EFFECTS OF ANTIBODY REMOVAL BY IMMUNOADSORPTION ON THE IMMUNE PHENOTYPE IN PATIENTS WITH ANTIBODY MEDIATED DISEASES - A *TARGET-TO-B* STUDY

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1) To study the effects of antibody removal by immunoadsorption on the immune phenotype over time in patients with B-cell related autoimmune diseases such as MG, AAV, anti-GBM disease, cryoglobulinemic vasculitis and other refractory antibody-...

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

Summary

ID

NL-OMON48107

Source
ToetsingOnline

Brief title
EFFECTS OF ANTIBODY REMOVAL - A *Target-To-B* STUDY

Condition

- Autoimmune disorders
- Neuromuscular disorders
- Nephropathies

Synonym
ANCA-associated vasculitis, anti-GBM disease and cryoglobulinemic vasculitis (vasculitis = small vessel inflammatory disease), Myasthenia Gravis

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: PPP allowance door Health Holland, de SGF, private partners en inkind contributie door Fresenius. ,'Target-To-B' consortium;which is a collaboration between six University Medical centres;RIVM and Sanquin;set up to investigate the role of B-cells in human disease. This project has received funding from the PPP allowance (Health Holland);The SGF and our private partners Pfizer B.V.;Janssen Vaccines & Prevention B.V. and Acerta Pharma B.V.

Intervention

Keyword: ANTIBODY MEDIATED DISEASES, IMMUNE PHENOTYPE, IMMUNOADSORPTION

Outcome measures

Primary outcome

The main study parameter is the change in immune phenotype over time in patients with B-cell mediated autoimmune disease, prior, and in response to immune suppression and IA as part of their standard treatment. The course of plasma levels of disease specific autoantibodies (e.g. anti-GBM, PR3- or MPO-ANCA) will be monitored for 12 months on a regular basis. Moreover, autoantibody typing (IgG isotypes, IgA, IgM) and characteristics (e.g. glycosylation/galactosylation profiles) as well as characteristics of B- and T-cells and plasma cell subsets, in-vitro profiles (e.g. PBMC activation and Ig release) and antibody effector functions will be analysed before and during the follow-up of this study. Clinical parameters and questionnaires will be collected to correlate the clinical course with differences in the immune phenotype. The results of antibody tests and cell subset data will be compared between patients with the same disease and between different diseases. If

feasible such as in AAV, these data will be also compared to a matched disease

control group with a similar immunosuppressive therapy but without an

indication for add-on IA.

Secondary outcome

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Study description

Background summary

Extracorporeal techniques for removal of pathogenic autoantibodies from a patient*s plasma are widely used in severe forms of B-cell related autoimmune diseases, including Myasthenia Gravis (MG), Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), anti-glomerular basement membrane (anti-GBM) disease and cryoglobulinemic vasculitis. The effects of antibody removal on B-cells and plasma cells are unclear but it may alter the immune composition, regulation and activity. The clinical response to immune-depleting therapies, such as immunoadsorption (IA), is variable, and frequently unpredictable. Better understanding of the dynamics of the immune system during therapy is needed to improve tailor made and precise choice of therapy for these immune-mediated disorders. This observational study is a part of the *Target-to-B* consortium, which is a collaboration between academic centres to investigate the role of the B-cell in human disease.

Study objective

1) To study the effects of antibody removal by immunoadsorption on the immune phenotype over time in patients with B-cell related autoimmune diseases such as MG, AAV, anti-GBM disease, cryoglobulinemic vasculitis and other refractory antibody-mediated diseases.
2) To prospectively collect disease-specific (clinical) outcome parameters according to the current standard clinical care protocols.
3) To evaluate immunological profiles or patterns in patient cohorts with the same disease and to study differences in these patterns between different auto-immune disease.

Study design

Multicenter, prospective, observational cohort study.

