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Research progress on emerging therapeutic approaches for autoimmune encephalitis

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Abstract. Autoimmune Encephalitis (AE) is a group of inflammatory disorders of the central nervous system caused by abnormal activation of the immune system, often presenting with psychiatric symptoms, seizures, cognitive impairment, and consciousness disturbances. Traditional treatments primarily include glucocorticoids, Intravenous Immunoglobulin (IVIG), Plasma Exchange (PLEX), and second-line immunosuppressants. While most patients show improvement, some cases progress to "refractory AE." In recent years, advances in immunology and molecular therapy research have led to the emergence of various novel therapeutic strategies, such as B-cell and precursor-targeted therapies, plasma cell and bone marrow suppression, FcRn inhibitors, cytokine pathway interventions, localized central immune modulation, and stem cell or cellular therapies. These innovative approaches provide new perspectives and options for treating refractory AE. However, current evidence is largely derived from case reports or small-scale studies, and there remains a lack of large-scale randomized controlled trials to validate their efficacy and safety. In the future, precision medicine and biomarker-guided individualized treatments, along with optimized combination and sequential strategies, hold promise for improving long-term patient outcomes.

Keywords: autoimmune encephalitis, emerging therapies, B-cell targeting, FcRn inhibitors, cytokine pathways, stem cell therapy

1. Introduction

Autoimmune Encephalitis (AE) is a group of inflammatory disorders of the Central Nervous System (CNS) caused by aberrant activation of the immune system, clinically characterized by acute or subacute onset of psychiatric symptoms, seizures, cognitive dysfunction, and impaired consciousness [1]. Advances in the detection of anti-neuronal antibodies, including those targeting the N-methyl-D-aspartate receptor (NMDAR), Leucine-rich Glioma-inactivated 1 (LGI1), Contactin-associated Protein-like 2 (CASPR2), Gamma-aminobutyric Acid B receptor (GABA_B), and Glutamic Acid Decarboxylase 65 (GAD65), have significantly improved the understanding and diagnosis of this disease [2]. The incidence of AE has been increasing annually, and its prognosis is closely linked to early recognition and standardized treatment.

First-line conventional therapies include glucocorticoids, Intravenous Immunoglobulin (IVIG), and Plasma Exchange (PLEX), while second-line treatments primarily consist of rituximab and cyclophosphamide. Although most patients achieve favorable recovery, approximately 20–30% exhibit poor response to standard immunotherapy, progressing to a "refractory AE" state, which often leads to long-term disability or even death [3]. In recent years, with advancements in immunology and molecular therapy research, a range of novel therapeutic strategies has emerged, providing new options for the treatment of refractory AE. This review will discuss the pathophysiological basis of AE, an overview of conventional treatments, and the progress in emerging therapeutic approaches, along with future directions for clinical translation.

2. Pathophysiological and therapeutic target framework for autoimmune encephalitis

Autoimmune encephalitis is closely associated with abnormal immune responses in the body, with its core mechanism being immune-mediated neuronal dysfunction. Based on the pathogenic antibodies involved, it can be divided into two categories: the first is the cell-surface antigen-mediated type, such as NMDAR, LGI1, and CASPR2 antibodies, which directly target neuronal receptors or ion channels, leading to impaired synaptic signaling and typically showing better responses to immunotherapy; the second is the intracellular antigen-related type, such as Hu, Ma2, and GAD65 antibodies, often mediated by cytotoxic T cells causing neuronal damage, which generally has a poorer prognosis. Within this pathological framework, several potential therapeutic targets have been proposed in recent years. These include eliminating or inhibiting B cells and their precursors to

reduce pathogenic antibody production; targeting plasma cells or long-lived plasma cells to address antibody sources not effectively covered by traditional CD20 inhibitors; blocking the FcRn pathway to accelerate IgG clearance; intervening in key inflammatory cytokine pathways such as IL-6, IL-1, or JAK/STAT to suppress excessive immune responses; developing specific treatments targeting the central nervous system's local immune environment and the blood-brain barrier; and restoring immune homeostasis through immune reconstitution or stem cell therapy [4]. These targets provide new directions and possibilities for the treatment of refractory autoimmune encephalitis.

