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Practice guidelines

Recommendations for the use of Rituximab in neuromyelitis optica spectrum disorders

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ABSTRACT

There is growing evidence of a preventive effect of Rituximab (RTX) in neuromyelitis optica spectrum disorders (NMO-SD). This monoclonal antibody against CD20 is becoming the most widely used preventive therapy in NMO-SD, as a first-line therapy or as a rescue therapy. Nevertheless, considerable heterogeneity still exists concerning the pre-treatment work-up, the vaccinations required before and under treatment, the number and dosage of infusions, prevention of the risk of infusion-related reactions, prevention of infections under treatment, and frequency of therapeutic cycles. Thanks to a collaborative work among NMO-SD experts belonging to the NOMADMUS project, we provide here recommendations for all these topics concerning RTX use in NMO-SD.

1. Introduction

The term neuromyelitis optica spectrum disorders (NMO-SD) refers to an auto-immune inflammatory demyelinating disease of the central nervous system, which is distinct from multiple sclerosis (MS). NMO-SD is potentially a life-threatening condition where disability is driven by acute attacks. Thus, the aim of maintenance therapy in NMO-SD is to avoid any further attack. The International Panel for NMO Diagnosis (IPND) has recently revised the diagnostic criteria for NMO-SD, allowing the diagnosis to be made earlier and a suitable preventive therapeutic strategy to be implemented [1]. NMO-SD is a rare disorder for which no prospective randomized trials have been achieved yet. However, there is a large body of evidence from retrospective studies suggesting that immunoactive drugs targeting B cell lineage are efficient in NMO-SD.

Among these drugs, rituximab (RTX) is a widely used preventive therapy in NMO-SD. RTX is a chimeric monoclonal antibody against CD20, a human B-lymphocyte antigen. CD20 is expressed at the membrane of B-lymphocytes from the early stages of development (pre-B cells) to mature B cells, but is no longer expressed at the membrane of plasma cells, which are the next stage of B cells and which produce antibodies.

There is growing evidence of a preventive effect of RTX in NMO-SD [2]. Some practitioners use RTX as a first line therapy in order to prevent relapses of NMO-SD [3], whereas others use it as a rescue therapy after unsuccessful first-line therapy [4].

Although RTX is increasingly employed in NMO-SD, considerable heterogeneity still exists concerning the following: pre-treatment work up, vaccinations required before and under treatment, number and dosage of infusions, prevention of the risk of infusion-related reactions, prevention of infections under treatment, and frequency of therapeutic cycles.

In order to provide guidelines about these topics, a consortium of NMO-SD experts belonging to the NOMADMUS study group met regularly and set up a working group. First of all, the working group established a spreadsheet for the above questions concerning the use of RTX, in order to collect the experience of each expert. Answers were discussed collegially, considering the experience of all the experts and the literature data. For each point, a proposition was made according to evidence-based data, national or international recommendations, or if a consensus emerged among the experts (majority of experts agreeing to a proposition). Finally, the working group drafted propositions of guidelines regarding the management of RTX in NMO-SD and submitted them to the members of the French societies for MS and NMO-SD (*Société Francophone de la Sclérose en Plaques* and *Observatoire Français de la Sclérose en Plaques*) for final revision. The use of RTX in paediatric patients suffering from NMO-SD is out of the scope of these guidelines.

Fig. 1 summarizes recommendations for RTX use in NMO-SD.

2. Question 1: work up before starting rituximab

We discussed whether the following laboratory tests were essential before starting rituximab: complete blood count, lymphocyte subset counts (CD19, CD4, CD8), serum protein electrophoresis, immunoglobulin subset amounts (IgG, IgM, IgA, ± IgG subclasses), serology tests for hepatitis C, hepatitis B, HIV and VZV, tuberculin skin test and/or quantiFERON®-TB Gold, and β-HCG. We also discussed whether chest X-ray or other radiological examinations (for example, dental panoramic, sinus X-ray…) were useful.

We all recommended complete blood count and lymphocyte subset counts, given that serum CD19+ lymphocytes reflect the circulating B-cell population quite well (although this antigen is not expressed at the membrane of all plasma cells). There was also a consensus for performing serum protein electrophoresis, immunoglobulin subset amounts, HIV, hepatitis B, hepatitis C and VZV serology tests.

One expert usually performs JC virus serology as some cases of progressive multifocal leukoencephalopathy (PML) have been described under RTX therapy, but almost exclusively in non-neurological indications. Nevertheless, the

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