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Efficacy and safety of intravenous immunoglobulin with rituximab versus rituximab alone in childhood-onset steroid-dependent and frequently relapsing nephrotic syndrome: protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction Guidelines for the treatment of steroid-dependent nephrotic syndrome (SDNS) and frequently relapsing nephrotic syndrome (FRNS) are lacking. Given the substantial impact of SDNS/FRNS on quality of life, strategies aiming to provide long-term remission while minimising treatment side effects are needed. Several studies confirm that rituximab is effective in preventing early relapses in SDNS/FRNS; however, the long-term relapse rate remains high (~70% at 2 years). This trial will assess the association of intravenous immunoglobulins (IVIgs) to rituximab in patients with SDNS/FRNS and inform clinicians on whether IVIg's immunomodulatory properties can alter the course of the disease and reduce the use of immunosuppressive drugs and their side effects.

Methods and analysis We conduct an open-label multicentre, randomised, parallel group in a 1:1 ratio, controlled, superiority trial to assess the safety and efficacy of a single infusion of rituximab followed by IVIg compared with rituximab alone in childhood-onset FRNS/SDNS. The primary outcome is the occurrence of first relapse within 24 months. Patients are allocated to receive either rituximab alone (375 mg/m²) or rituximab followed by IVIg, which includes an initial Ig dose of 2 g/kg, followed by 1.5 g/kg injections once a month for the following 5 months (maximum dose: 100 g).

Ethics and dissemination The study has been approved by the ethics committee (Comité de Protection des Personnes) of Ouest I and authorised by the French drug regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé). Results of the primary study and the secondary aims will be disseminated through peer-reviewed publications.

Strengths and limitations of this study

- This study will be conducted as a national multicentre randomised controlled trial providing the first reliable data on the use of intravenous immunoglobin in combination with rituximab in patients with idiopathic nephrotic syndrome.
- The lack of blinding of the patients and the physicians is a limitation to the study design; however, the objectivity of the primary outcome reduces the risk of bias.
- Intravenous administration of the intervention addresses concerns of non-compliance.

Trial registration number NCT03560011.

INTRODUCTION

Background

Idiopathic nephrotic syndrome (INS) is the first glomerulopathy in children with an incidence estimated between 2 and 3/100,000 inhabitants and a high prevalence of 1/6250 because of the extensive course of the disease. The response to steroid therapy (steroid-sensitive nephrotic syndrome vs steroid-resistant nephrotic syndrome (SRNS)) is of high prognostic significance. Cohort studies, including the French NEPHROVIR study, found that around 90% of the patients are steroid sensitive.[1 2] However, 60% will

become steroid dependent or frequent relapsers with a major risk of morbidity related to the complications of the relapses (mostly infections due to immunoglobulin (Ig) loss and thrombosis) and to the side effects of the treatments used in those patients. The pathophysiology of INS is still incompletely understood. In 1974, Shaloub brought evidence for an immune origin of the disease.[3] Since then, standard immunosuppressive drugs such as calcineurin inhibitors or mycophenolate mofetil (MMF) demonstrated the ability to maintain remission while on treatment. Unfortunately, their effect is only suspensive with 75% of relapse after cyclosporine A (CsA) withdrawal[4] and over 90% of relapse after MMF withdrawal,[5] although maintenance of remission is needed to maintain normal renal function in the long run. Cyclophosphamide demonstrated a long-lasting effect in children with steroid-dependent nephrotic syndrome (SDNS) with a sustained remission rate of 42% at 2 years but its use is limited by its side effects.[6] However, there is currently no consensus on the treatment of SDNS or frequently relapsing nephrotic syndrome (FRNS) and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines only list potential steroid-sparing agents without giving indication which to prefer. Several strategies using low-dose steroid therapy (once every other day) and the immunosuppressive drugs mentioned previously have been proposed.[7 8] However, they are associated with significant side effects such as diabetes, high blood pressure, infections and renal fibrosis. Moreover, the long duration of the disease (median time 10 years) has been recently shown to significantly impact the quality of life of patients.[9] Thus, treatment and strategies aiming to provide long-term remission while minimising treatment side-effects in patients with FRNS/SDNS need to be investigated.

In 2004, rituximab (RTX), a humanised anti-CD20 antibody depleting B cells has been reported to induce sustained remission of the nephrotic syndrome in a patient treated for idiopathic thrombocytopenic purpura.[10] Since then, many reports confirmed that RTX is able to induce long-lasting remission even after B cell recovery in patients with SDNS.[11–13] This finding deeply modified our view on the pathophysiology of the disease with the involvement of B cells and not only T cells as previously described. This implication of B cells is further supported by the strong correlation between B cell recovery and INS relapse in patients relapsing after RTX therapy with a recent report underlying the role of memory B cells (CD19+/CD27+).[14]

Two recent randomised trials demonstrated an improvement of the relapse-free survival with RTX when compared with placebo or long-term steroid therapy.[15 16] Similar results have been found in a recently published French randomised controlled trial NEPHRUTIX since the relapse rates at 6 months was 10% in the RTX arm compared with 100% in the placebo arm.[17] However, the remission rates after 2 years in patients treated with RTX is only 30%–40%. Strategies using repeated RTX injection with long B cell depletion duration greatly increase the relapse-free survival rate to over 60% but increase the risk of infection and persistent hypogammaglobulinaemia.[12 18 19]

Intravenous Ig (IVIg), which is used for therapeutic purposes, is a polyspecific IgG preparation purified from plasma pools of several thousand healthy donors. IVIg preparations primarily contain human IgG molecules, with small amounts of IgA and IgM. The distribution of IgG subclasses in IVIg is comparable to that of IgG in normal serum and the half-life of infused IVIg is approximately 3 weeks. IVIg was initially used as a substitution for Igs that were lacking in patients with primary and secondary immune deficiencies. However, since the demonstration in 1981 that IVIg ameliorates immune thrombocytopenic purpura,[20] IVIg is increasingly being used for the treatment of a wide range of autoimmune and systemic inflammatory diseases.[21] In addition to antibody-mediated diseases, IVIg is also effective in several disorders caused by dysregulation of cellular immunity, such as Kawasaki disease, dermatomyositis, multiple sclerosis and graft versus host disease in recipients of allogeneic bone marrow transplants.[22] Clinically, the beneficial effects of IVIg extend beyond the half-life of infused IgG; therefore, its effects cannot be a result of a passive clearance or competition with pathogenic autoantibodies. Together, these observations evoke the possibility that IVIg therapy induces lasting changes in the cellular compartment of the immune system. Several studies demonstrated the ability of IVIg to modulate B cells immune response in vitro and in vivo through several mechanisms such as apoptosis promotion by modulating B-cell receptor (BCR) signalling after binding to CD22,[23] silencing programme induction of B cells and neutralisation of cytokines such as the B cell survival factor (BAFF) and a proliferation-inducing ligand.[24] In vivo, IVIg therapy in women with recurrent spontaneous abortion is accompanied by a small decrease in the peripheral blood B cell numbers.[25] Aside from their effects on B cells, IVIgs have been found to modulate T cell function especially by expanding and enhancing the functions of regulatory T cells[26 27] and by decreasing T cell activation and proliferation through multiple pathways, including interleukin 2 production inhibition.[28–30] Tha-In *et al* found that IVIgs were as effective as calcineurin inhibitors to inhibit T cells proliferation in vitro and also impact dendritic cells functions.[31] Many studies also report effects of IVIg on innate immune system.[32]

Thus, we hypothesised that the adjunction of IVIg to a single course of RTX may further modulate B cells function and allow a prolonged effect on INS without the need for long-lasting B cell depletion. Moreover, maintaining a high IgG level may be beneficial in decreasing the risk of infection in those vulnerable patients. Treatment modality was derived from the protocol commonly used to treat antibody-mediated rejection in renal transplant recipients both in adults and in children.[33] In a retrospective pilot study comparing 12 patients treated

with RTX and IVIg to 32 controls receiving one injection of RTX alone, we found a great improvement of relapse-free survival at 2 years from 40% in the RTX alone group to 70% in group receiving both RTX and IVIg with the difference remaining significant after adjustment for age, associated immunosuppressive treatments and B cell depletion duration (unpublished observations, J Hogan). The proposed clinical trial aims to establish evidence for the use of IVIg in addition to RTX in patients with FRNS and SDNS.

METHODS/DESIGN

Objectives

Primary objective

Our primary objective is to assess the effect of a single infusion of RTX followed by Ig injections (once a month during 5 months) on the occurrence of the first relapse within 24 months following the initiation of treatment in patient with childhood onset FRNS/SDNS compared with a single infusion of RTX.

