Treatments for Autoimmune Encephalitis

Written by: Sophie Liebergall, Ph.D. Neuroscience Student with PennNeuroKnow

Though it can be challenging for doctors to correctly identify and diagnose autoimmune encephalitis (AE), once patients do indeed receive a proper diagnosis there are treatment options that can go a long way in alleviating their symptoms sending them down the road to recovery. A recent study reports that 94% of patients with AE have significant improvement in or complete resolution of symptoms in the first few years after their diagnosis.[1,2] One important key to success is promptly starting treatment which both reduces the likelihood of long-term symptoms and prevents relapses.

The job of your body's immune system is to find and eliminate invaders, like bacteria and viruses, that may be harmful. But in the case of AE, the immune system mistakes the brain as an invader and mounts an attack, leading to inflammation in the brain.[3] This inflammation is what causes the symptoms of AE, like hallucinations, memory problems, and seizures. Therefore, all current medical treatments for AE are aimed at decreasing **inflammation**.[4] But even if the ultimate goal is always to reduce brain inflammation, there may be slight variations in the choice of therapies depending on the type of AE and the patient's unique medical history.

Physicians divide the treatments for AE into **first-line** and **second-line** therapies. First-line therapies are treatments that doctors generally prescribe first when a patient is diagnosed with AE. Second-line therapies are treatments that doctors reach for when the first-line therapies didn't work, or if there are lingering symptoms following initial improvement with first-line therapies.

In this article, we'll walk through some of the common treatments for AE, why doctors may or may not choose them for a given patient, and how these treatments are thought to reduce AE symptoms.

First-Line Treatments

Steroids

If you or a loved one has been diagnosed with AE, you're probably familiar with steroids, the medicine that doctors often use first when treating AE. When many people hear the term "steroids," they think of Barry Bonds or other professional athletes who have used performance-enhancing drugs to get an edge on the competition. But in reality, "**steroids**" is an umbrella term used to describe a group of chemicals that share a similar shape. Whereas athletes looking to circumvent the rules use steroids called anabolic steroids, doctors treating AE prescribe steroids called **glucocorticoids**.[4]

Though doctors can administer glucocorticoids to a patient as a pill or in an IV, we actually make glucocorticoids naturally in our bodies all the time! Our homemade glucocorticoids are essential for a wide range of our bodily functions – from controlling how our body manages sugars and fats, to telling our brain to be alert to our surroundings, to damping down inflamation.[5] When prescribing glucocorticoids to patients with AE, doctors try to take advantage of the anti-inflammatory properties of these chemicals.

How exactly do glucocorticoids put the brakes on inflammation? They act quickly and powerfully at the source of inflammation: the cells of your immune system (**Figure 1**).[5] Once they breach the walls of an immune cell, glucocorticoids enter the nucleus, which serves as the control canter of a cell. It's in the nucleus that the cell writes out the instructions for making the proteins that it needs to mount an immune attack. By breaching this nucleus control center, glucocorticoids can override the machinery that the cell uses to write these instructions. This ultimately prevents the immune cells from causing inflammation.

