Immunotyping lymph nodes, bone marrow, muscle and blood in myositis

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

Summary

ID

NL-OMON57222

Source
ToetsingOnline

Brief title
Immunotyping in myositis

Condition

- Autoimmune disorders
- Muscle disorders

Synonym
inflammation of muscles, myositis

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: ReumaNederland

Intervention

Keyword: B cells, Immunotyping, JAK/STAT, Myositis

Outcome measures

Primary outcome

Identifying the cellular and molecular changes in immune system and functional characterisation of B cells, T cells, stromal cells and their signalling pathways in peripheral blood, lymph nodes and bone marrow as well as inflamed muscle tissue in IIM patients.

Secondary outcome

Not applicable

Study description

Background summary

Idiopathic inflammatory myopathy (IIM) is an auto-immune disorder leading to muscle weakness with considerable loss of function and quality of life. The underlying pathogenesis and cellular and molecular alterations of the immune system in this disease remain largely unknown. A better understanding of these alterations in bone marrow, lymph nodes, muscle tissue and peripheral blood is needed to gain insight in the mechanisms driving IIM and useful biomarker information for diagnosis and prognosis and may help to identify potential new treatment strategies. Both B and T cells have an important role in immunopathology of myositis. The role of B cells in IIM is supported by the presence of autoreactive B lineage cells in inflammatory lesions which produce autoantibodies and beneficial effect of B cell depleting, anti CD20 therapy. However, a considerable proportion of patients respond poorly to this treatment. The Janus kinase (JAK)/signal transduction and activator of transcription (STAT) pathway is a crucial downstream signaling pathway which is important for many functions in B lineage cells, including proliferation, differentiation, survival and antibody production. Our preliminary data showed that that JAK/STAT signaling is crucial in B cell responses in IIM patients, as a JAK/STAT inhibitor tofacitinib significantly reduced B cell proliferation and plasmablast differentiation in peripheral blood cultures. Current immunosuppressive treatments do not deplete certain plasmablasts and long-lived

plasmacells in lymph nodes, bone marrow and muscle tissue, where they can survive and promote further disease activity by persistent autoantibody production. Consequently, there is an unmet need in targeting autoantibody producing plasmacells. This potential novel target for therapy has several advantages over currently available treatments as targeting of intracellular signaling pathways requires small molecules that are able to reach the lymph nodes/bone marrow and usually have a short half-life, which makes it possible to stop treatment directly in case of infections and cause less complications than B cell depleting agents. Furthermore current treatments result in long-term impairment of humoral immune response, which may increase the susceptibility to infections.
We hypothesize that JAK/STAT signalling in (autoreactive) B lineage cells is essential for proliferation, differentation into plasma cells and/or maintenance of these cells in bone marrow niches, and autoantibody production contributing to disease activity in IIM.

Study objective

The primary goal of this study is to identify immunological alterations in blood, lymphoid tissue, bone marrow and muscle in IIM patients. Furthermore, our objective is to specifically profile autoreactive B lineage cells from IIM patients isolated from inflamed muscle tissues, lymph nodes, bone marrow and peripheral blood and to investigate the immunological and downstream molecular effects of targeting JAK/STAT and other signalling pathways in IIM B lineage cells.

Study design

Observational study

Study burden and risks

Patients/healthy subjects will have a needle biopsy of a lymph node in the groin, a bone marrow biopsy from the pelvis, additional blood collection and a muscle biopsy. For patients, some of these procedures are part of the normal diagnosis of myositis, such as a muscle biopsy and blood tests. During the blood test we will take extra blood (97cc extra) for this research project and during the muscle biopsy we will take a small amount of extra muscle tissue from myositis patients for this research project. The muscle biopsy by needle biopsy in healthy subjects is performed for this research and is not part of regular care. For healthy subjects it is possible to give permission to undergo only a lymph node biopsy and bone marrow biopsy without a muscle biopsy.
The research will increase the insight into the pathogenetic processes that play a role in the onset and persistence of myositis. This insight may lead to the identification and validation of new biomarkers that bring "personalized medicine" in myositis a step closer. In addition, new insights into the

pathogenesis can lead to the development of new therapies or therapeutic strategies. In view of the relatively small risk of complications, we consider this study justified.

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

- Adult patients (18-80 years) with idiopathic inflammatory myopathy (IIM), according to diagnostic criteria:
• Dermatomyositis
• Overlapmyositis
• Antisynthethase syndrome
- Informed consent

Exclusion criteria

Exclusion criteria:
- Patients who are not able to give informed consent
- Pregnancy
- Present or previous (< 2 year) treatment with any cell depleting therapies, including anti-B-cell therapy or other investigational agents (e.g., abetimus sodium, anti CD40L antibody, BG9588/ IDEC 131).
- Immunosuppressive treatment within the last 24 months with the exception of:
• Oral prednisone with a maximum dose of 60mg/day since one week, without clinical response
• Oral prednisone with a maximum dose of 20mg/day since two weeks, without clinical response
- History of infection:
• Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria)
• Hospitalization for treatment of infection within 60 days of Day 0.
• Use of parenteral (IV or IM) antibiotics (anti-bacterial, antiviral, anti-fungal, or anti-parasitic agents)
- History of malignancies neoplasm within the last 5 years except basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the uterine cervix treated locally and with no evidence of metastatic disease for 3 years
- Have a history of a primary immunodeficiency, including significant IgG deficiency (IgG level < 400 mg/dL) or IgA deficiency (IgA level < 10 mg/dL)
- Have current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within 365 days prior to Day 0
- Have a historically positive HIV test or test positive at screening for HIV
- Have any other clinically significant abnormal laboratory value in the opinion of the investigator

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:	Pending
Start date (anticipated):	01-09-2024
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	10-12-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL85907.018.24