Secondary objectives

- To compare the time to first relapse.
- To compare the total number of relapse over the 24 months of follow-up.
- To compare the cumulative dose of steroid over the 24 months of follow-up.
- To compare the tolerance and safety of the two strategies.

Our hypothesis is that the adjunction of IVIg to RTX to treat patients with FRNS/SDNS will induce sustained remission of proteinuria even after oral treatment withdrawal and will improve relapse-free survival when compared with RTX used alone.

Study design

The trial will be an open-label multicentre, randomised, parallel group in a 1:1 ratio, controlled, superiority trial testing a single infusion of RTX followed by Ig injections (once a month during 5 months) compared with a single infusion of RTX, involving patients with childhood-onset FRNS/SDNS (figure 1). Because of the nature of the intervention, clinical investigators and patients will not be blinded to group assignment. Patients will be recruited from 22 tertiary nephrology care centres in France (table 1). Inclusions started in April 2019 and are expected to be completed in April 2021. The expected study completion date is April 2023.

Eligibility criteria

Study inclusion criteria comprises the following:

1. Childhood-onset nephrotic syndrome (first flare <18 years old).
2. ≥2 years old at inclusion.
3. Steroid dependent: patient with at least 2 relapses confirmed during corticosteroids tapering or within 2 weeks following steroids discontinuation, or patient with at least 2 relapses, including one under steroid-sparing agent (MMF, calcineurin inhibitors, cyclophosphamide and levamisole) or within 6 months of treatment withdrawal.
4. Frequent relapsers: 2 or more relapses within 6 months after initial remission or 4 or more relapses within any 12-month period with a relapse within 3 months prior to inclusion.

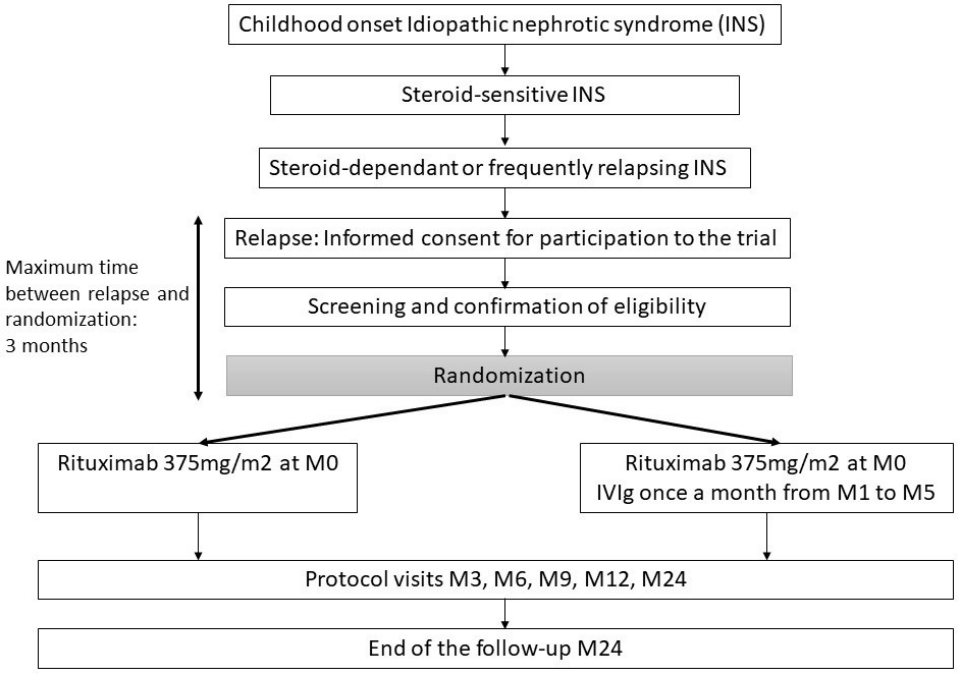

Figure 1 Flow diagram of the open-label randomised, multicentre, parallel-group, controlled, superiority trial, RITUXIVIG.