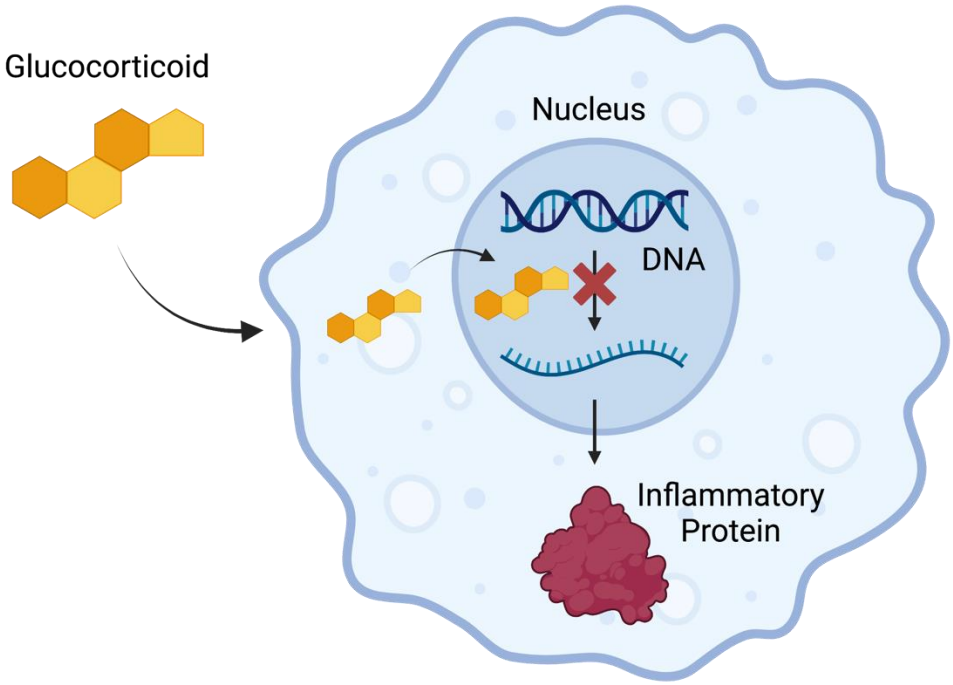

Figure 1. How do glucocorticoids treat AE?
Glucocorticoids enter the nucleus of an immune cell, where they override the messages that the cell writes as it tries to make inflammatory proteins.

Unfortunately, glucocorticoids don't just interfere with the instructions that immune cells use for making inflammatory proteins. They also interfere with the instructions that many *other* kinds of cells in the body rely on for carrying out *their* own important functions.[6] For example, glucocorticoids can affect the instructions that the cells in your bones use to tell themselves to grow and retain their strength. This can lead to the weakening of your bones, which is a common side effect of glucocorticoids.[7] Other side effects

include problems with your body's metabolism, like the redistribution of body fat, as well problems with your skin, like impaired wound healing.[6] When patients with AE are first diagnosed, they are often very sick, so very high doses of glucocorticoids may be required to stabilize their condition.[8] But as AE symptoms improve, doctors try to slowly reduce the amount of glucocorticoids that a patient is prescribed to prevent some of the harmful and uncomfortable side effects of these powerful medications.

Plasma Exchange (PLEX)

Rather than targeting the inner workings of the immune cells, other treatments for AE target the proteins that are made by the immune cells. One type of protein that immune cells make is called an antibody. **Antibodies** selectively stick to invaders and flag them for destruction by other cells in the immune system.[9] But in the case of AE, the body accidentally makes antibodies against its own proteins in the brain. When the immune system sees these flags, it mistakenly attacks the healthy brain.

Plasma exchange (PLEX) is a therapy that tries to remove these antibodies that erroneously tell the immune system to attack the brain.[10] Antibodies are generally transported in the plasma, which is the liquid-y component of blood. During PLEX therapy, tubes are placed in your veins so that your blood can pass through a machine as it is pumped around your body (**Figure 2**). This machine acts like a coffee filter, separating the liquid part of your blood (the coffee) from the blood cells (the grounds). Because the liquid part of your blood contains the harmful antibodies, the liquid is discarded and replaced with the plasma of a healthy donor. This healthy plasma is then recombined with your own blood cells that were trapped in the coffee filter, and sent back into your body through another tube.

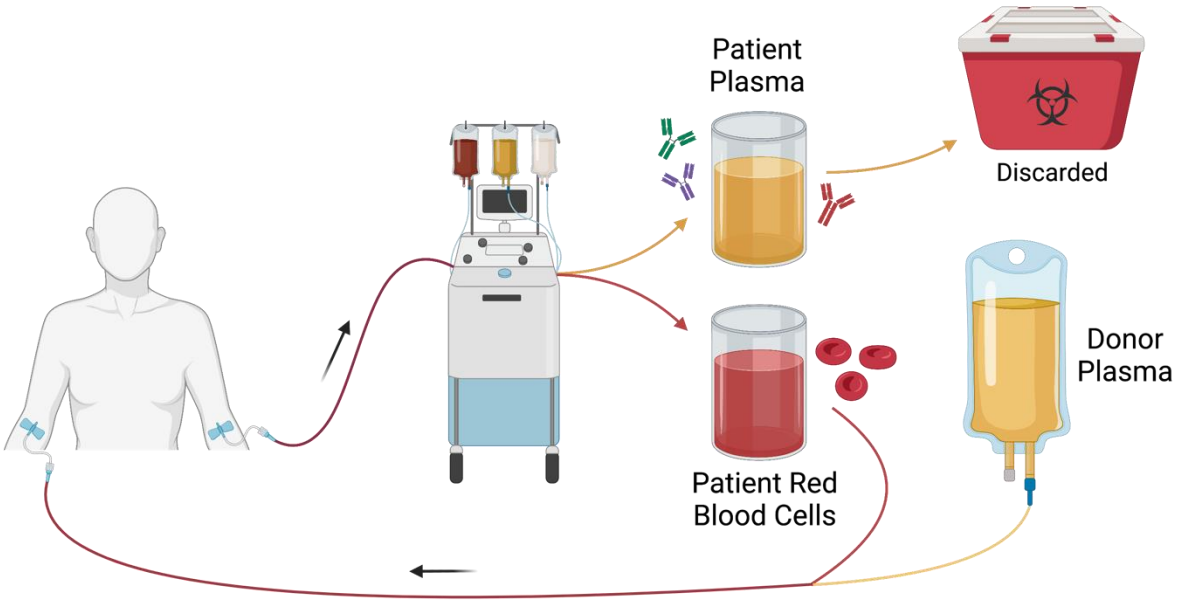

Figure 2. What happens during plasma exchange (PLEX) therapy?

