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

Elisabeth Maillart, MD, Florence Renaldo, MD, Caroline Papeix, MD, PhD, Kumaran Deiva, MD, PhD, Julie Bonheur, MD, Teresa Kwon, MD, PhD, Odile Boespflug-Tanguy, MD, PhD, David Germanaud, MD, PhD, and Romain Marignier, MD, PhD

Correspondence

Dr. Maillart
elisabeth.maillart@aphp.fr

Neurol Neuroimmunol Neuroinflamm 2020;7:e683. doi:10.1212/NXI.0000000000000683

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 disease¹ and poor outcome. Several evidence suggest that the crucial role of aquaporin-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 immunoabsorptions/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/m² 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

From the AP-HP (E.M., C.P.), Pitié-Salpêtrière Hospital, Department of Neurology and Centre de Référence des Maladies Inflammatoires Rares du Cerveau et de la Moelle; Robert Debré Hospital (J.B.F.R., O.B.-T., D.G.), AP-HP Department of Child Neurology; Université de Paris (F.R., O.B.-T., D.G.); Department of Pediatric Neurology (K.D.), National Referral Center for Rare Inflammatory Brain and Spinal Diseases, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre; Robert Debré Hospital (T.K.), AP-HP Departments of Child Nephrology, Paris; and Service de neurologie (R.M.), sclérose en plaques, pathologies de la myéline et neuro-inflammation, and Centre de Référence des Maladies Inflammatoires Rares du Cerveau et de la Moelle, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Lyon/Bron, France.

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

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

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

No targeted funding reported.

Disclosure

E. Maillart reports personal fees from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva and grants from Novartis and Roche, outside the submitted work. F. Renaldo reports no disclosures. C. Papeix reports personal fees from Biogen, MedDay, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva, outside the submitted work. K. Deiva has received consulting fees and travel grants from Novartis, Biogen, Sanofi, Merck, and Servier. J. Bonheur reports no disclosures. T. Kwon, O. Boespflug-Tanguy, and D. Germanaud report no disclosures. R. Marignier served on the scientific advisory board of MedImmune and received travel funding and speaker honoraria from Biogen, Genzyme, Novartis, Merck Serono, Roche, Sanofi-Aventis, and Teva. Go to Neurology.org/NN for full disclosures.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* November 18, 2019. Accepted in final form January 13, 2020.

Appendix Authors

Name	Location	Role	Contribution
Elisabeth Maillart, MD	AP-HP, Pitié-Salpêtrière Hospital, Department of Neurology, Paris, France	Corresponding Author	Designed and conceptualized the study; analyzed the data; drafted the manuscript for intellectual content
Florence Renaldo, MD, PhD	Robert Debré Hospital, AP-HP, Department of Child Neurology, Paris, France	Author	Interpreted the data; revised the manuscript for intellectual content
Teresa Kwon, MD, PhD	Robert Debré Hospital, AP-HP Departments of Child Nephrology, Paris, France	Author	Interpreted the data; revised the manuscript for intellectual content
David Germanaud, MD, PhD	Robert Debré Hospital, AP-HP Departments of Child Neurology, Paris, France	Author	Interpreted the data; revised the manuscript for intellectual content
Caroline Papeix, MD, PhD	AP-HP, Pitié-Salpêtrière Hospital, Department of Neurology, Paris, France	Author	Interpreted the data; revised the manuscript for intellectual content
Kumaran Deiva, MD, PhD	Department of Pediatric Neurology, National Referral Center for Rare Inflammatory Brain and Spinal Diseases, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France	Author	Interpreted the data; revised the manuscript for intellectual content

Appendix (continued)

Name	Location	Role	Contribution
Julie Bonheur, MD, PhD	Robert Debré Hospital, AP-HP Departments of Child Neurology, Paris, France	Author	Interpreted the data; revised the manuscript for intellectual content
Odile Boespflug-Tanguy, MD, PhD	Robert Debré Hospital, AP-HP Departments of Child Neurology, Paris, France	Author	Interpreted the data; revised the manuscript for intellectual content
Romain Marignier, MD, PhD	Department of Neurology, Hôpital Neurologique GHE, Lyon, France	Author	Designed and conceptualized the study; analyzed the data; interpreted the data; revised the manuscript for intellectual content.

References

1. Absoud M, Lim MJ, Appleton R, et al. Paediatric neuromyelitis optica: clinical, MRI of the brain and prognostic features. *J Neurol Neurosurg Psychiatry* 2015;86: 470–472.
2. Hauser S. Efficacy and safety of ofatumumab versus teriflunomide in relapsing multiple sclerosis: results of the phase 3 ASCLEPIOS I and II trials. Paper presented at: 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 13, 2019; Stockholm, Sweden.
3. Basu B. Ofatumumab for rituximab-resistant nephrotic syndrome. *N Engl J Med* 2014;370:1268–1270.
4. Marignier R, Bernard-Valnet R, Giraudon P, et al. Aquaporin-4 antibody-negative neuromyelitis optica: distinct assay sensitivity-dependent entity. *Neurology* 2013;80: 2194–2200.
5. Collongues N, Ayme-Dietrich E, Monassier L, de Seze J. Pharmacotherapy for neuromyelitis optica spectrum disorders: current management and future options. *Drugs* 2019;79:125–142.
6. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014;83:142–150.
7. Wincup C, Menon M, Smith E, et al. Presence of anti-rituximab antibodies predicts infusion-related reactions in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:1140–1142.

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DOI 10.1212/NXI.0000000000000683

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