Table 1 List of the participating centres in France

City	Hospital name
Amiens	CHU d'Amiens
Besançon	CHU de Besançon
Bordeaux	CHU de Bordeaux
Caen	CHU de Caen
Clermont Ferrand	CHU Clermont Ferrand
Créteil	CHU Henri Mondor
Lille	CHU Jeanne de Flandre
Lyon	Hôpital Mère Enfant
Montpellier	CHU de Montpellier
Nancy	CHU de Nancy
Nantes	CHU de Nantes
Nice	CHU Lenval
Paris	CHU Armand Trousseau
Paris	CHU Tenon
Paris	CHU Necker
Paris	CHU Robert Debré
Reims	CHU de Reims
Rouen	CHU de Rouen
Toulouse	CHU de Toulouse
Tours	CHU de Tours
Lyon	Hôpital Edouard Herriot
Limoges	Hôpital de la mère et de l'enfant
Total	22

5. In remission: protein-to-creatinine ratio ≤0.2 g/g (≤0.02 g/mmol).

Study exclusion criteria comprises the following:

1. Patients with SRNS.
2. Patients with genetic mutations known to be associated with nephrotic syndrome.
3. The presence of another active glomerular disease.
4. Patients previously treated with RTX.
5. Patients with no medical insurance.
6. Prior hepatitis B, hepatitis C or HIV infection or any severe and progressive infection.
7. Known congestive heart failure, left ventricular hypertrophy or cardiomyopathy.
8. Pregnancy or breastfeeding (a pregnancy test is performed before inclusion in the study in women of childbearing age and effective contraception will be given to these patients at inclusion. This contraception will be continued for 1 year after the last infusion of RTX).
9. Patients with hyperprolinaemia.
10. Known hypersensitivity to one of the study medications.
11. Scheduled and non-postponable injection of live attenuated vaccine.
12. Adults under guardianship.
13. Patients with neutrophils $<1.5\times10^9$/L and/or platelets $<75\times10^9$/L.

Outcomes

The primary outcome is the occurrence of the first relapse within 24 months following the initiation of treatment. Within this study, relapse shall be defined as a protein to creatinine ratio of 2 g/g of creatinine (0.2 g/mmol) or higher. No clinical manifestation is requested to define relapse. Second, we will monitor time to first relapse from the beginning of treatment, the total number of relapses occurring during the 24-month follow-up period, the cumulative dose of steroid taken during the 24-month follow-up, calculated as cumulative dose of corticosteroid for the enrolment episode plus the cumulative dose of corticosteroid for each relapse, the initiation of a new immunosuppressive therapy and the adverse events during the study period such as infectious complications, treatment tolerance, nausea and neutropenia.

Screening

When investigators observe a recurrence of INS in study candidate patients, they describe this clinical trial to the relevant subjects and obtain their written consent to participate in the trial. After consent is obtained, screening tests are performed to verify eligibility as a subject. If the eligibility of the patient is confirmed after the screening tests, the patient is randomised. The randomisation must be performed within 3 months of the last relapse.

Randomisation

After obtaining written consent from all adults or from both parents of children (online supplemental material), randomisation will be performed using a web-based application and a secured access (CleanWeb) in a 1:1 ratio to arm A: single infusion of RTX (375 mg/m²) or arm B: single infusion of RTX (375 mg/m²) followed by intravenous polyvalent Ig once a month for 5 months according to a computer-generated list of randomly permuted blocks (mixed blocks). No stratification of the randomisation was planned. Randomisation and concealment will be achieved using a centralised, secure, computer-generated, interactive, web-response system accessible from each study centre. The randomisation time is the study time zero (M0). Blinding was not allowed given the nature of the intervention. However, this lack of blinding is partially counterbalanced by the objective nature of the primary outcome measure (biological criteria), and the final analysis will be blinded to allocation of groups.

Procedures

At day 0, all patients will undergo antibiotic prophylaxis with trimethoprim/sulfamethoxazole 800 mg three times per week until B cell reconstitution. All patients will receive a premedication with methylprednisolone and dexchlorpheniramine or hydroxyzine. Patients in both arms will then receive a single injection of RTX 375 mg/m².

