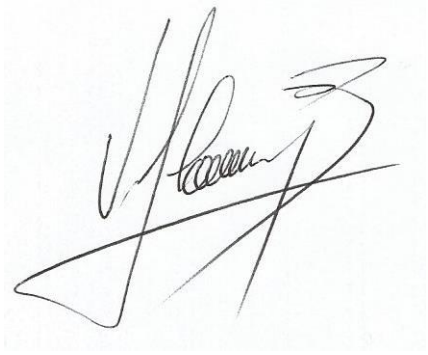
LACTRIMS
LATIN AMERICAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

**RESOLUCIÓN N° 37**
(17/06/21)

El Comité Ejecutivo de LACTRIMS resuelve aprobar la financiación y dar el aval Cientifico al Proyecto de Investigación presentado por los Drs. Edgar Carnero Contentti, Fernando Hamuy, Juan Ignacio Rojas : “Therapeutic strategies, effectiveness, and safety of Rituximab in NMOSD and MOGAD patients: multicenter cohort study in Latin America”.
El mismo cuenta con informe Técnico favorable del Coordinador General de Proyectos Dr. Victor Rivera.
Se solicita al Autor:1-Presentar organigrama del desarrollo del Proyecto
2-Cronograma de liberación de Fondos de Financiación,debiendo designar una Cuenta Bancaria donde girar desde la cuenta de LACTRIMS,y provisión de acuse de recibo de Recepción de los mismos.
3-Hacer constar en la redacción final el aval y financiamento de LACTRIMS.



Dr. Fernando Hamuy Diaz de Bedoya
Presidente
LACTRIMS

Dr. Gustavo Baez Valiente
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**Propuesta de trabajo colaborativa grupo LACTRIMS**

| Study Information | |
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| **Title of Study** | ***Therapeutic strategies, effectiveness, and safety of Rituximab in NMOSD and MOGAD patients: multicenter cohort study in Latin America*** |
| **Investigators** | ***Edgar Carnero Contentti, Fernando Hamuy, Juan Ignacio Rojas*** |
| **Rationale for Study** | Neuromyelitis optica spectrum disorder (NMOSD) is autoimmune disease mostly characterized by recurrent episodes of optic neuritis and myelitis, alone or in combination. NMOSD is characterized, in most patients, by the presence of autoantibodies (ab) against aquaporin 4 (AQP4-ab). A small percentage of seronegative NMOSD patients might test positive for myelin oligodendrocyte glycoprotein (MOG)-ab, serological markers with putative pathophysiological role.<br>Recently, three therapies have been approved for NMOSD, however an "off-label" indication, with long-term immunosuppressants (e.g.: azathioprine, methotrexate, and mycophenolate mofetil (MMF)) have been used. A large body of evidence from large retrospective studies and meta-analysis suggested that rituximab is effective in preventing relapses in NMOSD. Despite this evidence, RTX is used off-label, both as a first line therapy, or as a rescue therapy after an ineffective first-line therapy (e.g.: azathioprine, methotrexate, and MMF).<br>Although RTX is increasingly used in NMOSD and MOGAD, considerable heterogeneity exists, mainly concerning the number and dosage of infusions and the frequency of therapeutic cycles.<br>Considering the previous, the objective is to develop a multicenter study of RTX treatment in patients with NMOSD and MOGAD, describing and |

<table>
<tr><td></td><td colspan="3">comparing efficacy and safety according to patients' characteristics and different regimen strategies,</td></tr>
<tr><td rowspan="2">Summarize the Primary, Secondary and Exploratory Objectives with the Associated Endpoints and Evaluation Criteria</td><td></td><td>Objective</td><td>Endpoint</td></tr>
<tr><td>Primary</td><td>To describe different regimen strategies of rituximab used in NMOSD and MOGAD patients.<br><br>To compare the effectiveness and safety of different regimen strategies of rituximab in NMOSD and MOGAD patients</td><td>1- Annualized Relapse Rate (ARR)<br>2-Proportion of patients and time to Expanded Disability Status Scale (EDSS) ≥6.0<br>3- Adverse events related to RTX (infusion reactions, infections, others)</td></tr>
<tr><td>Study Design</td><td colspan="3">This is a retrospective cohort study with secondary use of data.<br>A digital database will be designed with all the efficacy and safety variables described in this concept sheet (see Statistical Analysis section for further details), where treating neurologist from neurological centers will transfer the data of NMOSD and MOGAD patients from their medical records. The selected patients will have to have been diagnosed with NMOSD and MOGAD (based on the 2015 NMOSD and the 2018 MOGAD validated diagnosis criteria), received RTX for the disease and have had an active medical follow-up for at least the first 3 years since disease onset (at least 3 visits per year). Disease onset is defined as the first relapse of the disease. Only renowned neurological centers with academic affiliation, large experience in managing NMOSD and MOGAD, acting as a second opinion referral centers and/or having a large clinical</td></tr>
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| | practice of NMOSD and MOGAD patients will be selected to participate. These centers perform the initial patient evaluation and follow-up visits following similar guidelines, obtaining homogenous data between the centers. They schedule follow-up visits every 3 to 4 months, and evaluate changes in relapse, disability, adverse events, and imaging in every visit following a structured and homogeneous medical record.<br><br>Data collection will be carried out for up to 5 months. No interim analysis is planned. | |
| **Population** | Adult patients diagnosed with NMOSD and MOGAD (based on validated diagnosis criteria) who received RTX treatment for at least 6 months and with an active medical follow-up for at least 3 years since RTX initiation. | |
| **Key Inclusion Criteria** | - Patients who agree to participate in the research.<br>- Definitive diagnosis of NMOSD and MOGAD according to validated diagnosis criteria.<br>- Being treated with RTX for at least 6 months<br>- At least 3 years of active medical follow-up since disease diagnosis registered in neurological centers medical charts, with ≥ 3 visits per year. | |
| **Key Exclusion Criteria** | - Insufficient documentation registered in center databases<br>- Patients who refuse to participate | |
| **Study Milestones** | **Study Start** (First Patient First Visit or Data Extraction Start) | 2021 |

