



Clinical trial results:

Title of the publication

Peptidase inhibitor 3 and chemokine ligand 27 may serve as biomarkers for actinic keratoses in organ transplant recipients (Eur J Dermatol. 2019 Jun 1;29(3):259-267. doi: 10.1684/ejd.2019.3559.)

former title:

Topical imiquimod 5% cream therapy versus photodynamic therapy with methyl-aminolaevulinate 16% cream of actinic keratoses in organ transplant recipients

Summary

EudraCT number	2010-024623-24
Trial protocol	AT
Global end of trial date	10 December 2018

Results information

Result version number	v1 (current)
This version publication date	29 May 2020
First version publication date	29 May 2020
Summary attachment (see zip file)	Peptidase inhibitor 3 and chemokine ligand 27 may serve as biomarkers for actinic keratoses in organ transplant recipients (Geusau_Peptidase inhibitor 3 and chemokine ligand.pdf)

Trial information

Trial identification

Sponsor protocol code	IPDTAKOTR/V04/24.09.11
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna, Department Dermatology
Sponsor organisation address	Waehringer Guertel 18-20, Vienna, Austria, 1090
Public contact	Univ. Klinik f. Dermatologie, Medizinische Universität Wien, Univ. Klinik f. Dermatologie, +43 1404007700, stanislava.tzaneva@meduniwien.ac.at
Scientific contact	Univ. Klinik f. Dermatologie, Medizinische Universität Wien, Univ. Klinik f. Dermatologie, +43 1404007700, stanislava.tzaneva@meduniwien.ac.at

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2018
Global end of trial reached?	Yes
Global end of trial date	10 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of topical imiquimod 5% cream versus photodynamic therapy with methyl-aminolaevulinate 16% cream in the treatment of actinic keratoses in OTR, each pat was his own control i.e. Molecular profiling of tissue samples in organ transplant recipients (OTR) to assess an early and minimally invasive identification of actinic keratosis (AK). The aim of this study was to compare mRNA expression profiles of genetic markers of AK before and after treatment, employing two different field-therapies, and to correlate the results with histological and clinical parameters.

Protection of trial subjects:

Ten patients (2 women and 8 men) with multiple AK and field cancerisation were enrolled into the study each patient was his own control

From the target lesions, 3-mm punch biopsies were obtained from each site initially, then at week 2 (immediately after the second PDT, and 2 weeks after the initiation of IMI, respectively), and 3 months after completion of the active treatment period. The punch biopsies were taken under local anaesthesia, and appropriate wound management was carried out.

For photodynamic therapy (PDT) as well as for photodynamic diagnosis (PDD), methyl-5-aminolevulinate 16% cream (Metvix© Cream, Galderma, France) was employed as photosensitizer, applied in a 1-mm thick layer, covering 50cm². Before the procedure, local anaesthesia (lidocaine 1%, without vasoconstrictor) was applied, if required. During illumination, cooling was carried out by the integrated air-forced cooling device and/or spray with thermal water (Avene, France).

All patients were evaluated for the intensity of pain during light exposure using a visual analogue scale (VAS), considering 0 as absence of pain and 10 as the most severe pain.

The skin areas were covered after each treatment or PDD and the patients instructed to prevent exposure to direct light for 48 hours and to apply a sunblock in the following days.

Background therapy:

Prior to initiation of the study, ketoconazole shampoo once daily and commercially available topical steroid foam was prescribed for one week for treatment of the scalp region, in order to reduce scales due to seborrheic eczema. If hyperkeratotic AKs were present at the same time, a local therapy with 10% salicyl vaseline once daily in the evening was given for one week. Afterwards there was a wash out period for a week without any local therapy.

All patients received painkillers after PDT, ef necessary

Evidence for comparator:

The reduction of the AKs in the photodynamic therapy (PDT) area vs topical imiquimod had to be assessed clinically, and mRNA expression profiles of various genetic markers before, during and 3 months after therapy were compared for the two treatment modalities.

Actual start date of recruitment	02 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited from a dedicated outpatient clinic for organ transplant recipients at the Department of Dermatology, Medical University of Vienna. The requirement was the presence of two anatomically separated contralateral areas of AKs on the face or forehead which could be selected, at a minimum distance of 5cm

Pre-assignment

Screening details:

At baseline, all patients were clinically evaluated, and two anatomically separated contralateral areas of the face or forehead were selected, at a minimum distance of 5cm, each area of comparable size and extent. A target lesion, a lesion located in the middle of this area was selected, an at least AK grade II with a diameter of at least 8 mm

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

it was an intraindividual trial; each patient was his own control

Arms

Are arms mutually exclusive?	No
Arm title	PDT-treatment

Arm description:

a distinct area of field cancerisation (Face) in organ transplant patients (OTP), treated employing PDT with two treatment cycles (two weeks apart) of methyl-aminolevulinate 16% cream-PDT
Prior to initiation of the study, ketoconazole shampoo, once daily, and commercially available topical steroid foam was prescribed for one week for treatment of the scalp region, in order to reduce scales due to seborrheic eczema

an at least AK grade II with a diameter of at least 8 mm was chosen as 'target lesion' in the treatment area and was biopsied, the 3mm tissue samples subsequently snap frozen in liquid nitrogen

From the target lesions, 3-mm punch biopsies were obtained from not only initially, but then at week 2 (immediately after the second PDT, and 3 months after completion of the active treatment period.

The treatment areas were also recorded by photodynamic diagnosis (PDD).