3. Overview of traditional treatment methods for autoimmune encephalitis

The treatment of autoimmune encephalitis currently relies primarily on a tiered immunomodulation strategy. First-line therapies include glucocorticoids, Intravenous Immunoglobulin (IVIG), and $_{\text{plasma exchange}}$ (PLEX). Among these, glucocorticoids rapidly suppress inflammatory responses, IVIG provides exogenous antibodies to block pathogenic immune effects, and PLEX directly removes circulating autoantibodies and inflammatory mediators [5]. For patients who respond poorly to first-line treatment, second-line therapies are often employed, such as rituximab (an anti-CD20 monoclonal antibody), which reduces antibody production by depleting B cells, and cyclophosphamide, which broadly suppresses immune activity by reducing lymphocyte function [6]. However, although most patients show improvement with conventional treatments, a significant proportion continue to experience persistent autoantibodies, symptom progression, or disease relapse, leading to so-called "refractory AE." This limitation suggests that traditional immunosuppressive regimens are insufficient to fully control the disease process, highlighting the urgent need to explore more precise and targeted novel therapeutic approaches.

4. Emerging therapeutic approaches for autoimmune encephalitis

With the deepening understanding of the pathogenesis of Autoimmune Encephalitis (AE), conventional immunotherapies—such as glucocorticoids, Intravenous Immunoglobulin (IVIG), Plasma Exchange (PLEX), and second-line agents like rituximab and cyclophosphamide—have demonstrated efficacy in most patients. However, a subset of cases remain refractory or experience relapses. Consequently, novel therapeutic strategies have emerged in recent years, aiming to more precisely target pathogenic mechanisms and improve patient outcomes.

4.1. B cell/progenitor-targeted therapy

B cells play a pivotal role in AE pathogenesis by producing pathogenic autoantibodies that directly contribute to neuronal injury. Rituximab, a conventional anti-CD20 monoclonal antibody, has been widely used to deplete CD20+ B cells [7]. However, its limitations include incomplete clearance of certain plasma cells and their precursors. Inebilizumab, an anti-CD19 monoclonal antibody, targets a broader spectrum of B cells, including plasmablasts, and has shown potential advantages in refractory anti-NMDAR encephalitis in clinical trials, suggesting possible superiority over traditional second-line therapies [8]. Additionally, next-generation anti-CD20 antibodies such as obinutuzumab, which exhibit enhanced cytotoxic effects, are being explored in AE, indicating a direction for optimizing B cell-targeted strategies [9].

4.2. Plasma cell/bone marrow targeting

Long-lived plasma cells are a major source of persistent pathogenic antibodies, which conventional CD20-targeted therapies fail to eliminate. Bortezomib, a proteasome inhibitor, induces plasma cell apoptosis and significantly reduces antibody levels, demonstrating efficacy in rescue therapy for refractory AE, albeit with risks of myelosuppression and infections [10]. Another approach involves daratumumab, an anti-CD38 monoclonal antibody that directly targets plasma cells via cytotoxic mechanisms. Systematic reviews and case reports suggest its potential in improving symptoms across refractory AE subtypes, offering a novel plasma cell-depleting option.

4.3. FcRn inhibitors

The neonatal Fc receptor (FcRn) plays a crucial role in prolonging the half-life of IgG. Blocking this pathway accelerates IgG degradation, rapidly reducing serum levels of pathogenic antibodies. Efgartigimod and rozanolixizumab are among the most studied FcRn inhibitors, with early case reports and small cohort studies indicating favorable tolerability and potential efficacy in refractory AE [11]. These agents provide a new strategy for rapid clearance of pathological IgG, potentially serving as alternatives or adjuncts to traditional PLEX.

