The in vivo mechanisms that control migration of pathogenic dermal T-cells to synovial joints during psoriatic arthritis: the role of dermal lymphatic vessels.

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Objective 1. To investigate whether LECs from the skin of PsA patients, in contrast to that of PsO, are capable of inducing a homing receptor profile that favors a T-cell migratory response towards the synovial joint on skin-derived, allogenic T-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON47603

Source
ToetsingOnline

Brief title
T-cell migration from skin to joints in psoriatic arthritis.

Condition

- Autoimmune disorders
- Joint disorders
- Epidermal and dermal conditions

Synonym
ie. chronic skin inflammation with joint inflammation, psoriasis and psoriatic arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Maasstadziekenhuis
Source(s) of monetary or material Support: reumafonds aanvraag loopt nog

Intervention

Keyword: Lymphatic system, Psoriasis, Psoriatic arthritis, T-cells

Outcome measures

Primary outcome

Objective 1.

Study parameter: To establish that skin-derived and synovium-derived LECs in PsA drive the in vivo mechanisms that coordinate the programming of dermal pathogenic T-cells to adopt a synovial joint homing profile, ie. enhanced expression of CD161, CCR6, CCR7, CCR2, CXCR6, and loss of skin homing receptors such as CCR4, CCR10 and CLA(based on recent literature)

Outcome

Expected results In these experiments, we expect to find that dermal LECs from PsA patients (in contrast to PsO and controls) are capable of imprinting skin-derived T-cells with a synovial joint homing phenotype that promote their egress towards synovial joint compartments.

Secondary outcome

Objective 2. To investigate whether the induction of tissue-imprinting receptors on allogenic skin-derived T-cells, as demonstrated in Aim 1, leads to enhanced T-cell migration into the afferent lymphatic vessels of a human dermal

sheet (crawl-in assay).

Outcome:

Should an effect of PsA-induced inflammatory changes in LECs on the homing profile of these skin-derived T-cells be confirmed, this will most likely have a direct impact on the T-cell migratory response as reflected by an increased entry into afferent lymphatics in the crawl-in assay.

Objective 3. To investigate whether overlapping properties may be present in LECs from the skin, synovial tissue and lymph nodes.

Study description

Background summary

Rationale
Psoriasis (PsO) is a common inflammatory skin disease that is characterized by acanthosis, edema formation, immune cell infiltration, abnormal vascular proliferation, and remodelling of the lymphatic system. Up to ~30% of PsO patients are affected by psoriatic arthritis (PsA), a devastating form of arthritis, which leads to disability and deterioration of quality of life. The progression of PsO to PsA is poorly understood and deserves further investigation.

Hypothesis: Lymphatic endothelial cells (LECs), the core components of the dermal lymphatic vasculature, may control the transmission of pathogenic skin-derived T-cells to other anatomical sites including synovial joints and entheseal regions in PsA.

Study objective

Objective 1. To investigate whether LECs from the skin of PsA patients, in contrast to that of PsO, are capable of inducing a homing receptor profile that favors a T-cell migratory response towards the synovial joint on skin-derived, allogenic T-cells from healthy donors.

Objective 2. To investigate whether the induction of tissue-imprinting receptors on allogenic skin-derived T-cells, as demonstrated in Aim 1, leads to enhanced T-cell migration into the afferent lymphatic vessels of a human dermal sheet (crawl-in assay).

Objective 3. To investigate whether overlapping properties may be present in LECs from the skin, synovial tissue and lymph nodes.

Study design

Study design Experimental, in vitro study.
Briefly, this study investigates whether LECs from the skin of PsA patients, in contrast to that of PsO, are capable of inducing a homing receptor profile on dermal T-cells that favors a T-cell migratory response towards the synovial joint. Thus, experiments are performed, where LECs isolated from skin biopsies of control subjects or patients with PsO and PsA are co-cultured with skin-derived donor T-cells, followed by morphological analysis using flow cytometry and a functional test, ie. migration (crawl-in) assay. To rule out autologous defects (patient-specific) in the cell-cell interactions, 80 mL blood (from all participants) and synovial fluid of an inflamed joint (knee, wrist or ankle; from PsA only) will be drawn for isolating peripheral blood mononuclear cells (PBMC) to study autologous effects and measuring circulating mediators. Thus, dermal LEC and T-cells (derived from PBMC) from one patient are co-cultured.

Study burden and risks

- The expected burden from this protocol is minimized to skin biopsies and synovial biopsies (from knee joint of patients with PsA only) that are performed under local anesthesia from (peri-lesional) skin at non-sun exposed skin.
Blood collection upon insertion of a (butterfly) catheter via vein of the under arm. Potential adverse effects include small hematomas during insertion (manual pressure over the site of bleeding is an adequate treatment) and pain or skin reactions at the catheter site.
- Additional samples are taken from skin tissues that are obtained from discarded human materials (skin and synovial tissue) during surgery. Risks are not to be expected.
- Additional samples are taken from lymph node tissues that are obtained from patients undergoing vascular surgery. Risks are not to be expected.

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

Inclusion criteria psoriasis patients:
- patients that are diagnosed with psoriasis by their dermatologist
- age * 18 years
- written informed consent by the patient;Inclusion criteria psoriatic arthritis patients:
- Psoriasis patients that are diagnosed with psoriatic arthritis by their rheumatologist (according
to the CASPAR criteria)
- age * 18 years
- written informed consent by the patient;Inclusion criteria healthy volunteer:
- age * 18 years
- WHO performance score 0
- age and sex matched (for psoriasis and psoriatic arthritis)
- written informed consent ;Inclusion criteria systemic sclerosis patients:
- Patients that are diagnosed with systemic sclerosis by their rheumatologist
- age * 18 years
- written informed consent given by the patient;Inclusion criteria systemic lupus

erythematodes patients:
- Patients that are diagnosed with systemic lupus erythematodes by their rheumatologist
- age * 18 years
- written informed consent given by the patient;Inclusion criteria vasculitis patients with skin involvement:
- Patients that are diagnosed with vasculitis by their rheumatologist
- age * 18 years
- written informed consent given by the patient;Human tissues;Inclusion criteria for tissue donors, ie. skin tissue: patients undergoing eyelid surgery; mammareduction/abdominoplasty; synovial tissue: knee-replacement therapy in PsA and osteoarthritis (orthopedic surgery), synovectomy wrist (plastic surgery)
- donors will be asked for their permission to use their materials anonymously; this will be recorded in their medical file.;Inclusion criteria for tissue donors, ie. patients undergoing vascular surgery. The 3 categories of vascular surgery patients that will be included are patients undergoing crossectomy in chronic venous insufficiency; carotid endarterectomy, and surgical bypass of aortoiliac occlusive disease in patients with intermittent claudicatio without any signs of infection or critical (limb) ischemia.
- written informed consent given by the patient

Exclusion criteria

- use of corticosteroids including topical or systemic for the last 6 weeks
- use of disease-modifying antirheumatic drugs (DMARDs) or immune-suppressive drugs for the last 6 weeks
- concomitant use of drugs affecting the lymphatic system and/or immune responses including non-steroidal anti-inflammatory drugs (NSAIDs), drugs targeting RAAS system, and anti-allergy medication. These agents must be discontinued at least 6 weeks before the screening visit.
- co-existence of chronic inflammatory disorders including eczema, asthma or chronic infection
- pregnancy
- active cancer
- any lymphatic, cardiovascular or immunodeficiency disorder

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-11-2017
Enrollment:	101
Type:	Actual

Ethics review

Approved WMO Date:	21-12-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	11-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL55149.101.15