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EDITORIAL

Emerging immune tolerance therapies for neuromyelitis optica spectrum disorder

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1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a lifelong, disabling autoimmune disease of the central nervous system (CNS) characterized by inflammatory lesions in the optic nerves, spinal cord, and/or brainstem/brain[1]. Relapsing course is found in 90% of patients, recovery from attacks varies, and inflammatory attacks or relapses can lead to permanent disability or even death [1,2]. In most patients, the disease is associated with the presence of pathogenic serum IgG antibodies targeting the water channel aquaporin-4 (AQP4-IgG) which is highly concentrated on astrocyte end-feet in the CNS. This phenomenon arises from a loss of immune tolerance to AQP4 [1,2]. It is worth noting that approximately 20–30% of NMOSD patients are seronegative for AQP4-IgG [1,2]. This population is likely heterogenous, creating challenging issues in clinical trial design and efficacy analysis [1,2]. NMOSD management aims to timely diagnosis and early treatment to reduce the frequency and severity of relapses [2]. Currently, there is no cure for this disease; however, five randomized controlled trials (RCT) have assessed the efficacy and safety of four new therapies, targeting the main pathogenic pathways of the disease in AQP4-IgG$^+$ NMOSD patients: eculizumab and ravulizumab (anti-complement), satralizumab (anti-IL-6 receptor), and inebilizumab (anti-CD19)[2]. Additionally, a phase 2/3, multicenter, double-blind, RCT (RIN-1) evaluating rituximab in NMOSD patients has been conducted in Japan [2]. All clinical trials demonstrated significant benefits in preventing future attacks [2]. Nevertheless, various limitations have been reported, including potential costs and infections, which may impact their use in real-world populations globally [2]. Notably, these therapies do not entirely control inflammatory activity, they are not antigen-specific, and none of them aim for the eradication of the cell-reactive immune cells, particularly memory cells [3]. Their efficacy is based on establishing a state of chronic immunosuppression, where certain specific immune responses may be altered, including those protective against infections and cancer [1–3]. Therefore, researchers have been trying to reset the immune system developing therapies that restore immune tolerance, inducing robust, long-lasting, and specific immune responses, without compromising protective immunity to pathogens.

2. Mechanisms of immune tolerance

Immune tolerance is an active state of unresponsiveness to otherwise immunogenic molecules. The breakdown of self-tolerance can result in the development of autoimmune diseases like NMOSD. Multiple mechanisms are involved in the establishment and maintenance of tolerance [4].

Central tolerance is established during T and B cell development in the thymus and bone marrow, respectively. In the thymus, T cells harboring T cell receptors (TCR) that do not recognize MHC-presented self-peptides are eliminated by neglect. At the same time, those with low affinity for MHC-peptide complexes differentiate into CD4$^+$ T cells or CD8$^+$ T cells. High-affinity TCR clones are controlled by various central tolerance mechanisms, including clonal deletion and receptor editing [5]. Some self-reactive T cells escape deletion and leave the thymus, but peripheral mechanisms can control them [6,7].

In the bone marrow, developing B cells express B cell antigen receptors (BCRs) through random rearrangement of V, D, and J genes, generating a diverse BCR repertoire. Autoantigen reactivity in B cells is controlled by immunoglobulin gene rearrangements or clonal deletion [8]. In NMOSD B cells endogenously express AQP4 in response to activation with anti-CD40 and IL-21 and can present this endogenous AQP4 to T cells with an AQP4-specific TCR. This process facilitates the elimination of AQP4-reactive clones from the thymic TCR repertoire, representing a mechanism of negative selection for AQP4-specific thymocytes [9].

Similar to T cells, some self-reactive B cells escape central tolerance and are regulated by peripheral tolerance mechanisms, including anergy or deletion [9]. Approximately 40% of self-reactive T and B cells escape central tolerance and must be controlled by peripheral tolerance to prevent autoimmune diseases. These peripheral mechanisms include anergy, apoptosis-induced deletion, and suppression by Treg cells [6,7,10]. Tolerogenic dendritic cells (DCs) also play an important role in maintaining immune tolerance. Immature DCs, with low expression of MHC class I, MHC class II, and co-stimulatory molecules, can induce T cell anergy, promote Treg differentiation, and

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delete effector T cells [11]. Beyond these tolerogenic properties, DCs maintain self-tolerance through downregulation of co-stimulatory molecules, expression of inhibitory molecules (e.g. PD-L1, ICOSL, BTLA), suppression of pro-inflammatory cytokines, and production of anti-inflammatory cytokines and metabolites (e.g. IDO, retinoic acid) [11,12]. Supporting these mechanisms, the introduction of checkpoint inhibitor therapies that block PD-1/PD-L1 or CTLA-4—now a frontline treatment for multiple cancers – can disrupt immune tolerance, leading to immune-related adverse events and potentially triggering tissue-specific autoimmunity, such as NMOSD.