Study burden and risks

Patients will be treated according to the international standard of care for the particular B-cell mediated autoimmune disease. Due to the observational character of this study, the only extra burden and risk associated with participation is due to additional blood and urine sampling as well as questionnaires. Most of the blood samples will be scheduled during the routine clinical follow-up as indicated in table 2. Notably, children above the age of six with one of the above mentioned disease (especially MG, AAV, anti-GBM syndrome or a refractory antibody-mediated disease) can be included as well. The reasoning for this is that the pathogenic immune responses in these diseases may be different in younger age compared to adult patients but the standard of care therapeutic approach does not differ until now. Gaining insights in the immune composition and responses during the treatment in younger patients can therefore possibly help to understand and improve future therapeutic options with respect to age. Besides this, the results of this study will provide overall funda-mental insights in the dynamics of the immune system and the role of the B-cell before, dur-ing and after therapy in all patients with particular autoimmune-mediated disorders. In the future, the results of this study will potentially benefit patients in terms of (age matched) tailor-made and specific choices of therapies for these B-cell mediated autoimmune diseases.

Contacts

Public
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL
Scientific
Universiteit Maastricht

Universiteitssingel 50
Maastricht 6229 ER
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet the following criteria:

#Patients with a new or previous diagnosis of:
* Anti-AChR or anti-MuSK Myasthenia Gravis
* MPO- or PR3-ANCA associated vasculitis
* Anti-GBM glomerulonephritis
* Cryoglobulinemia vasculitis with severe organ involvement
* Refractory and severe antibody-mediated diseases*

Patients with an indication for plasma exchange or IA based on:
1. AChR or MuSK-positive MG with at least one of the following features:
- Insufficient clinical response to immunosuppressive therapy of severe ocu-lar, bulbar or generalized muscle weakness.
- Exacerbation with severe bulbar or respiratory dysfunction.

2. MPO- or PR3-ANCA vasculitis defined at least by one of the following features:
- Renal involvement indicated by renal biopsy and/or glomerular erythrocy-turia WITH active glomerulonephritis and newly reported eGFR < 50 ml/min/1.73 m^2 and/or rapidly deteriorating renal function.
- Pulmonary hemorrhage. Anti-GBM syndrome with at least one of the fol-lowing features:

3. Anti-GBM syndrome with at least one of the following features:
- Anti-GBM glomerulonephritis proven by renal biopsy and/or urine sediment suspecting active glomerulonephritis and newly reported eGFR < 50 ml/min/1.73 m^2 and/or rapidly deteriorating renal function.
- Pulmonary hemorrhage with anti-GBM autoantibodies (> 10 IU/ml).

- Serological evidence of circulating anti-GBM autoantibodies (> 10 IU/ml).

4. Cryoglobulinemia vasculitis with at least one of the following features:
- Symptomatic hyperviscosity syndrome.
- (Life-threatening) organ involvement (e.g. renal involvement (proven by renal biopsy and newly reported eGFR < 50 ml/min/1.73 m² and/or rapidly deteriorating renal function), pulmonary hemorrhage, progressive neuropa-thy).
- Severe, refractory cutaneous vasculitis.

5. Refractory antibody-mediated diseases
- This category may include autoimmune haemolytic anemia or other anti-body positive B-cell mediated autoimmune diseases.
- Based on case-based peer review between the investigators, patients with rare refractory antibody-mediated diseases can be considered for inclu-sion. In case of paediatric patients, additional reviewing by the paediatric immunologist involved in the *Target-to-B* consortium (Prof. dr. T. Kuijpers) can be obtained before inclusion.

Exclusion criteria

- Pregnancy at time of study entry.
- Previously reported allergic reactions to the immunosuppressive therapies or IA.
- Plasmapheresis or IA within 3 months before inclusion.
- Intravenous immunoglobulin within 3 months before inclusion.
- Patients aged < 6 years.
- Treatment with >7 days of oral cyclophosphamide or >1 IV dose of cyclophos-phamide within 3 months prior to inclusion and/or >7 days of predni-sone/prednisolone (>30 mg/day or > 1 mg/kg/day in paediatric patients) within 1 month prior to inclusion expect for patients with MG and/or >1 dose of rituximab within 9 months prior to inclusion.

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):	07-12-2020
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO

Date:	26-03-2020
Application type:	First submission
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	NL70185.068.19