Whole blood is removed from the patient's vein, then separated into its plasma and red blood cell components. The patient's plasma is discarded and replaced with donor plasma, which is recombined with the patient's red blood cells and returned to the patient's blood stream.

PLEX is generally safe and effective, and it can be especially useful for patients who are particularly vulnerable to the side effects of glucocorticoids.[8] However, a major downside of PLEX is that it requires the placement of the tubes that are used to remove and return the blood to the body for the duration of the treatment. These tubes can be a source of infection or bleeding, and can make it logistically challenging for patients to receive PLEX if they aren't already in the hospital.

Intravenous Immune Globulin (IVIG)

Intravenous immune globulin (IVIG) is another AE treatment that tries to interfere with the antibodies that mistakenly target a patient's healthy brain in AE. Our blood contains thousands of different antibodies, most of which are designed to target the foreign invaders that we have encountered during our lifetimes. IVIG is the result of taking the blood of thousands of different people, extracting the antibodies from that blood, and then combining the antibodies of all of the different donors.[11] This creates a very concentrated slushy of thousands and thousands of antibodies that target all sorts of different proteins. When IVIG is administered to a patient, these antibodies then enter their bloodstream and circulate with the rest of the patient's blood.

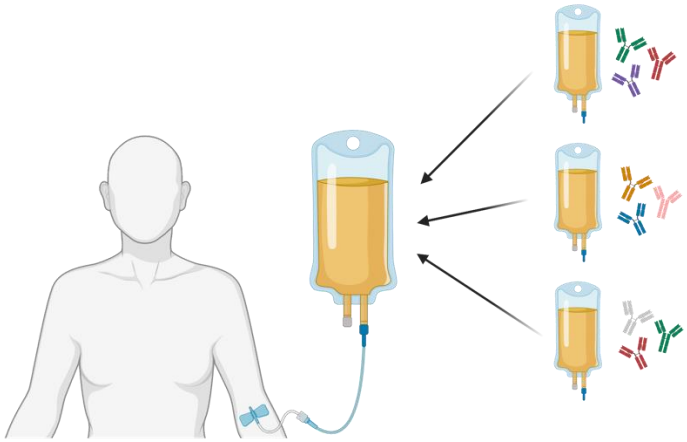

Figure 3. What is intravenous immune globulin (IVIG) therapy?
The antibody-containing serum of thousands of donors is combined and then administered to the patient through an IV.

Given that AE is caused by a rogue antibody, it may seem crazy that doctors would give patients many more highly concentrated antibodies to treat AE. But, IVIG is very effective with minimal side effects beyond an increased risk of blood clots in some patients.[12] So how does it work? Doctors think that IVIG overwhelms the immune system by flooding it with so many antibodies that the AE-causing antibodies just get swept up in the rush. In other words, the immune system may be so distracted by the

onslaught of other antibodies that it forgets about the antibody that was driving the AE symptoms.[11]

Second-Line Treatments

Rituximab

If the first-line therapies don't provide sufficient relief for a patient with AE, the most common second-line therapy is a drug called **rituximab**.[8] Rituximab, which was initially designed to treat cancer, is, itself, an antibody.[13] But, interestingly, its job is to "tag" the cells in the body's own immune system that *make* other antibodies. This causes the body's immune system to kill its own antibody-producing cells, ultimately halting the production of antibodies.

This means that rituximab can stop the immune system from making the harmful brain-targeting autoantibodies that cause AE symptoms. But Rituximab doesn't just suppress the production of the AE-causing antibodies – it suppresses the production of *all* antibodies, including those necessary for fighting infections. This can leave patients vulnerable to bacterial and viral invaders that they would normally be able to fight off. Additionally, rituximab is known to cause other side effects like fevers, fatigue, and nausea.[13] Nevertheless, rituximab has been shown to be an effective at restoring functioning for patients with AE who need additional treatment on top of first-line therapies.[14]

Cyclophosphamide

Cyclophosphamide is another cancer drug that has been repurposed as a second-line agent in the treatment of AE.[8] Cyclophosphamide works by entering the nucleus of a cell and attaching chemical "decorations" to the cell's DNA.[15] These "decorations" confuse the machinery that a cell uses to duplicate its DNA, which impairs the ability of a cell to replicate itself. Thus, cyclophosphamide can significantly impair the function of cells that rely on frequent replication to do their job, like immune cells.

