Trial Description

Title

Efficacy and safety of adjuvant immunoadsorption in pemphigus

Trial Acronym

IA-Pem

URL of the trial

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Brief Summary in Lay Language

Within IA-pem study immunoadsorption will be applied for pemphigus disease. The aim of this study is to investigate the efficacy, safety, reliability of this procedure, its influence on the healing of the skin, and the consumption of additional drugs such as Cortisone in relation to the use of immunoadsorption.
In addition information about direct and indirect cost of the disease and quality of life in pemphigus patients will be collected.
In pemphigus disease, the cellular defense system (immune system) attacks itself (autoimmune reaction). The mechanisms that normally remove exogenous substances (e.g. pathogens) are now attacking the body's own structures. As part of the immune response proteins are generated: the antibodies. These antibodies recognize specific cells or pathogens and cause their destruction. If antibodies as in pemphigus attack the body's own cells they are called autoantibodies.
In pemphigus vulgaris, these autoantibodies are directed against cell structures in the upper skin layer (epidermis). Cells in the normally solid network of the skin cells in the epidermis are breaking apart (acantholysis). The skin loses mechanical stability and gets easily tearable. Blisters can form (Pemphix: Greek blister). The cause for this disease is so far not known. Probably a genetic predispositon to develop pemphigus is hereditable.
In contrast to the most other autoimmune diseases (e.g. rheumatoid arthritis or multiple sclerosis) pemphigus autoantibodies are directly pathogenic. This was clearly shown in numerous studies in cell culture and in animal experiments. So it seems appropriate to remove these pathogenic pemphigus autoantibodies from the blood of the patients. For this purpose various procedures including immunoadsorption were used in the past 10 years. To date more than 1,000 immunoabsorption treatments in pemphigus have been carried out. This study will investigate if adjuvant immunoadsorption for the treatment of pemphigus is superior to drug treatment.

Brief Summary in Scientific Language

Aim of the IA-Pem study is to investigate if adjuvant immunoadsorption is superior to standard immunosuppressive treatment in inducing clinical remission in pemphigus. The primary outcome measure (and most relevant clinical aim in the treatment of pemphigus) is time to clinical remission defined as healing of all blistering and erosive lesions. Healing of the initial lesions determines tapering of systemic corticosteroids (which are the major cause of severe side effects) and

later on of adjuvant immunosuppressants. Clinical remission is the most relevant therapeutical goal for pemphigus patients who are severely disabled by lesions of the oral mucosa and the skin, respectively.

Although there is no generally accepted therapeutic standard, most dermatologists agree that tapering doses of prednisolone plus another immunosuppressant such as azathioprine or mycophenolate mofetil / - sodium is the generally accepted first-line therapy of pemphigus in Central Europe and the US.
Patients in arm 1 (BMT- best medical treatment - group) will receive Prednisolone at an initial dose of 1.0 mg/kg/d plus
Azathioprine (1.5-2.5 mg/kg/d; according to serum TPMT activity) or
Mycophenolate mofetil or Mycophenolate sodium (in case of intolerance to azathioprine).
Evidence has accumulated from multiple monocenter uncontrolled trials that IA is effective in pemphigus. To finally demonstrate that immunoadsorption is an effective, corticosteroid-sparing, and safe adjuvant treatment for pemphigus, a prospective controlled study is required. The pathogenic role of autoAb against desmoglein 1 and 3 has been clearly established. The removal of serum autoAb is therefore a rational treatment option.
Patients in Arm 2 (BMT+IA -Immunoadsorption - group) are in addition to medication treated with immunoadsorption on four consecutive days (= 1 treatment cycle) or if not possible at least within 6 days using Immunosorba® (Fresenius Medical Care). A total of two to four cycles will be performed in three-week intervals.
The study will follow a randomised, prospective, multi-center, parallel-group study design to compare adjuvant immunoadsorption to standard immunosuppressive treatment in pemphigus. About 26 centers in Germany will take part in this study and 82 patients are needed for the final analysis. The recruitment period will be 24 months. The duration of the study period will be 12 months follow-up after randomisation for each patient. Visits are scheduled at 3, 6 and 9 weeks and 3, 6, 9 and 12 months. The duration of the whole study will be 4 years.

