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Long-term follow up of patients in European Vasculitis Study Group clinical trials

Submission date
16/02/2010

Recruitment status
No longer recruiting

Registration date
07/05/2010

Overall study status
Completed

Last Edited
13/03/2020

Condition category
Circulatory System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Small vessel vasculitis is an inflammation of small blood vessels. This is often associated with circulating antibodies to substances normally found in the white blood cells; ANCA (anti neutrophil cytoplasmic antibodies), hence called ANCA-associated vasculitis (AAV). Any organ in the body could be affected by this inflammation. However, most commonly the upper and lower respiratory tract (nose to lungs) and kidneys are involved. Untreated the inflammation of the blood vessel could result in organ failure for example kidney failure with need for dialysis or transplantation or respiratory insufficiency and in worst cases death. In the past, the outlook for patients has been poor, but, after the introduction of immunosuppressive therapy patient survival has improved dramatically. However, the side effects of the treatment have caused short and long term problems for patients. Therefore, a European network started in the 1990's 'European Vasculitis Society (EUVAS)' with the aim to harmonize and improve the outcome from treatment of AAV. Several prospective randomized clinical trials (RCTs) have been conducted under EUVAS leadership (NORAM, CYCAZAREM, CYLOPS, MEPEX). The follow-up within these RCT was 12-18 months. As the recurrence rate of AAV is high, the side-effects of immunosuppression still was considerable and sometimes delayed a five year follow up of patients within the first four EUVAS' trials were launched 2004. The results from the 5-year follow up revealed that the risks of death and kidney failure and other complications remain high. Therefore there is need to both follow-up a more recently recruited cohort to assess whether outcomes are improving and also to obtain longer follow up on the original cohort in order to obtain robust data, particularly regarding the cumulative incidence of cancer and cardiovascular events.

Who can participate? What does the study involve?
This is a prolonged follow-up study of patients who have participated in EUVAS randomized controlled studies. A questionnaire regarding patient- and kidney survival, incidence of cancer and cardiovascular disease is to be completed by the physician responsible for the patient in the initial RCT. Details on patient outcome will then be transferred as coded data (the patient identity is not revealed) into a data set for further statistical analyses.

What are the possible risks and benefits of participating?
Participation in this long term follow up study will not generate any direct benefits to the

patients There should not be any risks as the data retrieved from the patients respectively are coded and anonymized when transferred to the data set. Ethical approvals were obtained for all the initial RCTs and have also been applied for according to national laws and rules and regarding this long term follow up. The investigation is conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments

Where is the study run up from?
The study is run from the EUVAS' centers which have participated in the previous EUVAS randomized clinical trials

When is study starting and how long is it expected to run for?
This long term follow up study started 2004, and is now prolonged to a 10 year or longer follow up during 2018-2019

Who is funding the study?
Skane University Hospital Malmö-Lund is the sponsor.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2006-001663-33

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Long-term follow up of patients who participated in previous Vasculitis trials

Study objectives
Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), Granulomtaosis with Polyangiitis (GPA, previously Wegener's granulomatosis ;WG, updated 05/04/2019) and microscopic polyangiitis (MPA) are primary vasculitides of unknown cause characterised by necrotising inflammation involving predominantly small blood vessels and the presence of circulating anti-neutrophil cytoplasm antibodies (ANCA) in the majority of patients at diagnosis. They are often grouped as ANCA-AAV because of striking similarities in histology, absence of immune deposits, response to therapy and the likely contribution of ANCA to the pathogenesis.

The primary aim of this study is to determine the long-term survival of patients with ANCA-AAV, who participated in randomised controlled trials conducted by the European Vasculitis Study Group (EUVAS) compared to the general population with a median follow-up greater than five years.
Secondary aims are to investigate the survival with independent renal function and renal function at five years follow up in addition to the frequency of other severe organ failure such as blindness and oxygen dependency. The survival without disease relapse and the severity and organ involvement of disease relapses will be studied.
Important adverse events such as the frequency and nature of malignant disease, cardiovascular disease, serious infections and skeletal fractures will be investigated. The causes of death will be noted.
Prognostic factors at entry and at 1 year on long-term survival and renal outcome will be identified including the predictive value of renal histology at presentation.
The performance of currently used disease assessment tools like the Birmingham Vasculitis Activity Score (BVAS) for disease activity, the Vasculitis Damage Index (VDI) for damage and the Short-form 36 (SF-36) for quality of life will be assessed. This study will help define the natural history of AAV, will serve as a reference base for new clinical trials and identify the major long-term goals and challenges for the management of AAV.

