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Anti-CD20 monoclonal antibody therapy for type II mixed cryoglobulinemia syndrome

Submission date
18/01/2012

Recruitment status
No longer recruiting

Registration date
03/02/2012

Overall study status
Completed

Last Edited
03/11/2017

Condition category
Haematological Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Background and study aims
Cryoglobulinemia is a medical condition in which abnormal cryoglobulin proteins in the blood cause problems such as inflammation of blood vessels (vasculitis). It is associated with hepatitis C virus (HCV) infection. There is evidence that antiviral treatment with interferon or with interferon plus ribavirin is effective. On the other hand, standard immunosuppressive treatments may lead to severe complications in HCV-positive patients. Thus, less toxic treatments are needed. Based on early results, rituximab may be a safe and effective alternative to standard immunosuppression. The aim of this study is to compare rituximab treatment with the best available treatment for type II mixed cryoglobulinemia.

Who can participate?
Patients aged 18-80 with type II cryoglobulinemic vasculitis, HCV-related or unrelated

What does the study involve?
Participants are randomly allocated to receive either conventional treatment or rituximab treatment. Conventional treatment is chosen by the clinician for the individual patient, and can include treatment with glucocorticoid, azathioprine or cyclophosphamide medications or plasmapheresis, a procedure where the blood is filtered to remove the cryoglobulins. Participants are followed up over 24 months: weekly from day 0 to day 28, monthly up to month 6, then every 2 months up to month 24. A general physical examination is performed, and vital signs (pulse rate, blood pressure and temperature) are taken.

What are the possible benefits and risks of participating?
As the study involves patients who require immunosuppressive treatment, possible benefits include the possibility to cure their vasculitis with a less toxic and more effective treatment. Rituximab can cause an infusion related reaction involving fever, chills or rigors. Other commonly reported reactions include nausea, urticaria (hives), fatigue, headache, itching, bronchospasm, dyspnoea (breathlessness), sensation of tongue or throat swelling, rhinitis (inflammation of the inside of the nose), vomiting, hypotension (low blood pressure) and flushing. While in most patients these reactions are mild to moderate in severity, there have been reports of severe reactions in lymphoma patients. Patients who experience a severe reaction should have their infusion interrupted immediately and should receive aggressive

treatment. The infusion should not be restarted before all the symptoms have disappeared. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in a repeated reaction.

Where is the study run from?
The study involves different Italian centers led by University of Udine (Italy)

When is the study starting and how long is it expected to run for?
March 2004 to December 2008

Who is funding the study?
University of Udine (Italy)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
MP17925

Study information

Scientific Title
Anti-CD20 monoclonal antibody therapy for type II mixed cryoglobulinemia syndrome versus best available treatment: a phase III controlled study

Study objectives
Type II mixed cryoglobulinemia (MC) or MC syndrome is a systemic vasculitis prevalently mediated by immune-complexes, and associated with hepatitis C virus (HCV) infection and B-cell lymphoproliferation. Despite the bone marrow pathologic findings often suggesting an indolent

B-cell malignancy, type II MC is definitely a non-neoplastic disorder, as finally demonstrated by molecular analyses of B-cell clonal expansion in extensively characterized patients with long-term follow-up.

B-cell expansion and lymphoproliferation occur in target organs of HCV infection. There is evidence of an antigen-driven proliferation of rheumatoid factor (RF) - positive clones, with a restricted immunoglobulin gene usage, leading to cryoglobulin production. Future studies should clarify the preferential and persistent expansion of such RF-positive clones in the course of HCV infection if compared to other chronic inflammatory/infectious conditions. Since only a fraction of patients with HCV infection have positive serum cryoglobulins or develop MC syndrome, additional mechanisms, virus-or host-related, are implicated. Recent studies were focused on insertions or deletions in HCV gene (HVR1-E2 region), HLA genetic predisposition, C4 deficiency, anti-endothelium and anti-alpha enolase antibodies, T-helper 2 profile and cytokines. Finally, serum cryoglobulins and RF usually persists even after the negativization of HCV RNA with the antiviral therapy. Since RF-positive B-cells may be stimulated by immune complexes containing quite different antigens, HCV infection might be crucial for the induction of MC, while not for the survival of RF-positive clones, which might prove pathogenetically relevant also in the lack of HCV persistence.

In the lack of such information, the treatment of HCV-associated MC remains difficult, and strategies should be necessarily focused both on the viral trigger (when present) and on downstream pathogenetic events.

There is general clinical evidence that effective antiviral treatment with interferon (old studies) or with interferon plus ribavirin (recent studies) is often accompanied by clinical efficacy, but results may differ in the different systemic features. Thus, even if antiviral therapy has a strong rationale and represents a cornerstone for the treatment of MC, additional pathobiologic events should be dissected and targeted for the different organ manifestations. Furthermore, antiviral therapy may be ineffective, counterindicated or not tolerated, and finally does not allow a rapid improvement in progressive or life threatening MC manifestations.