4.4. Cytokine/immunomodulatory agents

Dysregulated cytokine signaling contributes significantly to AE immunopathology. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, has been used in refractory anti-NMDAR and anti-GAD65 encephalitis, with notable clinical improvement in some patients [12]. Beyond IL-6 blockade, the IL-1 receptor antagonist anakinra and the JAK inhibitor tofacitinib have shown efficacy in small case series, particularly in patients with elevated inflammatory cytokines [13]. Additionally, low-dose IL-2 therapy has been explored to expand regulatory T cell (Treg) populations and restore immune tolerance, though its clinical application remains investigational.

4.5. CNS-targeted/local immune modulation strategies

Some refractory AE patients exhibit persistent intrathecal antibodies or inflammation, suggesting compartmentalized immune responses as a therapeutic target. Intrathecal Methotrexate (IT-MTX) has been attempted in highly refractory cases to directly suppress CNS immune activation. Another approach involves natalizumab, which blocks lymphocyte migration across the blood-brain barrier, thereby reducing central inflammation [14]. However, evidence for these strategies remains limited, warranting further validation of safety and efficacy.

4.6. Immune reconstitution/cellular therapies

For extremely refractory AE, immune system resetting has emerged as a potential solution. Autologous Hematopoietic Stem Cell Transplantation (aHSCT), effective in multiple sclerosis and Neuromyelitis Optica Spectrum Disorder (NMOSD), has shown long-term remission in sporadic AE cases, albeit with significant infection and treatment-related risks [15]. Beyond transplantation, CAR-T cell therapy and Treg-based approaches are under early investigation, theoretically offering selective elimination of pathogenic cells or enhanced immune tolerance, though current evidence remains preclinical or anecdotal.

4.7. Other potential directions

Beyond mainstream strategies, the complement pathway has been implicated in certain AE subtypes. Eculizumab, effective in NMOSD, is being explored in AE but remains investigational. Additionally, metabolic and neuroprotective interventions (e.g., mitochondrial protectants, neurotrophic factors) may mitigate neuronal injury, while rehabilitation and neural repair are emphasized as essential adjuncts to pharmacotherapy to improve long-term cognitive and functional outcomes.

Emerging AE therapies reflect a multidimensional evolution, spanning peripheral B cells, plasma cells, FcRn blockade, cytokine modulation, CNS-targeted strategies, and systemic immune reconstitution. While current evidence is largely derived from small-scale studies or case reports—lacking robust randomized controlled trial data—these advances offer hope for refractory AE and pave the way for personalized, precision immunotherapy in the future.

5. Clinical translation challenges

Despite recent advances in emerging therapies for Autoimmune Encephalitis (AE), their clinical translation faces several challenges. First, the lack of robust evidence remains a major hurdle, as most current therapies are supported only by case reports or small-scale studies, with a paucity of multicenter randomized controlled trials to validate efficacy and safety. Second, long-term safety profiles remain unclear, particularly concerning the risks of infections and malignancies associated with profound immunosuppression, given the limited systematic follow-up data. Additionally, standardized guidelines on treatment timing and sequential strategies are lacking, and optimal drug combinations or sequencing approaches have yet to be explored. Moreover, the absence of reliable biomarkers complicates treatment response prediction and prognostic evaluation. Finally, cost and accessibility pose practical limitations, as novel monoclonal antibodies and stem cell therapies are prohibitively expensive, hindering widespread clinical adoption.

6. Conclusions and future perspectives

Autoimmune encephalitis has emerged as a rapidly evolving focus in neuroimmunology. While conventional immunotherapies improve outcomes for most patients, the persistence of refractory cases underscores the importance of emerging treatments. Strategies targeting B cells, plasma cells, FcRn, and cytokines have shown promise, with some agents already entering clinical trials. However, current evidence primarily stems from case reports and small studies, necessitating large-scale randomized controlled trials to confirm efficacy and safety.Looking ahead, deeper insights into molecular immunology, combined with

precision medicine approaches, will pave the way for biomarker-guided individualized therapy and optimized sequential/combination strategies, shaping the future of AE management.

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