Publications from original trials:
1. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009 May 19;150(10):670-80.
2. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005 Aug;52(8):2461-9.
3. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med. 2003 Jul 3;349(1):36-44.
4. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J AmSocNephrol. 2007 2007/07//;18(7):2180-8.
(added 02/07/2019):
5. Jones RB, Cohen Tervaert JW, Hauser T et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010;363:211-220.
6. Hiemstra TF, Walsh M, Mahr A et al. Mycophenolate Mofetil vs Azathioprine for Remission

Maintenance in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Controlled Trial. JAMA. 2010;304(21):2381-8
7. Jones RB, Hiemstra TF, Ballarin J al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis. 2019;78:399-405

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. West Midlands Multi-centre Research Ethics Committee approved amendment 1 on 22/09/2004 (ref: MREC/98/7/37)
2. Swedish Ethical Committee Lund Dnr 2013/272 (added 02/07/2019)

Study design
Current study design as of 05/04/2019:
Observational long-term follow up of patients who participated in EUVAS' multi-centre randomised controlled trials after 10 years or longer

Previous study design:
Observational long-term follow up of patients who participated in four multi-centre randomised controlled trials after median follow- up of five years

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis (WG)) or microscopic polyangiitis (MPA)

Interventions
Current interventions as of 05/04/2019:
1. Survival
2. Renal survival (including incidence and latency to start of renal replacement and time to transplant)
3. Immunosuppressive therapy including cumulative cyclophosphamide exposure during 10 years of follow up
4.Incidence and nature of malignancies including non-melanoma skin cancers and myelodysplasia
5. Relapse and renal relapse
6. Cardiovascular events (CVA, MI, PVD, thrombo-embolic events)
7. Diabetes mellitus
8. Infections requiring hospitalisation
9. Skeletal fractures
10. Cause of death
11. Vasculitis Damage Index at 5 years and latest time of follow up

Previous interventions:
A questionnaire will be send to all participating investigators and data collected on the

occurrence and time to event of the following outcomes:
1. Survival
2. Renal survival (including incidence and latency to start of renal replacement and time to transplant)
3. Renal function at 5 years as assessed by 4 factor Modification of Diet in Renal Disease (MDRD) formula
4. Organ failure (such as blindness, pulmonary disease requiring long-term oxygen therapy etc)
5. Immunosuppressive therapy including cumulative cyclophosphamide exposure
6. Incidence and nature of malignancies including non-melanoma skin cancers and myelodysplasia
7. Relapse and renal relapse
8. Cardiovascular events (CVA, MI, PVD, thrombo-embolic events)
9. Diabetes mellitus
10. Infections requiring hospitalisation
11. Skeletal fractures
12. Cause of death
13. Vasculitis Damage Index at 5 years

Intervention Type
Other

Phase
Not Specified

Primary outcome(s)
Long-term survival of patients with ANCA associated vasculitis compared to age, sex, year and country matched background population (Kaplan Meier analysis, comparison to background population according to Hakkulinen method)

Key secondary outcome(s))
1. Prognostic factors at presentation-multi-variable analysis
2. Cumulative damage according to Vasculitis Damage Index at 1 and 5 years
3. Relapse rate and relapse free survival by Kaplan Meier method
4. Renal function as survival with independent renal function by Kaplan Meier method and estimated glomerular filtration rate
(eGFR) at 5 year follow up.
5. Incidence and time point of severe organ failure (eg blindness, oxygen dependency)
6. Cumulative incidence of malignancies including non-melanoma skin cancer and myelodysplasia
7. Cardiovascular morbidity and mortality

Completion date
31/12/2019

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 11/07/2019:
1. Patients with newly diagnosed Anti-Neutrophil Cytoplasm Antibody Vasculitis recruited into one of EUVAS' randomized controlled trials, NORAM, CYCAZAREM, MEPEX, CYCLOPS, RITUXVAS, IMPROVE, MYCYC performed by European Vasculitis Society (EUVAS)

Previous participant inclusion criteria:
1. Patients with newly diagnosed Anti-Neutrophil Cytoplasm Antibody Vasculitis recruited into one of four randomised controlled trials, NORAM, CYCAZAREM, MEPEX, CYCLOPS performed by European Vasculitis Study Group
2. The patients were recruited during the period of 1995 to 2002

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Patients withdrawn from original study due to incorrect diagnosis
2. Consent withheld by patient

Date of first enrolment
01/09/2004

Date of final enrolment
24/01/2020

Locations

Countries of recruitment
United Kingdom

Belgium

Czech Republic

Denmark

Finland

France

Germany

Ireland

Italy

Mexico

Netherlands

Spain

Sweden

Switzerland

Study participating centre
Dept. of Nephrology and Transplantation
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Sponsor information

Organisation
Skane University Hospital Malmö-Lund, Sweden

ROR
https://ror.org/02z31g829

Funder(s)

Funder type
Research council

Funder Name
Vasculitis Foundation

Alternative Name(s)
The Vasculitis Foundation, VF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

Funder Name
European Renal Association – European Dialysis and Transplant Association

Funder Name
Region Skåne

Alternative Name(s)

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Sweden

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2011		Yes	No
Results article	results	01/04/2011		Yes	No
Results article	results	01/05/2011		Yes	No
Results article	results	01/08/2011		Yes	No
Results article	results	01/12/2011		Yes	No
Results article	results	01/02/2012		Yes	No
Results article	results	01/06/2012		Yes	No
Results article	results	01/10/2012		Yes	No
Results article	results	01/01/2013		Yes	No
Results article	results	01/06/2013		Yes	No

Results article	results	01/08/2013		Yes	No
Results article	results	01/01/2015		Yes	No
Results article	results	01/03/2015		Yes	No
Results article	results	01/03/2015		Yes	No
Results article	results	01/04/2015		Yes	No
Results article	results	14/12/2016		Yes	No
Results article	results	01/05/2017		Yes	No
Results article	results	01/12/2017		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes