PATHOGENESIS AND THERAPY OF IMMUNE MEDIATED NEUROPATHIES

Project title
"Anti-nerve reactivity as predictor of response to immune therapy in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): A proof of concept study with rituximab in patients with CIDP not responding to conventional immune therapy"

Pre-clinical Supervisor: Michela Matteoli, michela.matteoli@hunimed.eu
Clinical Supervisor: Eduardo Nobile-Orazio, eduardo.nobile_orazio@humanitas.it

Laboratory name: Pathogenesis and therapy of Immune mediated neuropathies

Abstract

1. Immunological study

Objectives
To identify the prevalence of different antibody reactivity to nerve antigens in a large population of CIDP patients recruited in the Italian Database, and their association with the clinical and neuro-physiologic phenotype, the severity of neuropathy, and response to conventional therapies effective in CIDP.

Methods
We will review the data from the 500 patients with CIDP and variants included in the Italian database on CIDP. For each patient, the clinical, electrophysiological, laboratory, pathological and clinical features, progression of CIDP, and response to therapy will be assessed. We will test the sera collected from all the patients at the time of inclusion for the presence of different anti-nerve antibodies. We will measure by ELISA antibodies to gangliosides, ganglioside complex or their mixture with galactocerebroside (Nobile-Orazio et al. 2008 & 2014) and to CNTN1, NF155, NF186, gliomedin and Caspr1 at the laboratory of Neuroimmunology at Humanitas Clinical Institute under the supervision of Dr. Claudia Giannotta. We will characterize the IgG isotype of positive patients. Positivity will be confirmed by cell-based immunoassay using positive controls provided by the authors (Querol et al., 2013 &2014) under the supervision of (Dr. Diego Franciotta from Mondino Institute in Pavia. The results will be compared to the value obtained in a large population of controls with other neuropathies or related disorders followed at our Institution.

Statistical analysis plan
The prevalence of different antibody reactivity to nerve antigens will be reported separately for each antigen as a percentage with a binomial 95% confidence interval (CI). The clinical and neurophysiologic phenotype will be described separately in patients with and without

antibody reactivity to each antigen using frequencies and percentages for categorical variables and means, standard deviations, medians or ranges for numerical variables. Patients with and without antibody reactivity will be compared using the chi-square or the Fisher's exact test for categorical variables, and the t-test or the Wilcoxon-Mann-Whitney test for numerical variables. The severity of the disease will be evaluated comparing INCAT scores between patients with and without antibody reactivity to each specific antigen separately, using the t-test or univariable and multivariable linear regression models. The response to conventional therapy effective in CIDP will be compared in patients with and without antibody reactivity to each specific antigen separately, using univariable and multivariable logistic regression models (with response to therapy as dependent variable, the presence of antibody reactivity as independent variable, and possible confounders as covariates). Results will be presented as odds ratios (OR) and adjusted odds ratios (adj. OR) with 95% CI.

2. Therapeutic study

Objectives

To evaluate efficacy and safety of rituximab in patients with CIDP not responsive to conventional immune therapies and to correlate the response to therapy with rituximab with the presence of antibody reactivity, and with CIDP clinical form (typical or atypical).

Methods

Patients not responding to conventional therapies for CIDP (IVIg, steroids and PE) will be offered to enter into an open label proof-of-concept study with intravenous Rituximab, given at the dose of 1g in one day, followed by the same dose after two weeks. The response to therapy will be assessed after 2, 6, 8, 10 and 12 months using the MRC sum score (0-60), the INCAT disability scale (0-10) and the RODs scale for CIDP. Nerve conduction studies will be performed before treatment, 6, and 12 months after treatment. The titre of anti-nerve antibodies will be assessed before treatment and after 6 and 12 months. We will inform all the patients about the possible benefit and adverse events of the therapy and we will ask them to sign an informed consent.

Sample size calculation

Given that among patients not responding to conventional immunological therapies, the percentage
of responders to immunosuppressive drugs is reported to be 25-30% (Cocito et al 2011, Eur J Neurol, 18:1417-1421), we plan to include in the study a total of 20 patients with CIDP not responding to conventional therapy. This sample size will provide a power of 80% to detect a 30% absolute difference in favour of Rituximab compared to the historical 27% response to other chemotherapies reported in non-responding CIDP patients, with a 5% level of significance.

Humanitas University
Via Rita Levi Montalcini 4
20090 Pieve Emanuele (Milano) Italy
Tel +39.02.8224.1 - Fax +39.02.8224.2394
info@hunimed.eu
Website: www.hunimed.eu
C.F. 97692990159

Statistical analysis plan

The proportion of patients that improve 6 and 12 months after therapy with rituximab (at least one point on the INCAT scale or two points on the MRC force scale or four points on the RODs scale) will be calculated with the corresponding 95% binomial confidence interval and compared to the percentage of responders to other immunosuppressive and immune modulatory agents reported in a previous report (Cocito et al 2011). The same analysis will be performed for the proportion of patients improved 12 months after therapy with rituximab (secondary endpoint 1). The proportion of responders to rituximab at 6 and 12 months will be compared between patients with and without antibody reactivity and between typical and atypical CIDP.

3. Bio-Bank study

Objective

To create a databank of biomaterials (sera and CSF) with an associated dataset including the clinical and electrophysiological data, response to therapy and the results of antibody reactivity associated with CIDP to allow future immunological studies that may help understanding the pathogenesis of CIDP and the finding of biomarkers for disease activity or response to therapy.

Methods

All the sera and, when available, cerebrospinal fluid from the patients will be collected at the time of inclusion in the study and stored at -80° to create a large biobank of biomaterials. These data might be used in future studies on the immunological abnormalities of CIDP and variants and may help to understand their pathogenesis and possibly to identify biomarkers of disease activity or response to therapy.

Main technical approaches

Clinical and immunological study in patients with CIDP combining the use of immunological investigations (ELISA, Western Blot, Cell Based Immunoassay) with the clinical and electrophysiological assessment of the patients and the assessment of their response to immune therapies in an open label prospective therapeutic study with rituximab.

Scientific references

1. Nobile-Orazio E, Gallia F, Terenghi F, et al. How useful are anti-neural IgM antibodies in the diagnosis of chronic immune-mediated neuropathies? J Neurol Sci 2008; 266:156-63
2. Nobile-Orazio E. Chronic Inflammatory demyelinating polyradiculoneuropathy. Where we are,where we should go. J Peripher Nerv Syst 2014; 19: 2-13
3. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Antibody to contactin-1 in chronic inflammatory demyelinating polyneuropathy. Ann Neurol 2013 ; 73: 370-380
4. Vural A, Doppler K, Meinl E. Autoantibodies Against the Node of Ranvier in Seropositive Chronic Inflammatory Demyelinating Polyneuropathy: Diagnostic, Pathogenic, and

Humanitas University
Via Rita Levi Montalcini 4
20090 Pieve Emanuele (Milano) Italy
Tel +39.02.8224.1 - Fax +39.02.8224.2394
info@hunimed.eu
Website: www.hunimed.eu
C.F. 97692990159

Therapeutic Relevance. Front Immunol. 2018 May 14;9:1029. doi: 10.3389/fimmu.2018.01029
5. Doneddu PE, Cocito D, Manganelli F, et al. Atypical CIDP: diagnostic criteria, progression and treatment response. Data from the Italian CIDP Database. Journal of Neurology Neurosurgery and Psychiatry 2019; 90: 125–132:

Humanitas University
Via Rita Levi Montalcini 4
20090 Pieve Emanuele (Milano) Italy
Tel +39.02.8224.1 - Fax +39.02.8224.2394
info@hunimed.eu
Website: www.hunimed.eu
C.F. 97692990159