A randomized, open-label, vehicle-controlled, parallel-cohort, dose-ranging study to explore the pharmacodynamics of topically applied imiquimod in healthy volunteers

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Primary objective- To explore the pharmacodynamic effects of topically applied IMQ (in combination with or without TS) - To identify dose-response relationship of topically applied IMQ Secondary objective- To assess safety and tolerability of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON43402

Source
ToetsingOnline

Brief title
Topical challenge with imiquimod in healthy volunteers

Condition

- Autoimmune disorders
- Epidermal and dermal conditions

Synonym
(dermatological challengemodel) (Skin inflammation model)

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR,Cutanea Life Sciences

Intervention

Keyword: Challenge, Imiquimod, Topical

Outcome measures

Primary outcome

To explore the pharmacodynamic effects of topically applied imiquimod and to

identify dose-response relationship.

Secondary outcome

To assess safety and tolerability of topically applied imiquimod

Study description

Background summary

The skin is the largest organ of the human body, accounting for approximately 16% of the total body weight. It plays critical roles in immunologic surveillance, protection from infection, thermal regulation, and tactile sensation. Dysfunction of the skin can lead to inflammatory skin disorders, such as atopic dermatitis and psoriasis. Pharmacological challenges have been used previously to induce local inflammatory reactions on the skin, with the purpose to develop models to mimic skin diseases temporarily for application in drug development programs. However, fully characterized suitable challenge models are not yet available.

Aldara 5% ® is a topical cream containing 50 mg/g imiquimod (IMQ). IMQ is an imidazoquinolone which is a class of immunomodulatory drugs. It mobilizes several cytokines with antiviral and tumoricidal properties. This cytokine recruitment occurs because of a highly intricate process involving the innate and adaptive immune response through cell surface receptors named toll-like receptors (TLRs) located on macrophages, Langerhans cells, and dendritic cells. TLR activation also causes a host of secondary effects on the molecular and cellular levels that are not yet fully understood. The predominant antitumor mechanism of imiquimod is specific binding to TLR-7 and TLR-8, activating the

central transcription factor, nuclear factor-kB and inducing secretion of pro inflammatory cytokines such as tumor necrosis factor alpha (TNF-*), interferon gamma (IFN-*), IFN-*, interleukin(IL)-6, IL-1a, IL-1b, IL-8, IL-12, IL-17, IL-22, IL-23 granulocyte macrophage colony-stimulating factor, and granulocyte colony-stimulating factor (innate immunity). According to literature all cytokine elevations and local effects are reversible.

IMQ is registered for various indications including basal cell carcinoma (BCC), actinic keratosis (AK) and genital and peri-anal warts. Topical administration of IMQ appears to be safe and reasonable tolerated with local skin reactions as main adverse events. Although, psoriasis exacerbations in psoriasis patients using IMQ were described previously. This not only occurred at treatment site, but also generalized. Topical IMQ on mice showed higher expression of IL-17 producing gamma-delta (**)-cells at untreated dermis, suggesting memory cells can travel to distant skin and accelerate secondary IL-17 driven response, which can lead to psoriasis exacerbation.

The overall aim of this study is the development of a challenge model to temporarily induce skin inflammation and to enable future application as proof-of-pharmacology or drug profiling in in drug developmental programs.

A recent study on healthy volunteers explored the biochemical effects of IMQ application compared to tape stripping (TS). A significant up-regulation in mRNAs encoding for interferon type I response was found for each treatment with more pronounced effect after TS. However, no assessment of IMQ in combination with TS was performed. Furthermore, relevant other pharmacodynamics and safety endpoints were omitted.

This challenge study is intended to explore the pharmacodynamic effects of topically applied IMQ and IMQ in combination with TS by means of biophysical, biochemical, imaging, clinical and patient-recorded parameters. Furthermore dose-response relationship will be identified and safety / tolerability will be assessed.

Study objective

Primary objective
- To explore the pharmacodynamic effects of topically applied IMQ (in combination with or without TS)
- To identify dose-response relationship of topically applied IMQ
Secondary objective
- To assess safety and tolerability of topically applied IMQ

Study design

This is a randomized, open-label, vehicle-controlled, parallel, dose-ranging

study.

Intervention

Application of imiquimod under occlusion

Study burden and risks

For this study, volunteers will visit the clinic 4 times, with one overnight stay period of 4 days. During visit both non-invasive and invasive examination will be performed. Some of the non-invasive assessments include blood pressure measurements, ECGs, photography of the skin, questionnaires and skun function measurements. Invasive assessments include blood samples and skin punch biopsies. In total, 4 blood samples will be taken and 6 skin punch biopsies.

The risks associated with the topical application of IMQ have been identified in healthy volunteers as well as patients with various indications for treatment, such as BCC, AK and genital warts. Treatment appears to be safe and well-tolerated, with local skin reactions including erythema, edema, vesicles, erosions/ulcerations, weeping/exudate, flaking/skaling/dryness and scabbing/crusting as main side effect. Since psoriasis exacerbations due to IMQ treatment have been described, psoriasis patients as well as patients with other auto-immune diseases and skin diseases are excluded to participate in this study to minimize potential risk(s). Furthermore, because of the potential systemic effects, IMQs mechanism of action will be explored not only at the treated skin surface, but also at a distant untreated dermal site and in venous blood (PBMCs). Adverse events due to the possible systemic effects have not been described and due to the topical route of administration with a very limited area of administration in this study (0,018% BSA) systemic effects are not expected. Therefore we assess the risks as acceptable for the subjects to participate in the study.

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

* Healthy male subjects, 18 to 45 years of age, inclusive
* Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg
* Fitzpatrick Skin type I-II (Caucasian type)
* Able to participate and willing to give written informed consent and to comply with the study restrictions.

Exclusion criteria

1. Any disease associated with immune system impairment, including auto-immune diseases, HIV and transplantation patients.
2. Family history of psoriasis
3. History of pathological scar formation (keloid, hypertrophic scar)
4. Have any current and / or recurrent pathologically, clinical significant relevant skin condition.
5. Previous use of imiquimod / resiquimod / gardiquimod
6. Known hypersensitivity to the investigational drug, comparative drug, drugs of the same class, or any of their excipients.
7. Requirement of immunosuppressive or immunomodulatory medication within 30 days prior to enrollment or planned to use during the course of the study.
8. Use of topical medication (prescription or over-the-counter [OTC]) within 30 days of study drug administration, or less than 5 half-lives (whichever is longer) in local treatment area
9. Tanning due to sunbathing, excessive sun exposure or a tanning booth within 3 weeks of enrollment.

10. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year.
11. Loss or donation of blood over 500 mL within three months prior to screening.
12. Any (medical) condition that would, in the opinion of the investigator, potentially compromise the safety or compliance of the patient or may preclude the patient*s successful completion of the clinical trial.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-04-2016
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALDARA 5% cream
Generic name:	imiquimod
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-03-2016
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-03-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-000331-41-NL
CCMO	NL56586.056.16