endeavors, no treatment has demonstrated effectiveness in clinical trials to date.
The development of treatments for infectious diseases has proven to be highly cost-effective. Rapid availability of these pharmaceuticals can limit the impact of infectious diseases; in the case of future pandemics, a health crisis can be mitigated by swift development and testing of vaccines. The controlled human infection model (CHIM) is an innovative and effective method for testing products in early clinical phase. CHIMs are frequently conducted using respiratory viruses, alternatively named *the viral challenge model* or *experimental infection studies*. In this context, CHIMs offer a scientific value that transcends conventional phase 1 studies; the controlled setting facilitates close safety monitoring, as well as the evaluation of efficacy endpoints and extensive viral and immunological assessments. This allows for an early evaluation and understanding of the efficacy of new pharmaceuticals, resulting in early assessment of whether these pharmaceuticals will be worth their investment.
URTIs in general, caused by viruses such as HRV, Influenza, Respiratory Syncytial Virus (RSV) or SARS-CoV-2, have similar symptomatologic and virological properties. A CHIM for rhinovirus can be of value to test pharmaceuticals directed at HRV, or respiratory viruses in general, such as viral entry blockers or nasally delivered antibodies. Despite a considerable body of literature reporting the use of CHIMs using HRV few compounds have demonstrated efficacy, and thus far, none have been licensed for clinical use. As these CHIMs are rather heterogenous considering their defined endpoints and used methods, their reproducibility remains limited, and the need for a validated rhinovirus CHIM to study drug efficacy in early clinical development persists.

Study objective

To validate a rhinovirus controlled human infection model, investigating the time course of infectious and immunological parameters after inoculation with an RV16 inoculum and to compare the response of volunteers without (part A) and with (part B) pre-existing immunity to RV16.

Study design

This is a two part, randomized, open-label validation study.

In Part A, healthy volunteers with low background immunity for RV16 will be included to identify the inoculation dose needed for an infection rate of >=80%. A maximum of 2 sequential dose-escalating cohorts will be formed. Each cohort will consist of a maximum of 10 subjects; one pilot group (n=3) and a confirmatory group (n=7).

After a dose level is established with an infection rate of at least 80%, the challenge will be repeated in Part B, again with dose-escalation, again with a pilot group of 3 and a confirmatory group of 7 participants, who are all seropositive for RV16.

In both parts, subjects will remain in self-isolation between baseline assessments and inoculation to prevent them contracting a different respiratory virus that may interfere with study data.

Intervention

Volunteers will be inoculated intranasally with escalating doses of the GMP-produced wild-type RV16-strain.

Study burden and risks

The airways are frequently exposed to respiratory viruses, which comprises about 150 different species of rhinoviruses, various strains of influenza and respiratory syncytial virus (RSV) A and B and some minor species. RV16 belongs to a major group of rhinoviruses that infects cells via the cell membrane bound protein ICAM-1. RV16 infects predominantly airway epithelial cells and to a lesser extent airway macrophages. Typically, the resulting innate and adaptive immune responses ensure that RV16 is cleared within 10 days after infection without any health issues apart from a common cold. In patients with respiratory diseases (asthma, COPD and cystic fibrosis) the infection may be prolonged, and the immune response is exaggerated resulting in a period of acute worsening of their symptoms. RV16 is a natural virus and about 50% of the human population has been infected with RV16 as based on the presence of antibodies to RV16.

Experimental RV16 infection has often been used to challenge healthy

individuals, mild (allergic) asthmatics and COPD patients. The rationale for using RV16 is that this rhinovirus strain causes mild common-cold symptoms as compared to other rhinovirus strains. In addition, RV16 is considered to be hardly contagious. No adverse effects of using RV16 in healthy individuals and patients have been reported.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signed informed consent prior to any study-mandated procedure;
2. Healthy male or female volunteers, 18 to 49 years of age, inclusive at screening; Good health is based upon the results of medical history, physical examination, vital signs, ECG, and laboratory profiles of both blood and urine
3. A total body weight >=50 kg and body mass index (BMI) >=18.0 and <=30.0 kg/m2 at screening;

4. All women of child bearing potential and must practice effective contraception during the course of the study;
5. Subject has adequate understanding of the procedures of the study and agrees to abide strictly thereby;
6. Subject is able to communicate well in Dutch with the investigator, and is willing to comply with the study procedures and restrictions;
7. Subject is able to tolerate the nasal wash procedure at screening;
8. Seronegative (Virus neutralizing titer <= 1:6) for RV16 at screening for part A; seropositive for RV16 (VNT >1:6) at screening in part B;
9. Willingness to stay in self-quarantine between baseline visit and day of inoculation.