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| (Month and Year MUST be entered for each item) | **Study End** (Last patient Last Visit or Data Extraction Completion) | 2021 |
| | **Completion of Study Report** *(Final Study Report to be sent to Roche no later than 12 months after Study End, no later than 6 months for pediatric studies)* | 2021 |
| | **Primary Publication Date** *(Publication to be sent to Roche no later than 24 months after Study End)* | 2022 |
| **Number of Patients and Centers** | **Total Planned Number of Patients** | Between 100-150 NMOSD /40 MOGAD |
| | **Planned Number of Centers** | 30 |
| | **Planned Number of Countries (List of Countries)** | 9 (Argentina, Brazil, Ecuador, Venezuela, México, Chile, Colombia, Panamá and Paraguay) |

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| **Sample Size Justification and Statistical Analysis** | The variables that are going to be collected from patients' medical records and transferred into a specifically designed digital database will be:<br><br>1. Demographic: age, sex, place of residence, date of disease onset, first symptom-locations, MRI at disease onset findings and lab test for NMOSD and MOGAD.<br><br>2 EDSS at every visit<br><br>3. Relapse activity at every visit.<br><br>4-Rituximab infusion protocol used by patient<br><br>5. Development of malignancies at every visit, including but not limited to:<br>- Melanoma<br>- Basal cell carcinoma<br>- Lymphoproliferative disorders (Lymphomas and Leukemias)<br>- Thyroid carcinoma<br>- Gynecological neoplasms<br>- Prostate cancer<br>- Other<br><br>6. Opportunistic infections at every visit, including but not limited to:<br>- Cryptococcal Meningitis<br>- Herpetic encephalitis<br>- Progressive Multifocal Leukoencephalopathy (PML)<br>- Tuberculosis<br>- Any other opportunistic infection that requires hospitalization<br>- Other |

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| | 7- Adverse events related to infusions<br><br>**Rituximab treatment protocol**<br><br>RTX infusion regimens will be classified according to the induction and maintenance regimens protocols applied as:<br><br>**Induction**:<br><br>- Induction regimen A (IND-A): two 1000 mg infusions 15 days apart.<br><br>- Induction regimen B (IND-B): four 375 mg/m2 infusions every week for 4 weeks.<br><br>**Maintenance:**<br><br>- Maintenance regimen A (M-A): fixed time-points (6 months) infusions of 1000 mg.<br><br>-Maintenance regimen A (M-A1): fixed time-points (6 months) infusions of 1000 mg with a reinfusion 15 days<br><br>- Maintenance regimen B (M-B): cytofluorimetric based reinfusion regimens.<br><br>M-B cytofluorimetric based reinfusion schemes were sub-classified according to the analyzed target cell population, as:<br><br>- Maintenance regimen B1 (M-B1): 375 mg/m2 re-infusions based on CD19+ cells reappearance, defined as CD19+ cells exceedingly the 1% of peripheral blood mononuclear cells<br><br>- Maintenance regimen B2 (M-B2): 375 mg/m2 re-infusions based on CD27+ memory B (CD19+) cells re-emergence when this population |

exceeded 0.05% of peripheral blood mononuclear cells in the first 2 years and 0.1% in the following years.

**Outcome measures**

The primary outcomes of the study will be the ARR, defined as the total number of relapses divided by the total number of patient-years and the time to first relapse (TTFR) over 2 years: a relapse will be defined as a new neurological symptom that occurred without fever or signs of infection and the lasted at least for 24 h. To count relapses after a complete induction treatment we excluded from the analysis the relapses that occurred in the first 3 months after RTX initiation, since RTX maximum efficacy might need several months to occur.

Relapses will be therefore counted from month 3 after RTX initiation to 24 months (2 years analysis) or to the last available follow-up.

Proportion of patients that reach EDSS of 6 and time to EDSS of 6 will be another outcome measure to evaluate.

**Safety**

We will define adverse events (AE) as any untoward medical occurrence during RTX treatment, even without a causal relationship with the treatment. An infusion related reaction (IRR), will be defined as any AE occurring during RTX in-hospital infusions. An AE will be considered "serious" if it resulted in any of the following outcomes, death, a life-threatening AE, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

**Milestones del proyecto**

**1- Invitación a conformar el equipo de trabajo (Julio 2021)**

**2- Conformación final de equipo de trabajo y acuerdo de trabajo (Julio 2021)**

**3- Desarrollo e implementación de proyecto y formulario de recolección de datos (Agosto2021)**

**4- Fin de recolección de datos (Septiembre 2021)**

**5- Procesamiento y análisis de los datos (Septiembre-octubre 2021)**

**6- Generación de reporte y manuscrito para comunicar (Noviembre 2021)**

**Costo de implementación del proyecto**

- **Milestone 1 a 3, 60% del presupuesto para startup ( 3000 dólares)**
- **Milestone 4 y 5, 30% del presupuesto ( 1500 dólares)**
- **Milestone 6, 10 % final del presupuesto (500 dólares )**
- **Costo total del proyecto 5000 dólares**