Organizational Data

- DRKS-ID: **DRKS00000566**
- Date of Registration in DRKS: **2010/11/23**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **183/10 , Ethik-Kommission des Fachbereichs Medizin der Philipps-Universität Marburg**

Secondary IDs

Health condition or Problem studied

- ICD10: **L10.0 - Pemphigus vulgaris**
- ICD10: **L10.2 - Pemphigus foliaceus**

Interventions/Observational Groups

- Arm 1: **Control intervention:**
  Treatment Arm 1: BMT (best medical treatment)
  Prednisolone at an initial dose of 1.0 mg/kg/d plus
  Azathioprine 1.5-2.5 mg/kg/d or Mycophenolate mofetil (2.0 g/d) or
  Mycophenolate sodium (1440 mg/d) in case of intolerance to azathioprine.

  Arm 1 and 2:
  Tapering doses of prednisolone and, after prednisolone has been omitted;
  azathioprine / mycophenolate mofetil or mycophenlate sodium will be reduced.
- Arm 2: **Intervention Treatment Arm 2: BMT+IA (immunoadsorption)**
  Immunoadsorption on four consecutive days (= 1 treatment cycle) using
  Immunosorba® (Fresenius).
  A total of two to four cycles required to achieve a clinical response will be
  performed in three-week intervals plus BMT
  Prednisolone (initial dose of 1.0 mg/kg/d) and
  Azathioprine (1.5-2.5 mg/kg/d) or
  Mycophenolate mofetil or Mycophenolate sodium.

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Other**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

Time to clinical remission, defined as complete healing of blistering and erosive lesions, respectively. Skin condition will be estimated by using ABSIS (Autoimmune Bullous Skin Disorder Intensity Score) at each visit.
Time to clinical remission (TTR), defined as the interval from randomisation to first

time when all lesions have healed.
Description of the primary efficacy analysis and population:
TTR will be compared between treatment groups by a two-sided logrank test with significance level 0.05. Additionally Kaplan-Meier estimates for the TTR distribution in each group as well as point estimate and 95% confidence interval of the hazard ratio will be given. The primary analysis will be done in the intention-to-treat population.

Secondary Outcome

- **Duration of clinical remission**
- **Number of patients in remission 6 and 12 months after randomisation.**
- **Cumulative doses of systemic corticosteroids and immunosuppressants until clinical remission**
- **Decrease in circulating desmoglein 1-/3-reactive IgG autoantibodies 3, 6, 9 and 12 months after randomisation**
- **Reduction in clinical severity score (ABSIS) 3, 6, 9 and 12 months after randomisation**
- **Proportion of patients with a prednisolone dose < 7.5 mg/d (threshold for Cushing's syndrome) 6 and 12 months after randomisation.**
- **Time until prednisolone is omitted**
- **Time until azathioprine/mycophenolate mofetil is omitted**
- **Time to reach minimal disease (lesions covering <0.5% of body surface and < 1cm2 of mucous membranes, respectively)**
- **Number of patients who have achieved DLQI scores 2-5 (= small impact on patient's quality of life) at 3, 6, 9 and 12 months after randomisation.**

Countries of recruitment

- DE **Germany**
- AT **Austria**

Locations of Recruitment

- University Medical Center **Klinik für Dermatologie, Charité Berlin**
- Medical Center **Klinik für Dermatologie, Städtisches Klinikum Dessau**
- University Medical Center **Klinik für Dermatologie, TU Dresden**
- University Medical Center **Klinik für Dermatologie, Erlangen**
- University Medical Center **Klinik für Dermatologie, Frankfurt a.M.**
- University Medical Center **Klinik für Dermatologie, Freiburg im Breisgau**
- University Medical Center **Klinik für Dermatologie, UKGM Standort Gießen**
- University Medical Center **Klinik für Dermatologie, Kiel**
- University Medical Center **Klinik für Dermatologie, Köln**
- University Medical Center **Klinik für Dermatologie, Lübeck**