Multiple defects in immune tolerance have been proposed to explain the presence of AQP4-IgG and the subsequent development of NMOSD. Some studies have found that the proportion of regulatory B cells (Bregs) and IL-10 expression are significantly lower in NMOSD patients compared to those with MS. Furthermore, during acute NMOSD relapses, CD19+CD24hiCD38hi and CD19+CD5+CD38hi Breg cells exhibit significant impairment, and IL-10 levels are also reduced [13].

Additionally, studies have demonstrated that the integrity of central and peripheral B cell tolerance checkpoints is compromised in AQP4-IgG$^+$ NMOSD patients. AQP4-IgG can originate from the pool of naïve B cells that escape B cell tolerance due to a dysfunctional selection process. However, some of these antibodies do not bind the autoantigen, suggesting that pathogenic antibodies require affinity maturation and somatic hypermutation, a process involving T cells that may also be improperly selected in the thymus.

Reactivity of T cells against the AQP4$_{156–170}$ epitope has been observed in many NMOSD patients [14], highlighting the potential role of AQP4-specific T cells. In the disease. Furthermore, NMOSD patients exhibit downregulation of the Treg key transcription factor FoxP3 at the mRNA expression level, suggesting an impairment in peripheral T cell regulation [15].

AQP4-IgG is the primary effector molecule in NMOSD pathogenesis. The localization of AQP4 at the astrocyte end-feet, adjacent to the basement membrane of blood vessels and ependyma, makes it an accessible target for circulating antibodies. This autoantibody, an IgG1, activates complement, triggers antibody-dependent cellular cytotoxicity, and recruits neutrophils and eosinophils to lesion sites. Additionally, AQP4-IgG induces astrocyte activation and increases IL-6 production, promoting plasmablast survival and raising AQP4-IgG levels. This process impairs blood-brain barrier (BBB) permeability, facilitating T cell infiltration and accelerating inflammation. Th17 cells specific for AQP4 May also contribute to BBB disruption, further driving disease pathogenesis. These combined mechanisms result in astrocyte injury and the downregulation of structural and functional proteins crucial for maintaining local homeostasis, including AQP4 and glutamate excitatory amino acid transporter [1,2].

NMOSD appears to be a well-suited disease for restoring immune tolerance, as AQP4 has been identified as a well-defined target autoantigen, with up to 80% of patients exhibiting AQP4-IgG in their blood. Previous strategies to achieve this goal have been reviewed, with guiding principles focused on eliminating self-reactive immune cells and reprogramming antigen presentation processes using AQP4-loaded tolerogenic DCs to promote self-antigen-specific cells anergy, induce T or B regulatory cells, or enhance their functions [12,16]. However, challenges exist regarding these approaches, including the biotechnological feasibility of these approaches, prior exposure to immunotherapy, a limited number of patients for this type of clinical trial, and the heterogeneity of the disease. Furthermore, the immunological phenotype of these patients may not always be amenable to immune tolerance. It is clear that immune tolerance therapies would only be used for AQP4-IgG-seropositive patients or patients with an AQP4-specific immune response (e.g. memory B cells, T cells). Additionally, the impact of immunosenescence on the thymus could compromise the immune repertoire, particularly affecting memory cells.

Novel approaches have been developed to induce antigen-specific immune tolerance without compromising protective immunity against pathogens. The use of tolerogenic DCs loaded with specific antigens has been explored in various settings [10,17]. However, a standardized method for generating tolerogenic DCs ex vivo remains elusive, with multiple protocols proposed, including the differentiation of DCs in the presence of low concentrations of GM-CSF, IL-10, or Vitamin D3 [10,11,17]. Additionally, many tolerance-inducing strategies rely on isolating FOXP3$^+$ Tregs or T$_R$1 cells from peripheral blood and expanding them in the presence of IL-2 [18,19]. Another promising approach involves engineering Tregs with chimeric antigen receptors (CARs), which may be particularly useful when pathology-driven antigen is poorly defined [20].

Nanoparticles represent another innovative strategy for antigen-specific tolerance, capable of targeting specific cells and delivering multiple charges. The immunomodulation of these nanoparticles, influenced by their physicochemical properties, can be tailored to enhance circulation, cell targeting, and uptake, thereby maximizing therapeutic efficacy [21]. Furthermore, nucleic acid-based approaches, including those utilizing DNA and mRNA, provide effective platforms for specific antigen delivery, allowing additional post-translational modifications within the host [22,23].

