Treatment strategies for autoimmune encephalitis

Yong-Won Shin, Soon-Tae Lee, Kyung-Il Park, Keun-Hwa Jung, Ki-Young Jung, Sang Kun Lee and Kon Chu

Abstract: Autoimmune encephalitis is one of the most rapidly growing research topics in neurology. Along with discoveries of novel antibodies associated with the disease, clinical experience and outcomes with diverse immunotherapeutic agents in the treatment of autoimmune encephalitis are accumulating. Retrospective observations indicate that early aggressive treatment is associated with better functional outcomes and fewer relapses. Immune response to first-line immunotherapeutic agents (corticosteroids, intravenous immunoglobulin, plasma exchange, and immunoabsorption) is fair, but approximately half or more of patients are administered second-line immunotherapy (rituximab and cyclophosphamide). A small but significant proportion of patients are refractory to all first- and second-line therapies and require further treatment. Although several investigations have shown promising alternatives, the low absolute number of patients involved necessitates more evidence to establish further treatment strategies. In this review, the agents used for first- and second-line immunotherapy are discussed and recent attempts at finding new treatment options are introduced.

Keywords: autoimmune encephalitis, immunotherapeutic agent, treatment option

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Introduction

Limbic encephalitis (LE), first described in 1960,1 is characterized by a subacute onset of episodic memory loss and confusion frequently accompanied by seizures, psychiatric symptoms, and lesion involving the medial temporal lobe and hippocampus. Infectious agents such as herpes simplex virus cause inflammation in the central nervous system (CNS) including the limbic area of the brain, but a substantial number of patients with LE are without clear evidence of CNS infection. The existence of autoantibodies and a response to immunotherapy in these patients suggests that an aberrant immune reaction is involved in the disease pathogenesis. Autoimmune etiology is increasingly recognized as a major cause of LE along with the finding of the high prevalence of anti-N-methyl-D-aspartate receptor (NMDAR) antibody-associated encephalitis after the discovery of the antibody2 and the continued identification of additional novel antibodies in LE. These antibodies often affect not only limbic structures but also other cerebral regions, and the term autoimmune encephalitis (AE), rather than autoimmune LE, is used with growing frequency to refer to this disease entity.

AE is classified according to the location of the antigen, either intracellular or on the cell surface, because each classification is associated with different clinical features, especially pertaining to cancer association and immune therapy responsiveness. Antibodies targeting nuclear and cytoplasmic proteins (onconeural antibodies) such as Hu, Ma, and Ri usually accompany malignancy,3,4 and LE coincident with the detection of these antibodies is termed ‘paraneoplastic LE.’ Patients producing these antibodies respond poorly to immunotherapy, but treatment of the cancer often results in neurological improvements.4–6 The intracellular location of the antigens, and...
Neuronal cell-surface antibodies (NSAbs) are another group of antibodies detected in AE. NSAbs target an extracellular epitope, and their corresponding antigens are often synaptic receptors or components of synaptic protein complexes. Anti-NMDAR antibodies are most common, followed by antibodies against leucine-rich glioma inactivated-1 (LGI1).\(^7\)\(^-\)\(^10\) The contactin-associated protein like 2 (Caspr2),\(^11\) \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR),\(^12\) gamma-aminobutyric acid (GABA)-A and -B receptors,\(^13\)\(^,\)\(^14\) dipetidyl-peptidase-like protein-6 (DPPX),\(^15\) and glycine receptor (GlyR)\(^16\) antibodies are other examples of recently identified NSAbs. Unlike encephalitis with antibodies to intracellular antigens, the frequency of cancer in cases involving antibodies targeting cell-surface antigens is, to a varying degree dependent upon the particular type of antibody, lower.\(^8\)\(^,\)\(^17\) Several sources of evidence support the theory that the pathogenesis of encephalitis is mainly antibody-mediated in AE associated with this group of antibodies.\(^18\) Patients producing NSAbs generally show a good response to immunotherapy and have a better overall prognosis.

Of note, glutamic acid decarboxylase 65 (GAD65) is an intracellular enzyme that catalyzes the conversion of GABA, however, AE presenting with anti-GAD65 antibodies is often non-paraneoplastic and shows better immune responsiveness than paraneoplastic LE.\(^19\)\(^,\)\(^20\) In addition, anti-GAD65 antibody is related to diverse diseases including AE, cerebellar ataxia, stiff-person syndrome (SPS), and type 1 diabetes.\(^21\) SPS is a rare condition characterized by axial and limb muscle stiffness and painful spasms, and is associated with antibodies against GAD65, GlyR, and amphiphysin.\(^22\) Anti-GlyR antibodies, in particular, are preferentially associated with progressive encephalitis with rigidity and myoclonus (PERM), an aggressive form of SPS spectrum disorder with additional symptoms including brainstem dysfunction, hyperekplexia, sensory symptoms, and dysautonomia.\(^23\) Anti-GlyR antibodies are directed against cell-surface antigens and patients with these antibodies are more responsive to immunotherapy,\(^23\) compared with those with anti-GAD65 (against intracellular antigens) or anti-amphiphysin antibodies (evidence of T-cell-mediated neuronal cell damage).\(^24\)

Early, appropriate, and intense treatment is important for achieving a good outcome in AE. However, treatment is challenging because the rarity of the disease limits clinical experience and the evidence base guiding the intervention. Moreover, multiple lines of treatment are essential in many cases, and rather experimental options are not infrequently required. In light of these issues, we review here the currently used AE treatment modalities and recent advances in immunotherapy. The present review focuses on AE associated with NSAbs and, without special notation, we will use the term ‘AE’ to refer to AE with NSAbs only.