- University Medical Center **Klinik für Dermatologie, Magdeburg**
- University Medical Center **Klinik für Dermatologie, Mainz**
- University Medical Center **Klinik für Dermatologie, Mannheim**
- University Medical Center **Klinik für Dermatologie, UKGM Standort Marburg**
- University Medical Center **Klinik für Dermatologie, LMU München**
- University Medical Center **Klinik für Dermatologie, TU München**
- University Medical Center **Klinik für Dermatologie, Münster**
- Medical Center **Hautklinik, Klinikum Nürnberg**
- University Medical Center **Universitäts-Hautklinik, Tübingen**
- University Medical Center **Klinik für Dermatologie, Ulm**
- University Medical Center **Klinik für Dermatologie, Würzburg**
- University Medical Center **Klinik und Poliklinik für Hautkrankheiten, Greifswald**
- University Medical Center **Dermatologische Klinik, Regensburg**
- University Medical Center **Klinik und Poliklinik für Dermatologie, Essen**
- University Medical Center **Klinik für Dermatologie, St. Josef-Hospital, Bochum**
- University Medical Center **Universitätsklinik für Dermatologie Medizinische Universität Wien, Wien**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2011/03/07**
- Target Sample Size: **82**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Inclusion criteria:

1) Patients with clinically active pemphigus presenting with lesions covering > 1.0% of body surface area or > 2cm² of mucous membranes

2) Diagnosis based on:

epithelium for IgG and/or C3 or Reactivity by desmoglein 3 or desmoglein 1 ELISA
3) Clinical features: blisters and/or erosions on the skin and/or mucous membranes
4) Newly diagnosed, active pemphigus (or) chronic refractory pemphigus (or) relapsed pemphigus
5) signed written Informed consent
6) Patients ≥ 18 years
7) Wash-out periods:
Rituximab, leflunomide ≥1 year, plasmapheresis/immunoadsorption ≥ 3 months, IVIG ≥ 2 months, TNF-α blocker ≥ 4 weeks, methotrexate, cyclophosphamide, cyclosporine A, dapsone, tetracyclines ≥ 1 week.
Chronic active patients (> 6 months) and relapsed patients on azathioprine may be switched to mycophenolate mofetil / mycophenolate sodium (no washout period required) and vice versa.

Exclusion criteria

Exclusion criteria:
1) Allergy against materials and/or medication used in the study
2) Mandatory treatment with angiotensin converting enzyme inhibitors
3) Coagulopathy
4) Severe cardiovascular disease (NYHA IV, myocardial infarction within the last 3 months)
5) Severe acute or chronically active systemic infections:
HBsAg-positive chronically active hepatitis B,
Hepatitis C,
HIV infection,
diagnosis of a latent or florid tuberculosis infection,
Acute viral infections (i.e. varicella zoster virus, severe herpes simplexvirus infection)
6) Fertile women not using adequate contraceptive methods
7) Women who are pregnant or breast feeding
8) Severe reduction of liver or renal function (serum GOT > 3-fold of normal value, serum creatinine > 3-fold of normal value)
9) Severe congenital immunodeficiency
10) Active gastro-duodenal ulcer
11) Acute or unstable psychiatric diseases with a high risk of exacerbation due to high-dose prednisolone.
12) Active or progressive malignoma or malignoma currently treated with chemotherapy/immunosuppressants or immunotherapy. In case of patients with preceding malignoma who are in complete remission an oncologist should be consulted prior to inclusion.
13) Hb < 9 g/dl or leukopenia <3.000/µl or thrombocytopenia <100.000/µl due to reduced bone marrow function
14) Illiteracy or insufficient language skills (German) to complete the questionnaires
15) Simultaneous participation in another clinical trial except if that other trial does not affect the study as approved and documented by the steering committee.

Addresses

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Philipps Universität Marburg

Primary Sponsor

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Sources of Monetary or Material Support

■ **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

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Kennedyallee 40
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- **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

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Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2015/03/09**

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*
**** This entry means that data is not displayed due to insufficient data privacy clearing.*