Cyclophosphamide is very good at killing the immune cells that cause inflammation, which makes it a useful treatment for AE. The side effects of cyclophosphamide, however, can include nausea and hair loss, as well as more dangerous conditions such as bladder injuries and problems with fertility.[16] Because of this, cyclophosphamide is generally recommended for patients whose symptoms aren't eliminated by first-line therapies or rituximab.

Symptomatic Treatment of AE

The immune-targeting therapies for AE aim at eliminating the source of a patient's symptoms. But oftentimes it can be beneficial to provide patients with additional therapies that can help alleviate the symptoms themselves. For example, the brain inflammation associated with AE can cause patients to experience seizures.[17] Seizures

are uncontrolled bursts of electrical activity in the brain. Depending on where a seizure starts and spreads, this electrical activity can result in phenomena ranging from the experience of strange sensations to full-body convulsions.[18] Many patients with AE may be prescribed anti-seizures medications, which act to quiet down the electrical activity in the brain and decrease the likelihood of the uncontrolled activity of a seizure.

Medical therapies targeting inflammation dramatically reduce symptoms in the majority of patients diagnosed with AE. Some patients, however, will continue to have symptoms even after treatment, and some may be resistant to treatment altogether. We are still early in our research efforts to try to understand how and why people get AE. And as we deepen our understanding of this complex disorder, hopefully we can work towards developing more treatments specifically targeting the underlying causes of AE that are more effective with fewer side effects.

References

1. Titulaer, M. J. *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *The Lancet Neurology* **12**, 157–165 (2013).
2. Abboud, H. *et al.* Residual symptoms and long-term outcomes after all-cause autoimmune encephalitis in adults. *Journal of the Neurological Sciences* **434**, 120124 (2022).
3. Dalmau, J. & Rosenfeld, M. R. *Paraneoplastic and autoimmune encephalitis*.
4. Lancaster, E. The Diagnosis and Treatment of Autoimmune Encephalitis. *J Clin Neurol* **12**, 1–13 (2016).
5. Ramamoorthy, S. & Cidlowski, J. A. Corticosteroids-Mechanisms of Action in Health and Disease. *Rheum Dis Clin North Am* **42**, 15–31 (2016).
6. Hodgens, A. & Sharman, T. Corticosteroids. in *StatPearls* (StatPearls Publishing, 2022).
7. Briot, K. & Roux, C. Glucocorticoid-induced osteoporosis. *RMD Open* **1**, e000014 (2015).

8. Abboud, H. *et al.* Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry* **92**, 757–768 (2021).
9. Janeway, C. A., Travers, P., Walport, M. & Shlomchik, M. J. *Immunobiology*. (Garland Science, 2001).
10. Bobati, S. S. & Naik, K. R. Therapeutic Plasma Exchange - An Emerging Treatment Modality in Patients with Neurologic and Non-Neurologic Diseases. *J Clin Diagn Res* **11**, EC35–EC37 (2017).
11. Patient education: Intravenous immune globulin (IVIG) (Beyond the Basics) - UpToDate. https://www.uptodate.com/contents/intravenous-immune-globulin-ivig-beyond-the-basics.
12. Lee, S. *et al.* The safety and efficacy of intravenous immunoglobulin in autoimmune encephalitis. *Ann Clin Transl Neurol* **9**, 610–621 (2022).
13. Hanif, N. & Anwer, F. Rituximab. in *StatPearls* (StatPearls Publishing, 2022).
14. Thaler, F. S. *et al.* Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis: Real-world Evidence From the GENERATE Registry. *Neurology - Neuroimmunology Neuroinflammation* **8**, (2021).
15. Ahlmann, M. & Hempel, G. The effect of cyclophosphamide on the immune system: implications for clinical cancer therapy. *Cancer Chemother Pharmacol* **78**, 661–671 (2016).
16. Ogino, M. H. & Tadi, P. Cyclophosphamide. in *StatPearls* (StatPearls Publishing, 2022).

17. Davis, R. & Dalmau, J. Autoimmunity, Seizures, and Status Epilepticus. *Epilepsia* **54**, 46–49 (2013).
18. Turek, G. & Skjei, K. Seizure semiology, localization, and the 2017 ILAE seizure classification. *Epilepsy & Behavior* **126**, 108455 (2022).
19. Feyissa, A. M., López Chiriboga, A. S. & Britton, J. W. Antiepileptic drug therapy in patients with autoimmune epilepsy. *Neurol Neuroimmunol Neuroinflamm* **4**, e353 (2017).

All figures made with biorender.com.