Case Report

Ofatumumab, a Fully Human Anti-CD20 Monoclonal Antibody, in the Treatment of Severe Refractory Anti-N-methyl-D-Aspartate Receptor Encephalitis: Two Case Reports

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Abstract

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a type of autoimmune encephalitis (AE) characterized by antibodies against NMDA receptor. As the most common AE, anti-NMDAR encephalitis affects 54% ~ 80% of patients with AE. It is associated with a high percentage of severe illness. It typically manifests as behavioral and psychiatric disturbance, epilepsy, cognitive decline, decreased level of consciousness, involuntary movements, autonomic dysfunction, central hypoventilation, etc. We report two refractory anti-NMDAR encephalitis. One of them describes a case of anti-NMDA encephalitis coexisting with MOG antibodies. The two patients were administered first-line therapy with glucocorticoids and intravenous immunoglobulin but did not improve clinically. Therefore, the patient was switched to the fully human anti-CD20 monoclonal antibody, ofatumumab. Their consciousness, behavioral and psychiatric disturbance, and capacity to conduct daily tasks improved markedly after sequential therapy with ofatumumab, as demonstrated by the modified Rankin scale (mRS) score. For the first time, we report a successful approach to the treatment of refractory anti-NMDAR encephalitis using the fully human anti-CD20 monoclonal antibody ofatumumab, which serves as an important reference for the treatment of AE.

Keywords: Anti-N-Methyl-D-Aspartate, case report, encephalitis, NMDA, ofatumumab

Introduction

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common type of autoimmune encephalitis (AE). Patients with NMDAR encephalitis usually presented with psychosis, behavioral changes, amnesia and epileptic seizures, frequently followed by dyskinesia and decreased levels of consciousness.[1] About 80% of patients improve with immunotherapy and, if needed, tumor removal, but the recovery is slow.[1] The treatment approach to anti-NMDAR encephalitis involves escalation of immunotherapy. Most clinicians use the first-line therapies including steroids, intravenous immunoglobulins, or plasma exchange and if severe or refractory, second-line therapies including rituximab or cyclophosphamide will be started.[2,3] Treatment with intravenous infusion rituximab requires premedication and hospitalization. Ofatumumab is a novel, fully human monoclonal antibody administered subcutaneously (20 mg) once a month[4] and was approved by the EMA and FDA to treat patients with relapsing multiple sclerosis.

Until now, none of the cases reported anti-NMDAR encephalitis treated by ofatumumab. Here, we first reported two cases of patient with refractory anti-NMDAR encephalitis that failed from first-line treatment and clinical symptoms significantly improved from ofatumumab therapy.

Presentation

Case 1

A 49-year-old male patient with preexisting type 2 diabetes mellitus was referred to a local hospital due to headache, visual disturbance, and mood disorders. After 4 days, a gradual worsening of headache occurred. The patient developed psychosis, behavioral disorders, bilateral lower extremity weakness, and urinary retention with a modified Rankin Scale (mRS) score of 3. Lumbar puncture showed mild pleocytosis with lymphocytes (white blood cell [WBC] count 20/μL) Laboratory examination by cell-based assay 00 revealed positive NMDAR IgG in serum and cerebrospinal

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fluid (CSF) (serum titer 1:10, CSF titer 1:10). Presence of IgG directed to MOG (serum titer 1:10, CSF titer 1:100). Laboratory tests, including malignancy workup [i.e., Ri, Yo, Hu, Ma2/Ta (PNMA2), LGI1, CV2/CRMP5, amphiphysin] yielded negative results. Herpes simplex virus (HSV) was negative via polymerase chain reaction (PCR). Brain magnetic resonance imaging (MRI) revealed a normal scan while abnormal signals in the spinal canal of 5 lumbar vertebra and 1 sacral vertebra. The residual bladder volume was estimated to be 442 mL using color doppler ultrasonography. The scores of Montreal Cognitive Assessment and Mini-Mental State Examination were 11/30 and 16/30, respectively. It suggested that the patient had experienced cognitive impairment. Considering the coexistence of the anti-NMDAR and anti-MOG antibody, the patient was eventually diagnosed as overlapping syndrome of anti-MOG antibody encephalitis and anti-NMDAR encephalitis (MNOS).

After diagnosed MNOS, the patient was treated with high-dose intravenous methylprednisolone (1,000 mg/d for 3 consecutive days), followed by reduced-dose intravenous methylprednisolone (500 mg/d for 3 consecutive days) and combined with intravenous immunoglobulin (IVIG, 2 g/kg for 5 days) [Figure 1a]. However, after first-line immunotherapy, the patient further deteriorated and was admitted to our hospital, while occurring hazy consciousness, urinary and bowel disorders, within dwelling urinary catheter, and cardiac monitoring as well as oxygen inhalation. The mRS score deteriorated to 5. To alleviate deterioration, we started the second-line treatment with Ofatumumab 20 mg subcutaneously

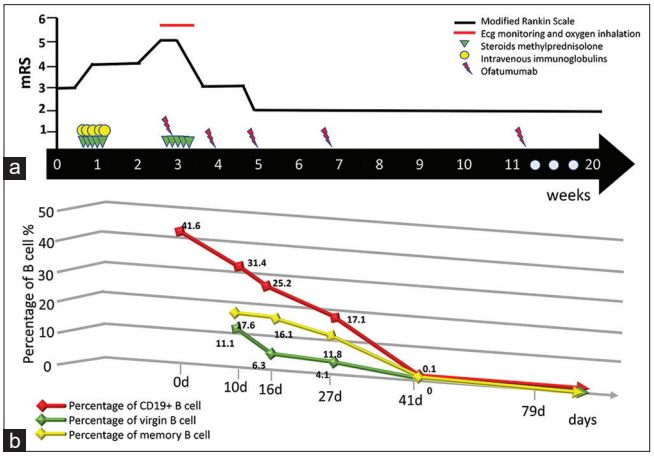

Figure 1: (a) Timeline of the patient I treatment. mRS: modified Ranking scale (0, No symptoms; 1, No significant disability; 2, Slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; 3, Moderate disability. Requires some help but is able to walk unassisted; 4, moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5, Severe disability. Requires constant nursing care and attention, bedridden, incontinent, 6 – Dead). (b) Time course of the proportion of CD19+, virgin, and memory B cells after Ofatumumab injection. In 41 days after starting Ofatumumab, the proportion of CD19+ B cells dropped to 0.06%, and the proportion of B cells fluctuated around 2% in subsequent monitoring

via family-based informed consent, while glucocorticoid therapy was initiated again.

Before ofatumumab administration, we checked the patient's B-cell counts (CD19+), and CD19+ B-cell counts of total lymphocytes in peripheral blood was 41.62% [Figure 1b]. After treated with ofatumumab, the patient's status gradually improved, his daytime irritability decreased, nighttime sleep was made possible, psychiatric symptoms improved, cognition gradually recovered, simple communication was possible, near-memory loss was corrected, and the urinary catheter was removed. The second and third injections were given subcutaneously at weeks 1 and 2, respectively. At the 16th day after receiving ofatumumab, the patient's mental status returned to normal and speech was more fluent than before with significant improved cognition and memory. He achieved basic self-care and was discharged from the hospital in good condition followed oral glucocorticoids outside the hospital. At the 27th day after receiving ofatumumab, the patient returned to our hospital. The cranial and spinal MRI showed a normal scan. He was administered the fourth injection of ofatumumab subcutaneously. At the 41st day, the patient experienced the second re-examination. He had consciousness, capability for self-care, and better memory than before but slightly slower response. The laboratory test revealed CD19+ counts of total lymphocytes was 0.06%. The absolute B cell counts had decreased to 0.815/μL, virgin B cell counts (CD19+CD27-IgD+) decreased to 0%, and memory B cell counts (CD19+CD27+CD38dim/-) was reduced to 0.16%; the values decreased significantly from the previous recheck and were close to the treatment target.

Case 2

An 18-year-old female student was admitted to the hospital with psychosis, behavioral disorders for previous 13 days. She complained of academic pressure repeatedly while her logic thinking was normal. A week later, it was difficult to communicate with the patient. Meanwhile, irritability and insomnia occurred. In addition, psychosis, behavioral disorders further aggravated. She was administered "risperidone and buspirone" to alleviate her psychiatric symptoms but failed to improve. When the patient was referred to our hospital, she was irritated, screaming, and belligerent with a mRS score of 3. A lumbar puncture revealed a slight increase in lymphocytes (10 cells/microliter) despite no abnormalities in laboratory test, malignancy screening, or cerebrospinal fluid submitted for second-generation sequencing. Cell-based assay was used to detect AE-related antibodies in the cerebrospinal fluid and serum. anti-NMDA receptor antibodies were positive in the cerebrospinal fluid (titer 1:100) and serum (titer 1:30). The PET-CT showed increased metabolism in the frontotemporal lobes, anterior cingulate gyrus, hippocampus, and striatum, and reduced metabolism in the parietooccipital lobes. Eventually, the patient was diagnosed with typical anti-NMDAR encephalitis.