On the other hand, standard immunosuppressive approaches may lead to severe complications in HCV-positive MC patients, including major infections, cytopenias, enhancement of viral replication, and may have direct oncogenetic properties. Thus, less toxic approaches are needed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Udine Ethics Committee, 13/10/2003, ref: 6/2003

Study design
Randomised controlled multicenter non-blinded phase III study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied

Mixed cryoglobulinemia HCV- related or unrelated

Interventions

NON-Rituximab (RTX) GROUP (conventional treatment, i.e., as chosen by the expert clinician in that individual patient among the following):
1. Glucocorticoids (maximal initial dose of 1 mg/kg/day of prednisone equivalents) with or without preceding 6-methylprednisolone pulses (500 to 1000 mg/day for 3 consecutive days), with subsequent reduction of the glucocorticoid dosage in the following months.
2. Azathioprine or cyclophosphamide, orally at 1-2 mg/kg/day, with or without glucocorticoids (as in point 1); if response was observed, azathioprine or cyclophosphamide might be suspended after the end of month +6 after randomization, and then reintroduced if clinical relapse occurred (as it occurs in the current clinical practice).
3. Plasmapheresis, with or without glucocorticoids (as in point 1); if response was observed, plasmapheresis could be suspended after the end of month +6 after randomization, and then reintroduced if clinical relapse occurred (current clinical practice). At least two plasmapheretic procedures per week were required in the first month after randomization, with subsequent reductions according to the response observed and to local protocols.

Rituximab (RTX) GROUP:
RTX 1 g intravenously on days 0 and 14, with premedication with 100 mg of methylprednisolone intravenously, paracetamol 1000 mg orally, and clorpheniramine maleate 10 mg intravenously, before each infusion. Only glucocorticoids were allowed as concomitant treatment, at the same dose given before randomization if already administered, or lower; if introduced with RTX, only low doses (≤ 0.1 mg/kg/day of prednisone equivalents) were allowed. In case of clinical disease relapse in this Group, retreatment with RTX, at the same schedule, was permitted in case of previous response to RTX.
Patients failing treatment in non-RTX Group could be switched to RTX in an open-label extension manner (RTX-switch Group).
Patients were randomized to treatment stratified for the following three disease manifestations:
1. Skin ulcers
2. Active glomerulonephritis (assessed by renal biopsy)
3. Peripheral neuropathy (assessed by electromyography); sensory: evolving or with severe pain unresponsive or insufficiently managed with analgesics and gabapentin or pregabalin; motor: of any type and duration).
Patients with two or three of these clinical manifestations simultaneously present were randomized within the group where the accrual of patients was lower.

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Rituximab

Primary outcome(s)

The proportion of patients surviving on treatment at the end and 12 months after randomization, i.e., after a follow-up considered sufficient to assess both the efficacy and safety of treatment.
Efficacy and safety issues were in fact considered equally relevant in the long term, and a single

end point integrating both of them was then chosen. Survival of treatment was statistically higher in RTX Group in comparison to non-RTX Group (conventional treatment).

Key secondary outcome(s))

1. The proportion of patients surviving on treatment at the end month +24, i.e., to evaluate the long-term efficacy and safety of treatment
2. The proportion of patients surviving on treatment at the end month +6, i.e., to evaluate the short-term efficacy and safety of treatment
3. The proportion of patients surviving on treatment at the end month +3, i.e., to evaluate the very early efficacy and safety of treatment
4. Superiority of RTX to decrease the global disease activity, as defined by the Birmingham Vasculitis Activity Score (BVAS)
5. Superiority of RTX for response in the single CV manifestations considered in the randomization scheme.
6. Efficacy of RTX in patients where conventional treatment had failed
7. Duration of response to RTX and efficacy of retreatment
8. Assessment of the profile of side effects of RTX, both in the short and the long term

Completion date

31/12/2008

Eligibility

Key inclusion criteria

1. Patients with CV with type II cryoglobulins
2. HCV related or unrelated, classified according to published criteria
3. With positive serum cryoglobulins
4. Suffered from severe active CV manifestations, i.e., skin ulcers, active glomerulonephritis, or worsening or refractory peripheral neuropathy
5. In patients with HCV-related CV, study inclusion implied that antiviral therapy with interferon plus ribavirin had failed, had been poorly tolerated, or was considered contraindicated
6. Patients aged 18-80 years
7. Negative for antibodies against the human immunodeficiency virus (HIV), hepatitis B virus core antigen, and for hepatitis B virus surface antigen

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Upper age limit

80 years

Sex
All

Key exclusion criteria
1. Active CV manifestations with immediate risk for patient survival
2. Acute renal failure or rapidly progressive glomerulonephritis
3. Severe concomitant uncontrolled illness CV-unrelated
4. Active or recurrent infections
5. History of cancer (except for CV-related indolent B-cell lymphoproliferation in the bone marrow, not requiring treatment)
6. Alcohol or drug abuse
7. Serum creatinin > 4 mg/dl
8. AST or ALT > 3 times the upper limit of normal
9. Haemoglobin < 8 g/dl
10. Neutrophils < 1000/mmc or total leukocytes < 1500/mmc
11. Platelets < 40.000/mmc
12. History of severe allergic reactions to monoclonal antibodies
13. Pregnancy (if reproductive potential, an accepted birth control method was required)
14. Previous treatment with RTX
15. Previous failure of all the following:
15.1. High dose glucocorticoids
15.2. Plasma exchange
15.3. Cyclophosphamide
15.4. Azathioprine

Date of first enrolment
01/03/2004

Date of final enrolment
31/12/2008

Locations

Countries of recruitment
Italy

Study participating centre
University of Udine
Udine
Italy
33100

Sponsor information

Organisation

University of Udine (Italy)

ROR
https://ror.org/05ht0mh31

Funder(s)

Funder type
Industry

Funder Name
Roche (Switzerland)

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co., Roche Holdings, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes