Epigenetic biomarkers to predict psoriasis disease progression * towards tailored therapy.

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Primary Objective: To define a top set of genes that most reliably (r >=0.95) distinguish psoriasis from normal skin. We will define this set from differential methylation genes to indicate potential biomarkers.Secondary Objective(s): Methylome...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON40335

Source
ToetsingOnline

Brief title
Psoriasis Epigenetics

Condition

- Skin and subcutaneous tissue disorders congenital
- Cornification and dystrophic skin disorders

Synonym
psoriasis, skin disease with fast proliferation and less differentiation of skin cells

Research involving
Human

Sponsors and support

Primary sponsor: Maastricht Universitair Medisch Centrum +
Source(s) of monetary or material Support: AbbVie,op basis van contract met

farmaceutische industrie: AbbVie

Intervention

Keyword: Biomarkers, Epigenetics, Psoriasis

Outcome measures

Primary outcome

The main study parameter is the sequence of DNA-methylation status (methylome) of the patient material. From these sequences a top set of genes (defined from differential methylation) will be defined that most reliably (r >=0.95, FDR<0.05) distinguish psoriasis from normal skin, indicating potential biomarkers that will be further studied in a future trial.

Secondary outcome

Secondary study parameter is the full transcriptome of the patient material. We will use this data to determine whether the methylation patterns that we find affect gene expression. Biomarkers of necessity reflect disease processes that are correlated to a particular outcome. Thus, for an epigenetic marker, if it is to be relevant to the disease it must have consequences on gene expression. We will not analyse the data for other parameters such as disease-causing mutations.

Study description

Background summary

Psoriasis is a chronic inflammatory disorder that affects skin and joints. Its pathogenesis is multifactorial, being determined by a number of genetic risk factors and environmental influences. The disease process involves defective skin barrier repair and an attendant deregulation of innate immune responses to

noxious agents, including bacteria and trauma, causing inflammation. Eventually, the adaptive immune system comes into play and maintains the inflammatory response through a.o. TNF-alpha and IL12/23 signalling. A subset of T helper cells, Th17, probably has a pivotal role in the sequence of events outlined above. However, the entire process likely starts in the epidermal barrier and its major constituent, the keratinocyte. Psoriasis is a chronic disease that once it has manifested will show varying activity with spontaneous remissions and relapses. Psoriasis negatively impacts quality of life and may be associated with significant comorbidities such as metabolic syndrome that may be attributable to chronic inflammatory activity. In addition, at least 30% of patients will develop psoriatic arthritis, which can lead to joint damage and invalidity. Thus, psoriasis potentially is a severe systemic disorder that can cause significant morbidity.

In analogy to rheumatoid arthritis, it is likely that early intervention with disease-modifying drugs (such as biologics) could prevent arthritic damage and other long-term complications in people with psoriasis. This concept has proven its worth in the treatment of rheumatoid arthritis, where early intervention with DMARD (disease-modifying antirheumatic drugs) has significantly reduced the incidence of invalidity. Among such DMARDS are targeted human and humanized monoclonal antibodies that suppress TNF alpha and IL12/23 signalling, such as adalimumab. These have proven to be highly effective in treating psoriasis, being capable of reducing PASI scores with up to 90%. They are also very effective against psoriatic arthritis. However, we cannot predict at present which patients will go on to develop arthritis and other long-term complications. It is quite possible that there are many patients who should receive biologics because they will develop complications, but do not get them now because their apparent disease severity does not seem to warrant it.

Therefore, it is highly desirable to have a set of biomarkers that can predict disease progression for individual patients. Being able to preselect individuals who stand to benefit the most from therapy with a biologic would make it economically feasible to use biologics in order to prevent long-term complications of psoriasis in such patients. These biomarkers are not yet available, although considerable effort is being spent on attempts to identify those (more than 1500 PubMed hits by mid-2013). Current efforts focus on genetic and (serum) inflammatory markers, but so far with little success. Certainly, there are no serum or tissue markers available that can indicate the risk of disease progression.

Here, we propose an innovative approach to prognostic biomarker development, using a biological phenomenon that has been largely ignored in psoriasis and other inflammatory skin disorders. We leverage our experience with novel high-throughput technology that has the potential to deliver relevant biomarkers in a relatively short time span.

It is well known that psoriasis has a strong hereditary component1, although

environmental influences have a crucial role in triggering disease expression. It is not known why the disorder persists once it has become manifest. There are no known genetic or environmental factors that could explain this phenomenon.

Study objective

Primary Objective:
To define a top set of genes that most reliably (r >=0.95) distinguish psoriasis from normal skin. We will define this set from differential methylation genes to indicate potential biomarkers.