The patient was initiated with intravenous methylprednisolone (1,000 mg/d for 3 consecutive days) and immunoglobulin

(IVIG, 2 g/kg for 5 days) [Figure 2a]. However, the patient did not improve clinically, including psychosis, behavioral disorders, delirium, new-onset seizure, and increased muscular tone. The patient further clinically improved showing a mRS score of 5. The electroencephalogram was further improved and the results indicated a moderately abnormal electroencephalogram. We initiated second-line therapy with ofatumumab to prevent further worsening.

Before starting ofatumumab, the level of CD19+ B cells in peripheral blood was 20.4% [Figure 2b]. Unlike the first patient, she started the first injection of ofatumumab, her clinical symptoms had improved on the 7th day of receiving ofatumumab, the patient developed a fever with temperature fluctuations of 37.4–38.2°C and suspended ofatumumab. On the 10th day, the patient was administered the second injection of ofatumumab. The patient's status of awareness improved on the 14th day; muscle hypertonia occurred and involuntary movements were reduced. And the patient was lethargic on the 19th day. She could complete simple commands while awake. Following the third injection of ofatumumab on the 27th day, the patient's psychosis had improved significantly, and she was irritable, despite bulimic. CD19+ B cells in peripheral blood had decreased to 0. The patient returned to the hospital for a check-up on the 95th day. Her bulimia nervosa improved than before, and she had emotional fluctuation. Additionally, she could basically take care of her own life but could not do schoolwork. At this recheck, the CD19+ B cells was 1.17%. Then, she received the fourth injection of ofatumumab.

Discussion

With increasing clinical evidence, treatment targeting B cells is investigated more and more in AE. One of the most extensively studied targets is CD20 that is mainly distributed in the B cell precursor stage to the plasma cell stage and is essential for the differentiation and development into plasma cells.[5,6] Rituximab

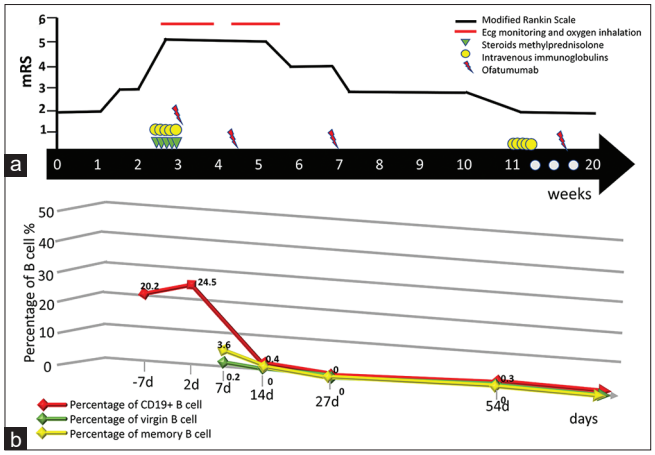

Figure 2: (a) Timeline of the patient II treatment. (b) Time course of the proportion of CD19+, virgin, and memory B cells after Ofatumumab injection. The proportion of CD19+ B cells decreased to 0% 27 days after the initiation of Ofatumumab, and the proportion of B cells fluctuated around 1% in subsequent monitoring

is a B-cell-depleting monoclonal antibody targeting CD20. It has been reported that rituximab can improve long-term prognosis in a variety of autoantibody-associated AE compared to intensive or recurrent first-line immunotherapy.[7] In a multicenter study, rituximab-treated NMDAR-AE patients had a substantially decreased recurrence incidence among 358 AE patients and were more likely to achieve independent living (mRS score ≤2).[8] However, infusion reactions following the administration of rituximab are frequent, occurring in 10–15% of patients with systemic lupus erythematosus in randomized studies,[9] and these reactions may be severe enough to prevent patients who have previously displayed a good clinical response from receiving further treatment. Human anti-chimeric antibodies were observed in 5–10% of patients with rheumatoid arthritis treated with rituximab,[10] perhaps reflecting the enhanced immune responsiveness of these patients. Ofatumumab has the distinct benefit of being a fully humanized CD20 monoclonal antibody with minimal immunogenicity.

Ofatumumab, unlike rituximab, binds to two separate locations inside the large and small extracellular loops of CD20 antigen, predominantly via complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity-induced B cell lysis. This binding to distinct conformational epitopes is distinguished by a slow dissociation rate and increased complement-dependent cytotoxicity.[11] Therefore, ofatumumab has more efficacy and efficiency in depleting B cells than previous anti-CD20 agents, allowing for subcutaneous delivery at lower dosages. Ofatumumab has been approved for the treatment of recurrent multiple sclerosis (MS) in adults, including clinically isolated syndromes, relapsing remitting disease, and active secondary progressive disease, in the United States, the European Union, and several other countries. In a study of 1,486 individuals with relapsing MS, the intended B-cell targets were best achieved and maintained in a 20 mg dosing regimen, which corroborates the rationale for the 20 mg injectable dose.[12] Ofatumumab is unique in three aspects: fully human, low dose, and subcutaneous administration. With these three innovations, it combines efficiency and safety with dose precision, which makes it a first-line treatment option for patients with MS. The fully humanized ofatumumab was approved by National Medical Products Administration (NMPA) for the MS indication in December 2021. Until now, there have been no reports of AE treated with ofatumumab.

In our cases, both patients I and II n continued to deteriorate after first-line immunotherapy, mRS scores deteriorated to 5. After initiation of ofatumumab monotherapy, the patient's level of consciousness gradually recovered, care dependence decreased, and cardiac monitoring and oxygen inhalation were gradually withdrawn. In contrast to patient II who showed significant improvement at 3 weeks, patient I showed marked remission within a week, which may be related to the different antibody titers of the patients. We monitored the counts of CD19+B-cell, virgin B-cell (CD19+CD27-IgD+), and memory B-cell (CD19+CD27+CD38dim/-) during ofatumumab

treatment [Figure 3]. In case 1, B-cell clearance was achieved after four subcutaneous injections of ofatumumab, i.e., after 41 days [Figure 1b], whereas in case 2 B-cell clearance was achieved after three injections, i.e., after 21 days [Figure 2b]. The differences were considered to be the result of different individual starting B-cell level.

There are limitations in our report. So far, there are no randomized controlled trials of ofatumumab in the treatment of anti-NMDA encephalitis. Secondly, the improvement in symptoms may be influenced by repeated first-line immunotherapies, which did not allow us to attribute the clinical improvement entirely to Ofatumumab alone. However, at 3–4 month-follow-up, both patients were able to take care of themselves independently, although they were unable to completely perform their previous work and studies. So ofatumumab may be a novel option for diseases such as immune encephalitis, inflammatory demyelinating disease, or antibody overlapping syndrome.

The current basic regimen for ofatumumab treatment is 20 mg subcutaneously at weeks 0, 1, 2, and 4, followed by 20 mg subcutaneously every 4 weeks, which can be influenced by changes in the patient's status, adverse effects, and other factors. The efficacy of this regimen is still unknown and clinical real-world data and randomized controlled studies from multiple centers are needed to assess the clinical improvement, long-term prognosis, relapse rate, and adverse effects of ofatumumab in AE. In our cases, satisfactory clinical outcomes were still observed in anti-NMDR encephalitis while first-line therapy failed. Thus, the case report provides reference for new treatment options of AE.

Authors' contributions

HFX collected and analyzed the data and drafted the manuscript. LZ, XJ, ML, SH, YS, and JJ contributed to drafting the manuscript. YSJ analyzed the data and contributed to drafting the manuscript. WL conceived the study, analyzed the data, and drafted the manuscript.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This study was approved by the ethics committee of Henan Provincial Peoples Hospital.

Consent for publication

Informed consents were obtained from the patients.

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Conflicts of interest

There are no conflicts of interest.

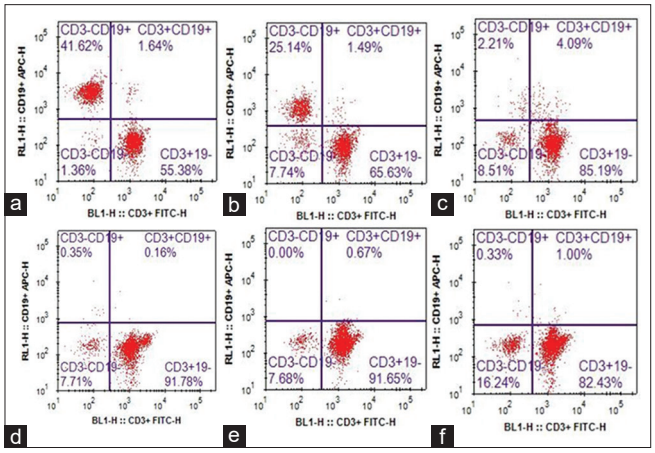

Figure 3: Analysis of lymphocyte phenotype after Ofatumumab treatment. (a-c) Case I was analyzed by peripheral blood lymphocyte flow cytometry at 0, 16, and 59 days after drug administration. (d-f) Case II was analyzed by flow cytometry of peripheral blood lymphocytes at 10, 16, and 59 days after drug administration

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