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Dramatic efficacy of ofatumumab in refractory pediatric-onset AQP4-IgG neuromyelitis optica spectrum disorder

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Neuromyelitis optica spectrum disorder (NMOSD) is a rare but severe demyelinating condition that affects mainly adult patients. However, childhood onset has been reported and is related to a very active disease[1] and poor outcome. Several evidence suggest that the crucial role of antiaquaporin-4 (AQP4) antibodies (Abs) in the pathogenesis of NMOSD justify the use of plasma exchanges and rituximab (RTX) as a treatment strategy targeting Ab and B-cells, respectively. Although RTX, a chimeric anti-CD20 monoclonal Ab, is associated with great efficacy in preventing NMOSD relapse, its use can be limited by severe infusion-related adverse event and infectious risk. Ofatumumab (OFA), a fully humanized anti-CD20 monoclonal antibody, has shown some efficacy in dysimmune diseases, including multiple sclerosis (MS).[2] In pediatrics, OFA has been used in RTX-resistant nephrotic syndrome.[3] We report here the case of a young girl with a very active AQP4-Ab NMOSD, with clinical worsening despite intensive immunosuppressant therapies. The use of OFA was associated to dramatic efficacy and great safety.

An 8-year-old girl born in Guyana, but living in France since 4 years, with unremarkable familial and medical history was admitted for a severe bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM) in March 2008. After 3 infusions of methylprednisolone and oral tapering steroids, she fully recovered. Five months later, another LETM occurred, revealing the presence of AQP4-Ab in the serum tested as previously described,[4] leading to the diagnosis of NMOSD. During the following 9 years, despite intensive immunosuppression by immunoadsorptions/plasma exchanges, mycophenolate mofetil, and RTX (figure), 9 severe relapses occurred, resulting in a permanent visual disability with right amblyopia (visual acuity using Snellen chart, with decimal equivalent [OD=0.1; OS=0.8, Expanded Disability Status Scale = 3]). RTX pediatric protocol was based on 2 infusions with an interval of 2 weeks (375 mg/m^2 for each infusion): initially at each relapse (considering the very young age of the patient) and then every 6 months, since 2013. From September 2014, the patient began to suffer from RTX infusion-related reaction, culminating in July 2015, with a hospitalization in an intensive care unit for anaphylactic-like reaction clearly related to RTX. The following infusions were performed in an intensive care unit. Beyond the persistence of clinical activity, B-cells were still detected despite RTX. Moreover the patient experienced a severe sepsis related to the infection of a central catheter used for both immunoabsorption/plasma exchanges and RTX. Because of these different adverse events and the persistence of relapses, subcutaneous OFA was introduced in August 2017: one injection of 20 mg every week during 4 weeks and then one injection of 20 mg every 4 weeks. In 2018, detection of antibodies (immunoglobulin G) against RTX retrospectively validated the therapeutic change. After 2

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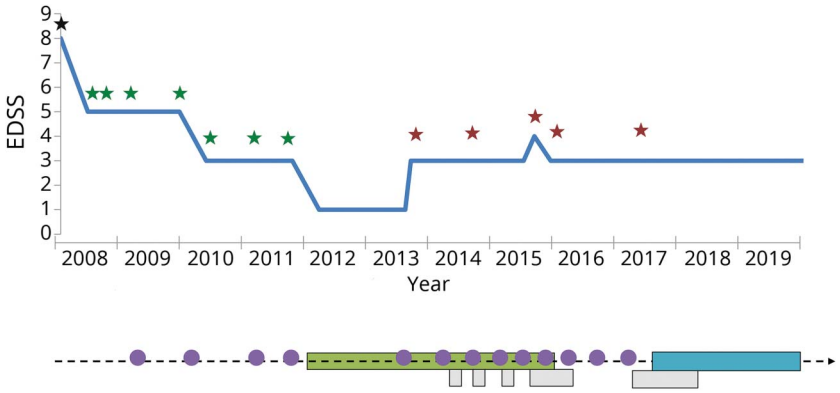
Figure Timeline of relapse frequency, disability course and different treatment regimes



Stars indicate relapses: black star = optic neuritis and myelitis; red star = optic neuritis; green star = myelitis. Purple circles indicate infusions of rituximab. Green bar indicates treatment by MMF; blue bar indicates treatment by OFA; grey bars indicate treatment by PLEX. EDSS = Expanded Disability Status Scale; MMF = mycophenolate mofetil; OFA = ofatumumab; PLEX = plasma exchanges; RTX = rituximab.

years of follow-up and 30 injections of OFA, no further relapse occurred. In November 2019, clinical examination was normal, except visual disability (Expanded Disability Status Scale = 3). In January 2019, MRI revealed no radiologic activity but an atrophy of optic nerves and a persistent spinal cord lesion from C2 to T5. Tolerance was perfect with no anaphylactic-like nor infectious event. Apart from complete B-cell depletion, no lymphopenia or hypogammaglobulinemia was noticed.

RTX, a chimeric monoclonal antibody anti-CD20, is used off-label in NMOSD. CD20 is expressed at the membrane of the B-cell from the stage of pre-B-cells to mature B-lymphocyte but also in less than 5% of T lymphocytes. Major mechanism of action of RTX is the result of destruction of B-cells caused by antibody-dependent cell-mediated cytotoxicity involving natural killer cells and by complement-dependent cytotoxicity.[5] Although RTX is associated to a good tolerance and safety profile in children with neuroinflammatory conditions, more than 10% of treated children presented infusion-related adverse event, suggesting the need for another B-cell-targeting treatment associated with a better tolerance.[6] Moreover, RTX may induce immunization with anti-RTX antibodies associated with infusion-related adverse events and/or inefficacy.[7]

OFA, a fully humanized monoclonal antibody targeting CD20, binds to an epitope distinct from the one recognized by RTX and is a more potent activator of complement-dependent cytotoxicity in vitro. The fully humanized design prevents the risk of antidrug-antibodies production. Similar to other subcutaneous monoclonal antibodies, injection-related systemic reactions are less expected than infusion-related ones. Moreover, the subcutaneous way of administration allows a quick self-administration and limits the infectious risk of IV administration, as reported in our case.

Although emerging treatments have been proposed in AQP4-IgG NMOSD, this observation suggests that subcutaneous OFA may be a well-tolerated and effective alternative in refractory AQP4-IgG NMOSD or in case of intolerance of RTX. Further studies will be necessary to explore the safety and efficacy of OFA in NMOSD in a controlled clinical trial.

Classification of evidence

This case report provides Class IV evidence that OFA in patients with AQP4-IgG-NMOSD might be effective. This is a single observational study without controls.

Study funding

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Disclosure

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