Secondary Objective(s):
Methylome analysis will also give answers to these questions:
1) Is the global methylation pattern in psoriatic skin different from normal skin in people with psoriasis?
2) Is global methylation of unaffected skin different between people with and without psoriasis (* can we detect an epigenetic predisposition?)
3) Which gene promoters are differentially methylated between the two major types of psoriasis and normal skin?
4) Do these genes together with the RNA data point to pathways already known to be involved in the pathogenesis of psoriasis, and are any novel pathways suggested that might present therapeutic targets?
5) Does the guttate psoriasis methylome differ from that of plaque psoriasis?

After we have found potential biomarkers, these will then be validated and developed in a prospective translational trial aimed at obtaining markers that predict disease progression.

Study design

Study design
The proposed study is a nonrandomized non-therapeutic observational clinical study with taking four biopsies and a blood sample as an intervention at t=0. While we are only using this patient material ex-vivo in a laboratory, there is no follow-up planned for the patients/subjects.

Duration
We expect the study to take approximately 18 ± 3 months: 3 months for patient recruitment, 6-9 months for DNA/RNA analysis and 9 months for data analysis and marker selection.

Setting
The study will take place at the Maastricht University Medical Centrum + during 2014. Patients are sent to de Department of Dermatology by their general practitioner or peripheral dermatologist. If patients meet the inclusion

criteria the resident or dermatologist will ask if they will participate in this psoriasis project. If the subject agrees, the investigator will include the patient in the study. If there is a partner joining the patient in the physicians room, the partner will be asked to participate in the study as a control individual. If there are insufficient partners willing to participate as a control individual, we will ask partners of patients with psoriasis not meeting the inclusion criteria.

Justification of study design
For this study we firstly would like to analyse the entire methylome and transcriptome, to define a set of differentially methylated genes that will indicate potential biomarkers. Therefore a nonrandomized non-therapeutic observational clinical study is adequate.

Flow chart
Not applicable

Study burden and risks

There is very little risk involved in participating in the study. Taking a biopsy and taking a blood sample are routine techniques that we use extremely often in clinical practice in normal diagnostics. We will use an anaesthetic for the skin before taking the biopsy. The lidocaine 1% sometimes gives an itching of painful feeling for a moment. Taking the biopsies causes no discomfort because of the anaesthetics. Taking the blood sample with a venapuncture is hardly painful. The overall burden is minimal.

There are some minor risks involved in taking the biopsies and the blood sample. These are also mentioned in the information for the subjects.
- After taking a biopsy a small scar may develop. Normally this scar is small and after a while it will be hardly visible. Some patients tend to develop excessive scar formation. If a subject is known to have excessive scar formation, this is an exclusion criterium for this study.
- During biopsy and venepuncture there may be some minimal blood loss. Normally we will stop it by compression. It is also possible that, after a while, the venepuncture or biopsy site can start bleeding again. Subjects will receive information on how to handle this kind of bleeding, which is innocuous.
- Another potential risk is a wound infection. This can be treated relatively easily. Subjects will receive information on how to recognize a wound infection and what to do in that case.
- In very rare cases taking the biopsy will damage a superficial cutaneous nerve. As a result, a small area of the skin will feel numb for some weeks to months. Usually, feeling will return to the affected area.

Psoriasis negatively impacts quality of life and may be associated with significant comorbidities such as metabolic syndrome that may be attributable to chronic inflammatory activity. In addition, at least 30% of patients will

develop psoriatic arthritis, which can lead to joint damage and invalidity3. This research will contribute to defining biomarkers for these long-term complications of psoriasis. As written in the introduction, early intervention could prevent arthritic damage and other long term complications in people with psoriasis4.

The risks and burden of participating in the study are minimal; the potential benefits could be very significant.

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

For psoriasis patients:
- Age: >18 years old

- No systemic therapy for psoriasis
- Clinical diagnosis: Psoriasis Vulgaris or Psoriasis Guttata (The diagnosis will be confirmed by a dermatologist)
- Topical therapy is OK if it IS possible to stop for 3 weeks;For the control group:
- Age: >18 years old
- No generalised skin disease

Exclusion criteria

For psoriasis patients:
- Age: <18 years old
- Systemic therapy for psoriasis
- Juvenile psoriasis
- Not meeting the inclusion criteria
- Excessive scar formation or keloid in medical history
- Other (skin) disease that could influence the psoriasis
- Minors or incapacitated subjects
- Allergic reaction to lidocaine in medical history
- Topical therapy if it is NOT possible to stop for 3 weeks;For the control group:
- Clinical diagnosis of psoriasis
- Other generalised skin disease
- Excessive scar formation or keloid in medical history
- Minors or incapacitated subjects
- Allergic reaction to lidocaine in medical history

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: Recruitment stopped

Start date (anticipated):	20-07-2014
Enrollment:	9
Type:	Actual

Ethics review

Approved WMO Date:	19-05-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL47424.068.14