**Pathogenic mechanism and diagnosis of autoimmune encephalitis**

Most T cells that recognize self-antigens are eliminated in the thymus and some self-reactive T cells that escape this process are controlled in the periphery by further deletion, induction of anergy, or suppression by regulatory T cells (Tregs).\(^25\) Self-reactive B cells are also subject to the processes of negative selection, such as deletion, receptor editing and induction of anergy, throughout the development in the bone marrow and spleen.\(^26\) Patients may become prone to autoimmune disease when there is a loss of tolerance to self-antigens, and dysregulated activation of T and B cells. In particular, activation of self-reactive B cells and their subsequent proliferation and differentiation into autoantigen reactive memory B cells and autoantibody-secreting plasma cells, play pivotal roles in antibody-mediated autoimmunity, including AE. Patients with AE respond to the treatments that aim to lower the titers of autoantibodies, such as intravenous immunoglobulin (IVIg) and plasma exchange (PLEX), emphasizing the role of autoantibodies in disease pathogenesis. Animal model studies replicating features of AE by passive transfer of cerebrospinal fluid (CSF) or immunoglobulins (Igs) from anti-NMDAR encephalitis patients to mice provided more direct evidence of autoantibody pathogenicity.\(^27\)\(^,\)\(^28\)

Pathogenic roles of autoantibodies include receptor crosslinking and internalization, complement activation and direct disruption of the epitope, as demonstrated in AE by several immunopathologic analyses and *in vitro* studies.\(^18\)\(^,\)\(^29\) In the case
of anti-NMDAR encephalitis, receptor internalization and reduced NMDAR currents were observed in rodent hippocampal neurons and HEK293 cells expressing GluN1 and GluN2 subunits of the NMDAR treated with patient antibody.30,31 Other experiments showed that the autoantibodies bind to a region within the amino terminal domain of GluN1 and cause disrupted interaction with ephrin B2 receptor and channel function.32,33

Anti-NMDAR antibodies are predominantly of the IgG1 subclass of IgG.34 However, activation of complement and neuronal injury is not evident in the brain tissues from patients with anti-NMDAR encephalitis or the passive transfer mouse model.27,34–36 In contrast, antibodies against LGI1 and Caspr2 are predominantly IgG437–39 and complement activation and neuronal injury is not evident in the brain tissues from patients with anti-NMDAR encephalitis or the passive transfer mouse model.27,34–36 Detection of anti-neuronal autoantibodies in the serum/CSF is used to confirm AE and specify the associated antibody. Immunohistochemistry (IHC) on cryopreserved rodent brain sections is widely used as a primary screening method to detect autoantibodies. This method has the advantage in detecting antibodies against a wide range of antigens, and has the potential to detect novel neuronal antigens; however, it lacks the ability to identify specific antibody targets. Cell-based assays (CBAs) are now widely used to detect specific NSAbs. CBAs is an immunoassay using cultured cells (i.e. HEK 293) presenting a specific epitope transfected with the complementary DNA, which has the advantage of preserving the conformational epitope.50 This method led to the discovery of anti-NMDAR antibodies,51,52 and the subsequent identification of several other NSAbs.11,12,14,53 Whereas there is recent evidence against the use of radioimmunoassay results for detecting antibodies to the voltage-gated potassium channel complex without confirmation of antibodies to LGI1 and Caspr2,54,55 NSAb detection using CBAs still shows great usefulness with high sensitivity and specificity, especially for CSF samples.50 To achieve the highest sensitivity and specificity, testing both serum and CSF using a combination of IHC and CBAs is recommended.50,56 However, equipment for identifying these antibodies is not widely available in institutions, and it may take several weeks to get the results. Recently proposed clinical diagnostic criteria for AE without antibody testing help to attain early diagnosis in institutions where antibody testing is not readily accessible.17

The differences in IgG subclass and complement activation have several clinical implications. Patients with anti-LGI1 encephalitis or anti-Caspr2 encephalitis generally show a less severe clinical manifestation and faster recovery than patients with anti-NMDAR encephalitis, which may reflect the limited ability of IgG4. Long-term cognitive impairment and hippocampal atrophy shown in follow-up MRI indicate irreversible neuronal damage that may be partly attributable to complement activation and cytotoxic T-cell-mediated neuronal injury. Conversely, reversibility of cerebral atrophy in anti-NMDAR encephalitis is consistent with immunopathological findings including the absence of complement and rare T-cell infiltrates.46,47 With regard to therapy, immunotherapeutic agents targeting complement, such as eculizumab,48 could be a viable option for AE without evidence of complement-mediated neuronal toxicity, but not for AEs without.

AE is diagnosed based on clinical characteristics, magnetic resonance imaging, electroencephalography, functional neuroimaging, work-up for systemic tumors, and detection of autoantibodies.49 Detection of anti-neuronal autoantibodies in the serum/CSF is used to confirm AE and specify the associated antibody. Immunohistochemistry (IHC) on cryopreserved rodent brain sections is widely used as a primary screening method to detect autoantibodies. This method has the advantage in detecting antibodies against a wide range of antigens, and has the potential to detect novel neuronal antigens; however, it lacks the ability to identify specific antibody targets. Cell-based assays (CBAs) are now widely used to detect specific NSAbs. CBAs is an immunoassay using cultured cells (i.e. HEK 293) presenting a specific epitope transfected with the complementary DNA, which has the advantage of preserving the conformational epitope.50 This method led to the discovery of anti-NMDAR antibodies,51,52 and the subsequent identification of several other NSAbs.11,12,14,53 Whereas there is recent evidence against the use of radioimmunoassay results for detecting antibodies to the voltage-gated potassium channel complex without confirmation of antibodies to LGI1 and Caspr2,54,55 NSAb detection using CBAs still shows great usefulness with high sensitivity and specificity, especially for CSF samples.50 To achieve the highest sensitivity and specificity, testing both serum and CSF using a combination of IHC and CBAs is recommended.50,56 However, equipment for identifying these antibodies is not widely available in institutions, and it may take several weeks to get the results. Recently proposed clinical diagnostic criteria for AE without antibody testing help to attain early diagnosis in institutions where antibody testing is not readily accessible.17

**Treatment overview**

Treatment options for AE range from broadly immune-suppressing agents to those targeting processes in antibody-mediated disease pathogenesis. As in most other inflammatory disorders, corticosteroids are used in the treatment of AE, acting to broadly inhibit the inflammatory process. However, corticosteroids possess less specificity for the antibody-mediated immune process, and their efficacy is limited in cases of AE, and they are associated with several systemic side effects. Other lines of treatment address various specific steps in AE’s pathogenesis. Therapeutic targets for these treatments include autoantibodies and other...
immune mediators (IVIg and PLEX), B cells and short-lived plasma cells (rituximab), and specific cytokines associated in the autoimmune and inflammatory process [tocilizumab and low-dose interleukin (IL)-2]. Antiproliferative agents targeting lymphocyte proliferation (cyclophosphamide, azathioprine, mycophenolate mofetil, etc.) are also used in refractory cases or to maintain remission.

Despite the numerous treatment options available, there are issues complicating the treatment of AE. First, peripherally activated B cells can cross the blood–brain barrier (BBB) and undergo clonal expansion and differentiation into antibody-secreting plasmablasts and plasma cells. Histopathological study and CSF analysis indicate intrathecal production of antibodies in anti-NMDAR encephalitis. Immunotherapeutic agents such as rituximab cannot permeate the BBB, which may limit the therapeutic effects of these agents. Second, there are long-lived plasma cells (half-life of >6 months) refractory to conventional immunosuppressive agents and agents targeting B or T cells, leading to the chronicity of autoimmunity with persistent autoantibodies. Long-lived plasma cells may reside in the bone marrow and intrathecal compartment and contribute to refractoriness and relapses. Proteasome inhibitors target these cells, but clinicians have very limited experience with their use in AE. Immunothe

### Table 1. Therapeutic agents used in autoimmune encephalitis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
</tr>
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<tbody>
<tr>
<td><strong>First-line immunotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>1 g daily, for 3–5 days</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>2 g/kg over 5 days (400 mg/kg/day)</td>
</tr>
<tr>
<td>Plasma exchange/immunoadsorption</td>
<td>1 session every other day for 5–7 cycles</td>
</tr>
<tr>
<td><strong>Second-line immunotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² weekly IV infusion for 4 weeks</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m² monthly for 3–6 months</td>
</tr>
<tr>
<td><strong>Alternative therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Initially 4 mg/kg, followed by an increase to 8 mg/kg monthly based on clinical response</td>
</tr>
<tr>
<td>Low-dose interleukin-2 (aldesleukin)</td>
<td>1.5 million IU/day, 4 subcutaneous injections with 3-week interval</td>
</tr>
<tr>
<td><strong>Steroid-sparing agents used for maintenance therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Initially 1–1.5 mg/kg once daily or divided twice daily, target 2–3 mg/kg/d</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Initially 500 mg twice daily, target 1000 mg twice daily</td>
</tr>
</tbody>
</table>

IV, intravenous.
Table 2. Summary of representative case series of each NSAb-associated disorder.

<table>
<thead>
<tr>
<th>Study</th>
<th>Associated NSAb</th>
<th>No. of patients</th>
<th>No. of patients with data available for treatment and outcome</th>
<th>Clinical manifestation</th>
<th>Tumor type</th>
<th>Tumor 1st line chemotherapy</th>
<th>First-line immunotherapy</th>
<th>Corticosteroids</th>
<th>IVIg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NMDAR</td>
<td>577</td>
<td>501</td>
<td>577/577: anti-NMDAR encephalitis</td>
<td>Ovarian teratoma, extranovarian teratoma (n = 4), and other tumors (n = 9)</td>
<td>Prostate cancer (n = 2), gastric neuroendocrine tumor (n = 1), colon carcinoma (n = 1), and bone metastasis with unknown origin (n = 1)</td>
<td>Prostate cancer (n = 2), gastric neuroendocrine tumor (n = 1), colon carcinoma (n = 1), and bone metastasis with unknown origin (n = 1)</td>
<td>Prostate cancer (n = 2), gastric neuroendocrine tumor (n = 1), colon carcinoma (n = 1), and bone metastasis with unknown origin (n = 1)</td>
<td>Gastrointestinal follicular lymphoma (n = 3) and chronic lymphocytic leukemia (n = 1)</td>
</tr>
<tr>
<td></td>
<td>LGII</td>
<td>76</td>
<td>48</td>
<td>63/76: LE; 3/76: non-LE; 10/76: encephalopathy</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
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<td>Thyroma (n = 3), lymphoma (n = 1), and previous treated cancer (n = 1)</td>
</tr>
<tr>
<td></td>
<td>Caspr2</td>
<td>38</td>
<td>21</td>
<td>16/38: LE; 11/38: Morvan syndrome; 3/38: Peripheral nerve hyperexcitability; 1/38: Cerebellar syndrome; 3/38: Others</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
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<td>Thyroma (n = 3), lymphoma (n = 1), and previous treated cancer (n = 1)</td>
</tr>
<tr>
<td></td>
<td>AMPAR</td>
<td>22</td>
<td>21</td>
<td>12/22: LE; 8/22: Limbic dysfunction with multifocal/diffuse encephalopathy; 1/22: Cognitive impairment; 1/22: Psychiatric features</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
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<td>Thyroma (n = 3), lymphoma (n = 1), and previous treated cancer (n = 1)</td>
</tr>
<tr>
<td></td>
<td>GABA&lt;sub&gt;R&lt;/sub&gt;</td>
<td>45</td>
<td>45</td>
<td>15/15: variable (including seizures [n = 7], memory impairment [n = 7], confusion or disorientation [n = 4], psychiatric features [n = 5]), hallucination [n = 2], anxiety [n = 4]</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
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<td>Thyroma (n = 3), lymphoma (n = 1), and previous treated cancer (n = 1)</td>
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<tr>
<td></td>
<td>GABA&lt;sub&gt;R&lt;/sub&gt;</td>
<td>20</td>
<td>20</td>
<td>20/19 for immunotherapeutic agent</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
<td>Thyroma (n = 3), lymphoma (n = 1), and previous treated cancer (n = 1)</td>
</tr>
<tr>
<td></td>
<td>GlyR</td>
<td>45</td>
<td>45</td>
<td>45&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
<td>Small-cell lung cancer (n = 4), thymoma (n = 4), breast cancer (n = 2), ovarian teratoma (n = 2), and lung cancer (n = 1)</td>
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<td>Thyroma (n = 3), lymphoma (n = 1), and previous treated cancer (n = 1)</td>
</tr>
<tr>
<td></td>
<td>DPPX</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>Thymoma (n = 4), adenocarcinoma of the lung (n = 11), carcinoma in situ of sigmoid (n = 1), and thoracic mass without pathologic diagnosis (n = 1)</td>
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</table>

(Continued)
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Titulaer and colleagues 72</th>
<th>Arino and colleagues 38</th>
<th>van Sonderen and colleagues 39</th>
<th>Hoftberger and colleagues 67</th>
<th>Pettingill and colleagues 153</th>
<th>Hoftberger and colleagues 154</th>
<th>Carvajal-González and colleagues 23</th>
<th>Tobin and colleagues 155</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEX</td>
<td>163/501 (33%)</td>
<td>0/48 (0%)</td>
<td>3/30 (10%)</td>
<td>6/21 (29%)</td>
<td>2/15 (13%)</td>
<td>5/19 (26%)</td>
<td>17/44 (39%)</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Second-line immunotherapy</td>
<td>134/501 (27%)</td>
<td>7/48 (15%)</td>
<td>7/30 (10%)</td>
<td>5/21 (24%)</td>
<td>0/15 (0%)</td>
<td>3/19 (16%)</td>
<td>4/44 (9%)</td>
<td>7/20 (35%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>101/501 (20%)</td>
<td>6/48 (13%)</td>
<td>5/30 (17%)</td>
<td>5/21 (24%)</td>
<td>0/15 (0%)</td>
<td>2/19 (11%)</td>
<td>2/44 (5%)</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>81/501 (16%)</td>
<td>3/48 (6%)</td>
<td>2/30 (7%)</td>
<td>1/21 (5%)</td>
<td>0/15 (0%)</td>
<td>1/19 (5%)</td>
<td>0/44 (0%)</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Other immunotherapy</td>
<td>31/501 (6%)</td>
<td>1/48 (2%)</td>
<td>1/30 (3%)</td>
<td>1/21 (5%)</td>
<td>0/15 (0%)</td>
<td>1/19 (5%)</td>
<td>7/44 (16%)</td>
<td>3/20 (15%)</td>
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**PLEX 163/501 (33%) 0/48 (0%) 3/30 (10%) 6/21 (29%) 2/15 (13%) 5/19 (26%) 17/44 (39%) 5/20 (25%)**

**Second-line immunotherapy 134/501 (27%) 7/48 (15%) 7/30 (10%) 5/21 (24%) 0/15 (0%) 3/19 (16%) 4/44 (9%) 7/20 (35%)**

**Rituximab 101/501 (20%) 6/48 (13%) 5/30 (17%) 5/21 (24%) 0/15 (0%) 2/19 (11%) 2/44 (5%) 5/20 (25%)**

**Cyclophosphamide 81/501 (16%) 3/48 (6%) 2/30 (7%) 1/21 (5%) 0/15 (0%) 1/19 (5%) 0/44 (0%) 3/20 (15%)**

**Other immunotherapy 31/501 (6%) 1/48 (2%) 1/30 (3%) 1/21 (5%) 0/15 (0%) 1/19 (5%) 7/44 (16%) 3/20 (15%)**

<table>
<thead>
<tr>
<th>Follow up, median (range)</th>
<th>24 months (4–186)</th>
<th>39 months [22–58]</th>
<th>36 months [3–168]</th>
<th>72 weeks [5–266]</th>
<th>18 months [2–20]</th>
<th>7 months [0.75–45]</th>
<th>3 years [18 months to 7 years]</th>
<th>6 months [0–68]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>mRS 0–2: 394/501 (79%)</td>
<td>mRS 3–5: 77/501 (15%)</td>
<td>mRS 6: 30/501 (6%)</td>
<td>mRS 0–2: 24/33 (73%)</td>
<td>mRS 3–5: 5/33 (15%)</td>
<td>mRS 6: 4/33 (13%)</td>
<td>mRS 0–2: 10/21 (48%)</td>
<td>mRS 3–5: 6/21 (29%)</td>
</tr>
<tr>
<td>Outcome</td>
<td>CPS0–1: 34 (71%)</td>
<td>CPS2–4: 14 (29%)</td>
<td>mRS 0–2: 10/21 (48%)</td>
<td>mRS 3–5: 6/21 (29%)</td>
<td>mRS 6: 5/21 (24%)</td>
<td>Improved: 8/12 (67%)</td>
<td>Declined: 1/12 (8%)</td>
<td>Huntington disease confirmed: 1/12 (8%)</td>
</tr>
</tbody>
</table>

| Treatment response- Complete response: 7/16 (44%) | Partial response: 8/16 (50%) | No response: 1/16 (6%) | Death: 8/20 (40%) | Complete remission or mild disability: 4/18 (22%) | Partial response to treatment: 5/18 (28%) | Unchanged: 6/18 (33%) | Worsened: 3/18 (6%) including 2 deaths |

*For Table 2, see text for details.*
immunotherapy responsiveness, and thus treatment should be individualized. There are no established guidelines for treatment, and diverse regimens are currently being used based on the patient’s clinical status and the clinician’s opinion. The three common factors derived from a recent systematic review for better outcomes and fewer relapses are the commencement of immunotherapy, early initiation of therapy, and commencement of second-line immunotherapy if first-line immunotherapy fails. Additionally, a thorough tumor screening in the early stages of the disease is important for desirable patient outcomes. Tumors such as ovarian teratoma, thymoma, and small-cell lung carcinoma are detected in a considerable proportion of AE cases. Ovarian teratomas, formerly believed to be benign tumors, are strongly associated with anti-NMDAR encephalitis, and resection of the tumor is an important part of the treatment.

First-line immunotherapy

Common first-line immunotherapeutic agents include corticosteroids, IVIg, and PLEX. Although there is no compelling evidence to suggest the superiority of any specific regimen, corticosteroids are frequently the first choice, followed by IVIg and PLEX. Corticosteroids with either IVIg or PLEX represent the usual choice when a combination of first-line agents is administered. For pediatric patients and patients with medical conditions that discourage the use of corticosteroids, such as diabetes mellitus and seropositivity for type 1 diabetes-associated antibodies such as GAD65, IVIg is often the initial treatment. PLEX is not easily performed on pediatric patients, patients with autonomic instability, or those who cooperate poorly. However, PLEX is useful when patients poorly tolerate corticosteroids and IVIg. The clinical effectiveness of each of these agents is confirmed by previous observations, but more formal studies are necessary to identify the ideal first-line treatment regimen.

Corticosteroids

Corticosteroids bind to intracellular glucocorticoid receptors and suppress the transcription of multiple proinflammatory genes that encode cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors and proteins. Glucocorticoids have an influence on almost all cytokines, and their use results in the depletion of T cells, inhibition of Th1 differentiation, macrophage dysfunction, and eosinophil apoptosis. At higher concentration, corticosteroids have additional effects on the synthesis of anti-inflammatory proteins, and also induce post-transcriptional effects. Furthermore, corticosteroids offer extra benefit to CNS inflammatory disorders by restoring BBB integrity and controlling brain edema.

While it is apparent from observations of the last decade that corticosteroids have therapeutic effects in cases of AE, there are several issues that should be considered in their use. First, the differentiation between AE and infectious encephalitis is often difficult in the acute stage, which frequently delays the initiation of corticosteroid therapy. Second, the reduction of the number of circulating B cells by glucocorticoids is much less than that of T cells, and the effect on serum antibody titer is also limited. Given the largely antibody-mediated disease pathogenesis, it should be considered that a combination of corticosteroids with other immunotherapeutic agents targeting Igs and B cells may be required for a more effective treatment of AE. Third, along with various medical complications, corticosteroids may induce or aggravate psychiatric symptoms associated with AE, such as depression, insomnia, agitation, and psychosis. Clinical and experimental studies also indicate neurotoxic effects of corticosteroids and their potential to induce neurodegeneration upon chronic exposure. As corticosteroids are the most commonly used agents in first-line immunotherapy for AE, investigations seeking to optimize the use of corticosteroids for better outcomes should be conducted. Clinicians must leverage the clinical benefits and harmful effects of steroids in the AE treatment pathway.

IVIg

IVIg is a blood product extracted from the collected pool of plasma from over a thousand donors. IVIg provides antibodies to a broad range of pathogens, and is used to provide passive immunity for patients with immunodeficiency. High-dose IVIg (1–2 g/kg) provide various anti-inflammatory and immunomodulatory effects by multidirectional mechanisms such as autoantibody neutralization, blockade of activating FcγR and upregulation of inhibitory FcγRIIB, inhibition of complements, cytokines, and leukocyte migration. In addition, IVIg saturates neonatal Fc receptor (FcRn), a homeostatic regulator of IgG catabolism, by...
rescuing IgG from lysosomal degradation, through competition, resulting in the acceleration of IgG breakdown. FcRn also contributes to the long half-life of IVIg, and replacement of IVIg is usually considered at 3–4 week intervals. IVIg has been shown to be effective in several autoimmune and inflammatory disorders, and indications for neurological disorders include chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Guillain–Barré syndrome, and myasthenia gravis.

IVIg can be used as a monotherapy in the treatment of AE, but is more often used after or in combination with high-dose steroids, or with PLEX, rituximab, or other immunotherapeutic agents. IVIg has a better side effect profile than corticosteroids and is more convenient and cost-effective compared with PLEX. However, their comparable efficacy to other first-line agents, and their clinical benefit as an add-on therapy, remains to be clearly established in AE. Considering the wide use of IVIg, and the perceived therapeutic effect according to clinical experiences, controlled studies are needed to establish the utility of IVIg in AE. A multicenter randomized trial for the use of IVIg in pediatric patients with infectious or immune-mediated encephalitis was launched in the UK only recently.

Most of the adverse effects associated with IVIg are mild and transient. There is a risk of anaphylaxis in patients with selective IgA deficiency, but the incidence is extremely rare. Screening of IgA antibody level prior to the administration of IVIg could be helpful but is not considered mandatory.

PLEX and immunoadsorption
PLEX effectively removes autoantibodies and other pathologic substances in the plasma. PLEX also alters the immune system by changing lymphocyte numbers and their distribution, T-suppressor cell function, and T-helper cell phenotypes. Steroids alone are frequently insufficient to ameliorate autoantibody-mediated immune process, and direct removal or neutralization of autoantibodies from the circulation by PLEX and IVIg may show a synergistic effect. In addition, PLEX increases the proliferation of antibody-producing cells and this could increase susceptibility of these cells to immunosuppressants and chemotherapeutic agents. A small retrospective study in anti-NMDAR encephalitis patients showed that there was greater clinical improvement with patients who received PLEX immediately after steroids compared with patients who received corticosteroids alone. A recent systematic review by Suppiej and colleagues for PLEX in pediatric anti-NMDAR encephalitis suggested a trend toward better outcomes when PLEX is administered early and when given in combination with steroids.

Immunoadsorption is a refined form of PLEX that enables the selective removal of Igs from separated plasma. Recent studies have shown that immunoadsorption could be an effective therapeutic modality as a part of first-line immunotherapy. Equivalent efficacy between immunoadsorption and PLEX was reported in a small study with 21 AE patients with either NSAb or onconeuronal antibodies.

Technically, PLEX does not remove antibodies from the CSF unless the BBB is severely damaged, and it is unclear whether the removal of systemic antibodies effectively decreases CSF antibody levels. However, recent reports on the use of immunoadsorption for the treatment of AE demonstrated a 64% decrease in CSF antibody titers at early follow up (median 5 days after the last session). Transient elevation of intrathecal IgG fraction and IgG index (‘spurious quantitative intrathecal Ig synthesis’) is frequently observed in the first 2 days following PLEX or immunoadsorption. However, this does not mean true elevation of intrathecal Ig synthesis, and clinicians should be aware of this phenomenon to avoid unnecessary diagnostic and therapeutic procedures.

Second-line immunotherapy
First-line immunotherapy is often insufficient in the treatment of AE, and secondary immunomodulatory agents are typically used. Observational studies show that second-line treatment results in better functional outcomes and lower relapse rates with manageable adverse effects. The decision to initiate second-line immunotherapy is made with consideration of the disease severity, response to the first-line immunotherapy, presence of relapse, and other clinical conditions. Consensus criteria on the appropriate time to initiate second-line immunotherapy are yet to be established, but a quick procession to second-line immunotherapy is favored in some institutions including in our group. Rituximab and cyclophosphamide are the most
commonly used second-line agents in AE treatment. However, these agents are not without their shortcomings, and are not effective in all patients. Additional therapeutic options should be introduced in the second-line immunotherapy but clinical experience is currently insufficient to permit doing so.

**Rituximab**

Rituximab is a partially humanized monoclonal antibody directed against CD20, a glycoprotein primarily found on the surface of B cells, initially approved for the treatment of non-Hodgkin B-cell lymphomas. It is widely used to treat various autoimmune disorders and appears to be effective in several autoimmune CNS and peripheral nervous system disorders.\(^9\) Rituximab depletes both naïve and memory B cells through antibody-mediated cellular toxicity, complement activation, and induction of apoptosis.\(^6\) A substantial reduction in relapse rate with the depletion of memory B cells has been demonstrated in neuromyelitis optica (NMO) or NMO spectrum disorder (NMOSD).\(^9\)–\(^9\) Circulating levels of B cells are usually below the detectable range for 6–8 months after treatment.\(^1\) Effective depletion of B cells in the peripheral blood is confirmed in AE patients,\(^9\) and subsequent depletion of short-lived plasmablasts is also reported in anti-NMDAR encephalitis.\(^1\) The high effectiveness of rituximab in IgG4-related disease further supports the use of rituximab in AE in which antibodies of IgG4 subclass predominate, such as in anti-LGI1\(^3\),\(^7\) anti-Caspr2,\(^3\)\(^7\) and anti-IgLON5 encephalitis.\(^3\) Rituximab does not target CD20-negative cells including long-lived plasma cells, thus reducing adverse immunosuppressive effects.\(^1\)\(^0\),\(^1\)\(^2\)

Lee and colleagues reported on the efficacy and safety of rituximab as a second-line immunotherapy for AE.\(^9\) In this retrospective study of 161 patients, additional rituximab treatment was associated with improvement of functional outcomes measured by the modified Rankin Scale (mRS). This study included AE with or without proven antibody (both NSAb and onconeuronal antibodies) status, and showed rituximab to be effective independent of patient antibody status. Infusion-related adverse effects were noted in 5 (6.7%) patients and infection (all pneumonia) in 9 (11.3%), but there were no life-threatening or recurrent infectious adverse events. Given the substantial efficacy and safety of rituximab in the treatment of AE, and the known association of better outcomes with early treatment,\(^7\) the authors proposed the incorporation of rituximab into the first-line treatment protocol. Additionally, one study of the use of rituximab in a pediatric population with autoimmune or inflammatory CNS disease further supported the administration of rituximab in the early stages of the disease.\(^1\) However, this study reported 11 (7.6%) patients with infectious complications, including two life-threatening or disabling infections and two deaths. The authors concluded that rituximab should be reserved only for those with significant morbidity and risk of mortality in the pediatric population.

Rituximab therapy increases the risk of reactivation of chronic viral infections such as hepatitis B, and serologic screening tests should be considered prior to initiation of the treatment.\(^1\)\(^5\) Progressive multifocal leukoencephalopathy is a rare CNS complication of rituximab therapy,\(^1\)\(^6\) and has not yet been reported in patients with AE.

**Cyclophosphamide**

Cyclophosphamide is an alkylating agent that inhibits cell proliferation, affecting both B and T cells. Along with rituximab, it is a constituent of the so-called R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) used for the treatment of non-Hodgkin lymphoma.\(^1\)\(^7\) It is a widely used chemotherapeutic agent as well as an immunosuppressant for life-threatening or severe rheumatologic and renal diseases such as ANCA-associated vasculitis, lupus nephritis, and other systemic vasculitides.\(^7\)\(^5\),\(^1\)\(^0\)–\(^1\)\(^0\) However, it is not typically used to treat autoimmune neurological disorders and is a less preferable agent than rituximab as a second-line agent in AE. Its potentially serious side effects such as myelosuppression, infertility, hemorrhagic cystitis, and an increased risk of malignancy lower the priority of its use. However, its low cost (compared with rituximab), direct suppression of lymphocyte proliferation (unlike first-line agents), and the greater accumulated clinical experience of its use (compared with the immunotherapeutic agents currently not included in the first- or the second-line therapies) contribute to the justification of its use in refractory cases. Gonadotropin-releasing hormone agonist administration or egg/sperm collection may be employed to preserve fertility following cyclophosphamide use.\(^1\)\(^0\)
**Alternative therapy**

Approximately 20–50% of patients with AE show inadequate responses to second-line therapies, and exhibit persistent neurological issues. Re-administration of first-line immunotherapeutic agents, extended use of second-line immunotherapy, and long-term maintenance of prednisolone or steroid-sparing agents such as azathioprine and mycophenolate mofetil, are among the options that have been used so far. Mycophenolate mofetil, in particular, has selective antiproliferative activity on lymphocytes and has shown better efficacy in inducing remission and a more favorable side effect profile than cyclophosphamide in other autoimmune disorders, supporting its use as a safer alternative to cyclophosphamide for second-line immunotherapy in AE. A small number of studies reported a more targeted therapy with monoclonal antibodies or direct infusion of immune mediators.

**Tocilizumab**

Tocilizumab is a monoclonal antibody targeting the IL-6 receptor. IL-6 induces B-cell proliferation and differentiation into antibody-producing cells, promotes differentiation of CD8+ cytotoxic T cells, induces differentiation of naïve CD4+ helper T cells into IL-17-producing T-helper cells, and inhibits differentiation of those cells into regulatory T cells, which all contribute to autoimmune tissue damage. Tocilizumab binds to both soluble and membrane bound IL-6 receptors and inhibits IL-6 from binding to its receptors, leading to the blockade of IL-6-mediated inflammatory cascades. The therapeutic effect of tocilizumab is demonstrated in various autoimmune diseases, including rheumatoid arthritis and systemic juvenile idiopathic arthritis. Among autoimmune neurological disorders, the efficacy of tocilizumab in therapy-resistant cases of NMO and NMOSD was demonstrated in several small studies. A case report of anti-Caspr2 encephalitis successfully treated with tocilizumab showed therapeutic potential of tocilizumab for therapy-resistant AE.

A recent observational study by Lee and colleagues showed that tocilizumab potentially improves clinical symptoms of AE in patients who do not respond adequately to rituximab. In this study, the patients who received tocilizumab showed superior clinical improvement at 1 month and at the last follow up compared with patients who received additional monthly rituximab or observation without additional immunotherapy. These results encourage the introduction of new agents with different mechanisms of action for use in refractory cases. However, the study was conducted retrospectively without standardized treatment and follow-up protocols, and 65.9% of the patients studied had seronegative AE. These results must therefore be confirmed by further studies with more sophisticated design and larger samples in order to establish tocilizumab as a viable alternative treatment option for therapy-resistant cases of AE.

Tocilizumab increases the risk of infection, but impaired IL-6 receptor signaling may blunt the fever response and elevation of C-reactive protein. Clinicians need to be wary of systemic infection in patients treated with tocilizumab. Other side effects include neutropenia, thrombocytopenia, and elevated liver enzymes and lipid levels. Regular checkup of complete blood count with differential, liver profile, and lipid levels is required after tocilizumab treatment.

**Low-dose IL-2 therapy and Treg modulation**

The number and function of Tregs are dysregulated in autoimmune conditions. IL-2 is a key regulator for Treg differentiation, survival, and function, and has a role in keeping tolerance over autoimmunity. IL-2 activates effector and memory T cells, and is classified as a proinflammatory cytokine. However, low-dose IL-2 administration can selectively expand Tregs without promoting effector T-cell responses because Tregs have lower activation thresholds to IL-2 than to effector T cells. In this regard, low-dose IL-2 therapy has been proposed as a promising new therapeutic option for autoimmune and inflammatory disorders with Treg insufficiency. Some studies report that low-dose IL-2 administration was clinically beneficial, with improvement of Treg number and functions in hepatitis C virus-induced vasculitis, alopecia areata, systemic lupus erythematosus, and graft-versus-host disease. A recent observational study by Lee and colleagues showed that tocilizumab potentially improves clinical symptoms of AE in patients who do not respond adequately to rituximab. In this study, the patients who received tocilizumab showed superior clinical improvement at 1 month and at the last follow up compared with patients who received additional monthly rituximab or observation without additional immunotherapy. These results encourage the introduction of new agents with different mechanisms of action for use in refractory cases. However, the study was conducted retrospectively without standardized treatment and follow-up protocols, and 65.9% of the patients studied had seronegative AE. These results must therefore be confirmed by further studies with more sophisticated design and larger samples in order to establish tocilizumab as a viable alternative treatment option for therapy-resistant cases of AE.

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Lim and colleagues evaluated the feasibility of low-dose IL-2 therapy with 10 patients with refractory AE. The patients underwent four to five cycles of low-dose IL-2 therapy and showed modest responses with a median mRS improvement from three to two. All four patients with...
anti-NMDAR encephalitis responded to the therapy, and two of six antibody-negative AE patients showed seizure reduction. Serious side effects were observed in two patients (decreased neutrophil count and ileus) but these events did not lead to the termination of the treatment. Increased eosinophil counts were common (8 of 10 patients) but resolved spontaneously. These results warrant further trials to clarify the efficacy of low-dose IL-2 therapy in AE.

**Bortezomib**

Bortezomib is a proteasome inhibitor particularly effective at depleting plasma cells and is approved for the treatment of multiple myeloma. Given that long-lived plasma cells are not the target of B-cell-depleting agents and are also resistant to glucocorticoid and antiproliferative agents such as cyclophosphamide, bortezomib and other proteasome inhibitors can represent alternative options for refractory cases. Currently, three reports with nine cases exist that have explored the treatment of severe anti-NMDAR encephalitis with bortezomib. Clinical improvement as well as a tolerable safety profile was reported with bortezomib use in these patients. However, a prolonged treatment period or intensive treatment combined with several immunotherapeutic agents obscured the effectiveness of bortezomib therapy, and the remission achieved could be part of the natural course of the disease or the effect of preceding agents. More experience with bortezomib therapy is needed before making any conclusions.

**Maintenance therapy**

AE is not always monophasic and relapse of AE has been noted even after 5–10 years. The rate of relapse stated in recent literature (approximately 10–20%, varying with the type of antibody) may still be underestimated, given the relatively short time period since the discovery of the relevant autoantibodies. Early aggressive therapy is reported to reduce relapse rates but the role of maintenance therapy is largely unexplored. Overlap with multiple sclerosis, NMO or NMOSD, and myelin oligodendrocyte glycoprotein antibody positive demyelinating syndrome in anti-NMDAR encephalitis suggests that long-term maintenance therapy is required at least for a specific population. Maintenance therapy is usually considered in clinical practice in order to maximize therapeutic gain and attain the highest functional state possible, as well as to make certain that the patient reaches complete remission free of relapse. One study found that additional monthly rituximab after 4 weekly infusions contributed to further mRS improvement. Sustained use of oral corticosteroids and monthly IVIg or PLEX may also be considered for patients with incomplete recovery. Azathioprine and mycophenolate mofetil are commonly used oral steroid-sparing agents for maintenance therapy in autoimmune neurological disorders such as myasthenia gravis and NMO. These agents may be used following acute treatment of AE for sustained remission, however, it remains to be evaluated whether long-term immunosuppression with oral agents is effective in reducing the relapse rate of AE. Intermittent administration of rituximab at regular 6-month intervals or depending on circulating B-cell numbers may be considered as another option for patients who respond well to rituximab therapy. The appropriate duration of maintenance therapy is currently unknown and the length of empirical use ranges widely from 6 months to several years according to the patient’s status and clinician’s opinion.

**Future directions**

Criteria and guidelines for the clinical diagnosis of AE have recently been developed by expert consensus. However, there have been no randomized controlled trials for the treatment of AE, and immunotherapeutic agents currently used in AE do not have a definite indication due to the low level of supporting evidence. Given the rarity of AE, international collaboration for prospective clinical trials is imperative to establish treatment guidelines. There are several additional issues that should be considered to establish better treatment strategies. First, an optimized regimen and dosing schedule is not yet determined. Regimens used for acute management differ among clinicians, and there is no clear standard to determine treatment failure and when to initiate different immunotherapeutic agents. The appropriate duration of immunotherapy for sustained remission must also be determined. Second, while treatment response, length of treatment, and outcome vary depending on the type of associated antibody, current immunotherapeutic regimens for AE are not tailored to the type of associated antibody. Third, the proportion of patients who show inadequate response to first- and second-line immunotherapy is not negligible, and yet several new
immunotherapeutic agents are still not applied in the treatment of AE. Investigation of more therapeutic options is needed to augment the therapeutic armamentarium for the treatment of AE. Attempt to induce immune tolerance, for instance, is an option that is yet poorly explored for the treatment of AE. In NMOSD and other autoimmune disorders, several innovative approaches to induce antigen-specific tolerance or other strategies to restore central and peripheral tolerance are being developed.144,145

Lastly, more investigations into biomarkers for AE are needed to aid early diagnosis and to predict treatment response, relapse, and outcomes. CSF profile and oligoclonal band positivity differ among associated antibodies.8,10 There is also a report that a low white blood cell count on the first CSF examination is associated with a good neurologic outcome at 6 months after admission in adult patients admitted to intensive care unit with anti-NMDAR encephalitis.146 However, the association between CSF profile and clinical outcome was not evident in other studies.57,147 In anti-NMDAR encephalitis, high antibody titer is associated with poor outcome and/or the presence of teratoma, and faster and greater decrease in CSF antibody titer during the first 1 month of the disease is associated with better outcome.56 Recovery and relapses are associated with decrease and increase of CSF antibody titer, respectively. However, the correlation between antibody titers and clinical symptoms is imperfect and the titer of autoantibodies often remains detectable long after remission.38,56,148 The prognostic utility of the persistence or drop in antibody titer for future relapses is uncertain. It should also be noted that antibody titer is not associated with long-term cognitive outcome in anti-LGI1 encephalitis38 and the association between antibody titer and clinical outcome in AE with other NSAbs are not well-established. C-X-C motif chemokine 13 (CXCL13) is a B-cell-attracting chemokine, and its levels correlate with the presence of CSF B cells, plasmablasts and intrathecal Ig synthesis.149 In a study of anti-NMDAR encephalitis, the level of CSF CXCL13 was found to be increased during the early stage of the disease and a high level of CXCL13 was associated with limited response to therapy and clinical relapse.150 However, CXCL13 is not a specific biomarker for anti-NMDAR encephalitis and was shown to be increased in infectious and demyelinating encephalitis.151 Another study with CSF biomarkers for neuronal (neurofilament light chain protein and total tau protein) and glial cell (glial fibrillary acidic protein) damage suggested that these markers reflect disease activity and long-term disability in AE.152 Investigations of additional chemokine/cytokines and other biomarkers for disease activity may provide valuable information to the clinician in the treatment of AE.

**Conclusion**

Although AE responds to immunotherapy and the majority of patients recover from the self-destructive autoimmune process, many patients fail to regain baseline cognitive and functional status. Early aggressive therapy is recommended in AE but steroid abuse should be avoided to prevent potential cognitive and other adverse effects. Each immunotherapeutic agent has its own strengths and weaknesses, and an appropriate combination of these agents is often needed to complement each other and achieve synergistic effects. Results from several studies favor the commencement of second-line therapy and demonstrate the therapeutic potential of a few alternative treatment options. However, the number of patients included in such studies is often very small, and the studies are uncontrolled and prone to severity bias due to the predominant use of these agents in more severe cases. Prospectively designed controlled trials are needed to confirm the efficacy and safety of currently proposed immunotherapeutic agents, along with efforts to uncover more therapeutic options and biomarkers.

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**Conflict of interest statement**

The authors declare that there is no conflict of interest.

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