Arm type	Experimental
Investigational medicinal product name	methyl-5-aminolevulinate hydrochloride (methyl-aminolevulinate 16% cream-PDT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

field therapy with PDT with two treatment cycles (2 weeks apart) of methyl-5-aminolevulinate-PDT

Arm title	imiquimod
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Arm description:

An area of field cancerisation was treated with Imiquimod 5% cream (three times a week for four weeks, carried out by the patients themselves) Prior to initiation of the study, ketoconazole shampoo and topical steroid foam was prescribed for one week

The selected treatment area was recorded by photodynamic diagnosis (PDD). From a target lesions, 3-

mm punch biopsies were obtained initially, then at week 2, and 2 weeks after the initiation of Imiquimod 5% cream as well as 3 months after completion of the active treatment period.

Arm type	Experimental
Investigational medicinal product name	Imiquimod 5% Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Cutaneous use

Dosage and administration details:

Imiquimod 5% cream (three times a week for four weeks, carried out by the patients themselves)

Number of subjects in period 1	PDT-treatment	imiquimod
Started	10	10
Completed	9	9
Not completed	1	1
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups

Reporting group title	PDT-treatment
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Reporting group description:

a distinct area of field cancerisation (Face) in organ transplant patients (OTP), treated employing PDT with two treatment cycles (two weeks apart) of methyl-aminolevulinate 16% cream-PDT
Prior to initiation of the study, ketoconazole shampoo, once daily, and commercially available topical steroid foam was prescribed for one week for treatment of the scalp region, in order to reduce scales due to seborrheic eczema

an at least AK grade II with a diameter of at least 8 mm was chosen as 'target lesion' in the treatment area and was biopsied, the 3mm tissue samples subsequently snap frozen in liquid nitrogen

From the target lesions, 3-mm punch biopsies were obtained from not only initially, but then at week 2 (immediately after the second PDT, and 3 months after completion of the active treatment period.

The treatment areas were also recorded by photodynamic diagnosis (PDD).

Reporting group title	imiquimod
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Reporting group description:

An area of field cancerisation was treated with Imiquimod 5% cream (three times a week for four weeks, carried out by the patients themselves) Prior to initiation of the study, ketoconazole shampoo and topical steroid foam was prescribed for one week

The selected treatment area was recorded by photodynamic diagnosis (PDD). From a target lesions, 3-mm punch biopsies were obtained initially, then at week 2, and 2 weeks after the initiation of Imiquimod 5% cream as well as 3 months after completion of the active treatment period.

Reporting group values	PDT-treatment	imiquimod	Total
Number of subjects	10	10	10
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69.6	69.6	
standard deviation	± 7.199	± 7.199	-
Gender categorical Units: Subjects			
Female	2	2	2
Male	8	8	8

End points

End points reporting groups

Reporting group title	PDT-treatment
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Reporting group description:

a distinct area of field cancerisation (Face) in organ transplant patients (OTP), treated employing PDT with two treatment cycles (two weeks apart) of methyl-aminolevulinate 16% cream-PDT

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week for treatment of the scalp region, in order to reduce scales due to seborrheic eczema

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The treatment areas were also recorded by photodynamic diagnosis (PDD).

Reporting group title	imiquimod
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Reporting group description:

An area of field cancerisation was treated with Imiquimod 5% cream (three times a week for four weeks, carried out by the patients themselves) Prior to initiation of the study, ketoconazole shampoo and topical steroid foam was prescribed for one week

The selected treatment area was recorded by photodynamic diagnosis (PDD). From a target lesions, 3-mm punch biopsies were obtained initially, then at week 2, and 2 weeks after the initiation of Imiquimod 5% cream as well as 3 months after completion of the active treatment period.

Primary: Reduction of number of lesions after 12 months treatment compared to baseline

End point title	Reduction of number of lesions after 12 months treatment compared to baseline ^[1]
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End point description:

CRR = proportion of healed AKs compared to baseline AKs; assumption: 80% CRR for PDT and 60% CRR for Imiquimod;

alpha: 0.05, beta: 0.80

statistical method: McNemar Test, paired T-Test

End point type	Primary
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End point timeframe:

4 weeks after completion of treatment - complete response rate (CRR)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was performed within each arm (between different timepoints) but not between the arms.

End point values	PDT-treatment	imiquimod		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: percent				
median (full range (min-max))	59.8 (20 to 100)	70.8 (20 to 100)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment procedure (either during PDT or self-application of Imiquimod) and the period after - in the healing period

Adverse event reporting additional description:

There were no serious adverse effects

Tolerance for PDT was very good (local anesthesia), all except 1 pat tolerated the full Tx. Most common side effect erythema (subsided within few days). Imiquimod Th: all patients erythema; 1 pat ulceration, 2 pat flue-like symptoms

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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Reporting groups

Reporting group title	PDT-treatment
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Reporting group description:

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Reporting group title	imiquimod
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Reporting group description:

An area of field cancerisation was treated with Imiquimod 5% cream (three times a week for four weeks, carried out by the patients themselves) Prior to initiation of the study, ketoconazole shampoo and topical steroid foam was prescribed for one week

The selected treatment area was recorded by photodynamic diagnosis (PDD). From a target lesions, 3-mm punch biopsies were obtained initially, then at week 2, and 2 weeks after the initiation of Imiquimod 5% cream as well as 3 months after completion of the active treatment period.

Serious adverse events	PDT-treatment	imiquimod	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	PDT-treatment	imiquimod	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	
General disorders and administration site conditions			
ulceration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
flu-like symptom			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

we were not able to recruit the planned number of patients
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Notes: