Treatments for Autoimmune Encephalitis

Just as the diagnosis of AE has evolved over the past several years, so have the treatment options. Research shows, that early and aggressive treatment of AE leads to the best outcomes. A number of options are available to treat AE. These therapies are broken down into what are considered “first-line”, “second-line” and alternative treatment options. Treatment options for AE range from broadly immune-suppressing agents to those targeting processes in antibody-mediated disease pathogenesis. Tumor screening is part of a diagnostic work up, and removal of a teratoma (if present) that could be triggering the autoimmune response, is a first step in the treatment of AE.

First-line immunotherapy

Corticosteroids

Corticosteroids act as an immunosuppressant, suppressing the immune system from making harmful autoantibodies and decreasing the inflammatory response to antibodies. Corticosteroids also work as anti-inflammatory agents by reducing swelling in the brain. Along with various medical complications, including high blood glucose levels, weight gain, blurred vision; corticosteroids may induce or aggravate psychiatric symptoms associated with AE, such as depression, insomnia, agitation and psychosis. Methylprednisolone is the most common form of corticosteroids prescribed to patients with AE.

Intravenous immunoglobulin (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 helps to ward off infection, modulates the immune system, and reduces inflammation, though the full extent of how IVIG works remains unknown. It is known that IVIG can work in many different ways, including increasing the removal of antibodies, inhibit binding of the harmful antibodies, and decrease the inflammatory response to antibodies. IVIG is administered intravenously.

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 plasmapheresis, rituximab, or other immunotherapeutic agents. Side effects include headaches, aseptic meningitis, dermatitis (peeling of skin on palms and soles), pulmonary edema, and allergic reactions.

Plasma Exchange/ Plasmapheresis

Plasmapheresis is a blood-cleansing intravenous procedure where blood is removed from a patient, treated, and then returned to the patient. The procedure works by removing the patient’s blood plasma, which contains the disease-causing autoantibodies. Plasma Exchange

and plasmapheresis are often used interchangeably, but they are different procedures. Plasma exchange (PLEX) is a procedure where plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or with donated plasma.
Potential risks to both of the above, including infection and bleeding, may emerge from the catheter insertion. Procedure side effects include blood clots and hypotension.

Second-line immunotherapy

Rituximab

Rituximab is cell-targeted antibody infusion that labels B cells to be removed and destroyed by the immune system, preventing them from becoming antibody producing cells and stimulating other immune cells. Lee and colleagues reported on the efficacy and safety of rituximab as a second-line immunotherapy for AE. In this retrospective study of 161 patients, additional rituximab treatment was associated with improvement of functional outcomes measured by the modified Rankin Scale. This study included AE with or without proven antibody status, and showed rituximab to be effective independent of patient antibody status.

Common side effects during infusion include serious infections fever, shaking, fatigue, or nausea. Other adverse effects include cardiac arrest, cytokine release syndrome, and types of immune toxicity. Rituximab is known under the brand name Rituxan.

Cyclophosphamide

Cyclophosphamide, is a chemotherapy drug that comes in tablet or injectable form. It works by slowing or halting the growth of immune system cells (affecting both B and T proliferating cells). Common side effects include nausea, vomiting, and hair loss. Less common but more serious side effects include damage to the bladder, fertility problems, and bone marrow suppression. Cyclophosphamide is known under the brand name Cytoxan.

Gonadotropin-releasing hormone agonist administration or egg/sperm collection may be employed to preserve fertility when cyclophosphamide is used. Please talk to your doctor, gynecologist, or endocrinologist on how and when best to administer treatment.

References:

Somers et al., Infertility – prevention and management, Rheum Dis Clin North Am., 2018
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596868/

Clowse et al.,Ovarian Preservation by GnRH Agonists during Chemotherapy: A Meta-Analysis, J Womes Health, 2009
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858300/

Alternative therapy

Tocilizumab

Tocilizumab, is a monoclonal antibody targeting the IL-6 receptor, which leads to the blockade of IL-6 mediated inflammatory cascades. IL-6 induces B-cell proliferation and differentiation into antibody-producing cells and T-cell differentiation, which all contribute to autoimmune response.

The therapeutic effect of tocilizumab is demonstrated in various autoimmune diseases, including rheumatoid arthritis and systemic juvenile idiopathic arthritis. Tocilizumab is used in AE, as a 'third-line' therapy, or for those that not adequately respond to rituximab.

Tocilizumab does increase the risk of infection. Other side effects include elevated liver enzymes and lipid levels, neutropenia, and thrombocytopenia. Regular checkup of complete count with differential, liver profile, and lipid levels is required after tocilizumab treatment. Tocilizumab is known under the brand name Actemra.

Bortezomib

Bortezomib, is FDA-approved for use in the treatment of multiple myeloma and mantle cell lymphoma. Bortezomib is a proteasome inhibitor, that is particularly effective at depleting plasma cells. Given that long-lived plasma cells are not the target of B-cell-depleting agents like Rituximab and are also resistant to glucocorticoid and antiproliferative agents such as cyclophosphamide, bortezomib may represent alternative options for refractory cases. The use Bortezomib in AE has not been fully studied yet, and its efficacy showed contradictory results in different studies.

Steroid-sparing agents used for maintenance therapy

The average relapse rate in AE is 10-20% depending on the type of antibody. Early aggressive therapy is reported to reduce relapse rates, but the role of maintenance therapy is largely unexplored. Maintenance therapy is usually considered in order to maximize therapeutic gain, as well to make sure that remission is achieved.

Azathioprine

Azathioprine, is an oral immunosuppressant, often used in MS patients, but now is used in many autoimmune conditions and recommended as a possible "maintenance therapy" in AE. It suppresses the immune system by interfering with the creation of DNA molecules. Side effects may include nausea, vomiting, increased risk for infections. Azathioprine is known under the brand name Imuran.

Mycophenolate mofetil

Mycophenolate mofetil, is an oral immunosuppressant, originally prescribed to patients undergoing organ transplant surgery, but now is used in many autoimmune conditions and recommended as a possible maintenance therapy in AE. Mycophenolate mofetil interferes with the formation of DNA in certain immune system cells that become overactive in cases of autoimmune disorders. Most common side effects include nausea, vomiting, diarrhea,

headache, dizziness or rash. Less common but more serious side effects include anemia, and blood clots. Mycophenolate mofetil is known under the brand name CellCept.

References:

Lancaster, The Diagnosis and Treatment of Autoimmune Encephalitis, J Clin Neurol, 2016
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712273/

Shin et al., Treatment strategies for autoimmune encephalitis, Ther Adv Neurol Disord, 2017
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5784571/

Abboud et al., Current and emerging therapeutics for neuromyelitis optica spectrum disorder: Relevance to the COVID-19 pandemic, Multiple Sclerosis and Related Disorders, 2020
https://www.msard-journal.com/article/S2211-0348(20)30325-4/fulltext