Table 2 Study timeline

Examinations	M0 inclusion/ randomisation	Month 1	2	3	4	5	6	9	12	18	24
Informed consent	○										
History	○										
Clinical examination	○										
Blood sample for biobanking	○							○*			○*
Serology (HIV, HBV and HCV)	○										
Haematological examination (total blood count and lymphocyte population count)	○	○	○	○	○	○	○	○	○	○	○
Creatininemia	○	○	○	○	○	○	○	○	○	○	○
SGOT/SGPT and GGT	○										
Serum electrolytes	○	○	○	○	○	○	○	○	○	○	○
Protidemia	○	○	○	○	○	○	○	○	○	○	○
BUN	○	○	○	○	○	○	○	○	○	○	○
Albuminaemia	○	○	○	○	○	○	○	○	○	○	○
Proteinuria†	○	○	○	○	○	○	○	○	○	○	○
Creatininuria	○	○	○	○	○	○	○	○	○	○	○
IgG serum level	○	○	○	○	○	○	○	○	○	○	○
Randomisation	○										
RTX infusion	○										
Hospitalisation for IVIg‡		○	○	○	○	○					
Follow-up visit (consultation)				○			○	○	○	○	○
Relapse		○	○	○	○	○	○	○	○	○	○
Time to first relapse		○	○	○	○	○	○	○	○	○	○
Adverse event	○	○	○	○	○	○	○	○	○	○	○
Pregnancy test*§	○										

*If relapse before M9 biobanking at relapse, if relapse after M9 biobanking at M9 and at relapse.
†Proteinuria is evaluated once a week using a urinary stick until 12 months after RTX injection and once every 2 weeks between 12 months and 24 months.
‡If patient randomised in arm B.
§For patients at childbearing age.
BUN, Blood Urea Nitrogen; GGT, gamma glutamyl-transférase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; IVIg, intravenous immunoglobulin; M0, month 0; M9, month 9; RTX, rituximab; SGOT, Serum Glutamo-Oxalacetique Transaminase; SGPT, serum glutamic-pyruvic transaminase.

Patients randomised in arm B will receive two doses of IVIg (1 g/kg/day) over the course of two consecutive days beginning at month 1 (M1). From M2 to M5, patients in arm B will receive 0.75 g/kg/day on two consecutive days per month. Doses shall not exceed 100 g. Depending on respective centre practices and patient tolerance, IVIg will be administered in the centre outpatient clinic or conventional hospitalisation units.

Blood sampling

During the clinical trial period, investigators will perform observation, examination and blood sampling according to a predetermined schedule. On all days of investigational drug administration, blood samples are taken immediately prior to administration (table 2).

For all randomised patients, a monthly biological investigation in a local laboratory, including IgG, white blood cell and lymphocyte population count, and urine analysis, including protein-to-creatinine ratio, on a sample will be performed during 6 months or until B cell reconstitution, whichever is longer. Additionally, proteinuria will be evaluated once a week using a first-AM urinary dipstick until 12 months after RTX injection and once every 2 weeks between 12 months and 24 months. If the results are positive, a confirmatory urine analysis will be carried out in

laboratory. All patients will also be included in a biorepository, including samples for DNA extraction and serum banking. The samples will be taken at M0, M9 (if no relapse before M9) and M24 (or at the time of relapse).

Follow-up visits will be carried out at M3, M6, M9, M12, M18 and M24 with an additional visit in case of relapse as routinely performed in clinical practice. All outcome measures (relapse, time of relapse, number of relapse and amount of corticosteroid taken) and adverse events will be assessed by the investigating physician during the follow-up visits.

Prohibited concomitant medications

Patients are instructed to stop all corticosteroids and immunosuppressive treatment (ie, MMF, levamisole, tacrolimus, CsA and prednisone) within 8 weeks of beginning the trial. In case of corticosteroids treatment, weekly decrease of the dose will be implemented and stopped after 1 month. In case of treatment with steroid-sparing agent, discontinuation will occur after 8 weeks.

Adverse events

Adverse events are, according to the definitions, any unfavourable or unintended event affecting patients on study. In cases of prolongation of hospitalisation, death or significant clinical sequelae, these events are defined as serious adverse events (SAEs), the occurrence of which the study sponsor (Assistance Publique – Hôpitaux de Paris, APHP) and the Data Safety Monitoring Board (DSMB) will be informed at short notice. During protocol treatment, all deaths, all SAEs that are life-threatening and any unexpected SAE must be reported to APHP using the SAE web form within 48 hours of the initial observation of the event.

Safety aspects of the study are closely assessed by the DSMB, which receives non-blinded data. Moreover, the first relapse of INS has been included as SAE to allow monitoring by the DSMB of any major discrepancy between the treatment groups.

Other adverse events monitored during the follow-up include infections requiring hospitalisation, infections not requiring hospitalisation, progressive multifocal leucoencephalopathy, neutropenia, acute kidney injury stage 3: increase in creatinine of ≥200% or estimated Glomerular Filtration Rate (eGFR) ≤35 mL/min/1.73 m^2 (if age <18 year) if patients with previously normal renal function, allergic reaction ≥grade 3 and infusion tolerance.

Data management

In the RITUXIVIG trial, the data are collected at each study visit. Data collection and data entry in the Electronic Case Report Form (eCRF) database are performed by the site investigators with the help of trained local research staff. A data management plan will be written and followed during all the data management and analysis process.

STATISTICAL METHODS

Sample size

The number of subjects required to compare the proportion of patients with at least one relapse within 24 months between the two groups (RTX and IVIg vs RTX alone) was estimated. The proportion of patients with relapse at 24 months in the 'RTX alone' group is assumed to be approximately 60% based on previous reports.[17 18] Assuming a reduction of 30% in the RTX and IVIg group with a power of 80% and a two-sided type I error of 5%, 42 patients per group are required throughout a 24 months' recruitment period. Considering that the number of lost to follow-up will be relatively low in this population (follow-up of patients at 2 years is ~95%), size will be increased to 45 patients per group to provide an initial power of 80% on the intention to treat population.

Statistical analysis

The proportion of patients with at least one relapse within 24 months (primary outcome) in the control group and the study group will be compared using a χ^2 test. The Kaplan-Meier method will be used to study the time to first relapse and a log-rank test will be used to compare the time to first relapse between the study groups.

Comparison of the number of relapses, the number of adverse events and the cumulative doses of steroids over the study period will be performed using either a log-transform t-test for normally distributed variables or a Mann-Whitney U test for non-normally distributed variables (normality will be tested using a Kolmogorov-Smirnov test). All statistical tests will be two sided using a significance level of 5%.

Monitoring

Monitoring for quality and regulatory compliance will be performed in each centre by the study coordinator from the study coordinating centre. The frequency depends on inclusion rates, questions and pending issues from earlier audits: once or twice a year. In addition, quality control of the data is planned to detect missing and inconsistent data. All missing data will be sought in the patients' medical records. If missing data cannot be recovered by the study monitors, a multiple imputation procedure based on a 'missing at random' assumption using a fully conditional specification method will be considered.

Confidentiality and data handling

The data will be handled according to the French law. The eCRFs will be hosted by a service provided into a secure electronic system via a web navigator and protected by an individual password for each investigator and clinical research technician. Participant's identifying information will be replaced by a related sequence of characters to ensure confidentiality. The trial database file will be stored for 15 years. The sponsor is the owner of the data.

Patient and public involvement

Patients were not involved in the planning and production of this study.

Ethics and dissemination

The study was approved by the ethics committee (Comité de Protection des Personnes) of Ouest I on 24 April 2018 and authorised by the French drug regulatory agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé—EudraCT n°2017-000826-36) on 17 May 2018. A manuscript with the results of the primary study and the secondary aims will be published in a peer-reviewed journal.

DISCUSSION

Childhood-onset steroid-dependent or frequently relapsing INS is a chronic disease with a long-lasting course and significant impact on patients' quality of life. There are currently no clear guidelines to choose the best treatment for these patients, and the current treatment strategies are all associated with a high rate of relapse. Therefore, clinical trials testing new strategies of treatment and assessing their long-term effects are needed.

The main goal of the RITUXIVIG trial is to demonstrate the superiority of the association of RTX and IVIg compared with RTX alone. This trial has several strengths, including its multicentre design, the intravenous administration of the drugs that alleviates concerns about compliance and the choice of a long-term outcome (relapse-free survival at 2 years) compared with previous trials. Despite the trial being open-label, the risk of bias should be low, given the absence of non-compliance risk and the objective nature of the primary outcome.

This trial will provide the first assessment of the use of IVIg in patients with INS and inform clinicians on whether IVIg's immunomodulatory properties can alter the course of the disease. Finally, this strategy may reduce the risk of infection associated with current strategies by reducing the amount of immunosuppressive drugs used and by the direct protective effect of IVIg against infections.

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