Exclusion criteria

1. Any history or evidence of any clinically significant or currently active major disease, or condition that, in the opinion of the investigator, may interfere with a subject completing the study and the necessary investigations (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, and body temperature) and ECG). Minor deviations from the normal range may be accepted, if judged by the investigator to have no clinical relevance;
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including blood biochemistry, hematology and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before inclusion to confirm eligibility or judged to be clinically irrelevant;
3. Chronic respiratory disease (asthma, emphysema, COPD, chronic rhinitis or sinusitis or other reactive airway diseases) in adulthood. Childhood asthma and non-active allergic rhinitis (including hay fever) will be permitted at the discretion of the investigator;
4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;
5. Any confirmed or suspected disease or condition associated with immune system impairment, including auto-immune diseases, HIV, asplenia or recurrent severe infections;
6. Prior inoculation with a virus from the same virus family as the challenge virus;
7. Prior participation in another controlled human infection study with a respiratory virus in the preceding 6 months taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study;
8. Participation in an investigational medical product, vaccine or device study within 3 months or 5 half-lives prior to the study period (whichever is longer), or more than 4 times in the past year;
9. Any known history of anaphylaxis or any significant allergy against the

excipients of the virus challenge inoculum;
10. Any anatomic or neurologic abnormality impairing the gag reflex, or associated with an increased risk of aspiration, or any abnormality significantly altering the anatomy of the nose or nasopharynx in a substantial way that may interfere with the aims of the study and in particular any of the nasal assessments or viral challenge;
11. History of frequent epistaxis (nose bleeds) in the six months prior to inoculation and/or any history of being hospitalized due to epistaxis;
12. Any nasal or sinus surgery within 3 months prior to the viral challenge;
13. Upper or lower respiratory tract infection or febrile illness (temperature >=37.9°C), in the period of 2 weeks prior to the viral challenge;
14. Symptoms of active hay fever or other allergies that involve the airways, during screening, prior to inoculation or expected during the investigational period based on prior seasonality;
15. Use of any medications (prescription or over-the-counter [OTC]), within 14 days prior to virus inoculation, or less than 5 half-lives (whichever is longer), and during the course of the study. Exceptions are paracetamol (up to 4 gram/day) and contraceptives. Other exceptions will only be made if the rationale is clearly documented and accepted by the investigator.
16. Use of chronic (more than 14 days) systemic immunosuppressant medications within the 3 months prior to virus inoculation, or isolated (non-chronic) use within 30 days prior to day -1. Incidental use of topical, intranasal or inhalation corticosteroids may be permitted up to 14 days prior to virus inoculation (day 1) at the discretion of the investigator;
17. Receipt of any vaccine within 6 weeks prior to virus inoculation and during the course of the study during the study period and during the course of the study;
18. Receipt of blood or blood derived products (including immunoglobulin) within 180 days prior to the viral challenge;
19. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent;
20. Smokers or ex-smokers with more or equal to 5 pack years smoking history
21. Smoking in the 30 days prior to the viral challenge;
22. Positive test for drugs of abuse at screening or prior to the viral challenge;
23. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study;
24. Females who are pregnant, breastfeeding, or are planning to become pregnant during the study;
25. Sharing a household, work closely or having close contact with infants (<3 years of age), pregnant women, immune-compromised and/or clinically vulnerable elderly (>=65 years old) individuals during the course of the study.
26. Nasopharyngeal swab indicative for rhinovirus or other respiratory virus infection determined by PCR at baseline visit;
27. Any known factor, condition, or disease that might interfere with treatment

compliance, study conduct or interpretation of the results, as deemed by the investigator.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-10-2023
Enrollment:	40
Type:	Anticipated

Ethics review

Approved WMO

Date:	27-10-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL84849.058.23