3. Current investigational therapies

Immune tolerance treatments in clinical development for NMOSD are summarized in Table 1. A phase Ib, open-label, multiple ascending dose clinical trial evaluated the safety and feasibility of administering autologous tolerogenic peptide-loaded Immature DCs. At the 24-week evaluation, no significant adverse events were reported. Immunological responses demonstrated significantly higher IL-10 levels in all patients, alongside trends of increased T$_R$1 cells and reduced T cell proliferation in response to AQP4. Overall, peptide-loaded tolerogenic DCs were deemed a safe and feasible method for inducing immune tolerance [24].

Hematopoietic Stem Cells Transplantation (HSCT) aims to eradicate the dysfunctional immune system through high-dose chemotherapy followed by stem cell infusion of stem autologous cells. An open-label prospective study [25]

Table 1. Immune tolerance treatments in clinical development for NMOSD.

Treatment and ClinicalTrials.gov Identifier	Study details	Intervention	Stage of analysis	Clinical phase	Main results
Regulatory Dendritic Cell (DCs) (*NCT02283671*)	– MS and NMOSD patients – Open label, Single Group Assignment – Primary purpose: Treatment (number of patients with adverse events) – Primary outcome: Safety – Secondary outcomes: relapses, disability (EDSS), quality of life measures and immunological responses	Intravenous administration of tolerogenic Dendritic cells loaded with myelin peptides	Actual enrollment: 20 (completed)	Ib (ascending dose of intravenous administration of the DCs)	No serious adverse events and well tolerated.
Hematopoietic Stem Cell Transplant (*NCT00787722*)	– NMOSD patients – Open label, Single Group Assignment – Primary purpose: Treatment (Survival and PASAT 25-foot walk 9-hole peg test) – Primary outcome: Safety – Secondary outcomes: relapses, disability (EDSS), quality of life measures and immunological responses.	Hematopoeitic stem cells, after preconditioning with cyclophosphamide methylprednisolone, rituximab and other chemotherapeutic agents.	Actual enrollment: 13 (completed)	I/II	11 out of 13 patients survived more than 5 years post-intervention
CT103A Cells (*NCT04561557*)	– Refractory NMOSD patients – Open label, Sequential Assignment, no randomized – Primary purpose: Treatment (dose-limiting toxicity and Incidence and severity of AEs) – Primary outcome: Safety – Secondary outcomes: pharmacokinetic, Pharmacodynamic and many others	Intravenous infusion of CAR-T cells vs BCMA after receiving cyclophosphamide and fludarabine (lymphodepletion)	Actual enrollment (estimated): 36 (Active, recruiting) Estimated Study Completion: 2027-05-31	I	N/A
CART cells (*NCT05828212*)	– Recurrent/Refractory NMOSD patients – Open label, Single Group Assignment – Primary purpose: Treatment (dose-limiting toxicity, maximum tolerable dose and Incidence and severity of AEs) – Primary outcome: Safety – Secondary outcomes: AAR, lesion load and Gd+ (MRI), immunological responses and many others	CD19 CAR-T cells injection	Actual enrollment (estimated): 9 (Active, recruiting) Estimated Study Completion: 2026-04-30	I	N/A
BAFFR CART (*NCT06561009*)	– Recurrent/Refractory NMOSD patients – Open label, Single Group Assignment – Primary purpose: Treatment (dose-limiting toxicity and Incidence and severity of AEs) – Primary outcome: Safety – Secondary outcomes: AAR, lesion load and Gd+ (MRI), immunological responses and many others	Anti-BAFFR CART	Estimated enrollment: 20 (Not yet recruiting) Estimated Study start: 2024-10-01 Estimated Study Completion: 2027-10-01	I/II	N/A

Abbreviations: AAR: Annualized Relapse Rate, AE: adverse effects, BAFFR: B cell activating factor-receptor, CART: Chimeric antigen receptor T cells, EDSS: expanded disability status scale, Gd: gadolinium, QoL: Health-related quality of life, MRI: magnetic resonance imaging, MS: multiple sclerosis, N/A: not available, VEP: Visual Evoked Potential.

involving 11 AQP4-IgG$^+$ NMOSD patients utilized a conditioning regimen of cyclophosphamide, anti-thymoglobulin, and rituximab successfully induced long-term disease remission and enhanced neurological function. Nine patients achieved remission, which correlated with a transition to an anti-AQP4 seronegative status. In contrast, those who remained seropositive experienced relapses. Among the patients in remission, three later became seropositive again, albeit at low levels, and exhibiting atypical characteristics, lacking complement fixation and cytotoxicity. This suggests that HSCT may have facilitated an immune reset by eliminating self-reactive T and B cell clones and restoring AQP4-specific tolerance, potentially reestablishing regulatory T cell control over B cell maturation and expansion. Common grade 3 toxicities included hypophosphatemia and neutropenic fever, along with infections like C. difficile diarrhea and respiratory issues. New autoimmune diseases, such as myasthenia gravis and hyperthyroidism, were also observed after HSCT [25]. A recent meta-analysis of 31 NMOSD patients treated with HSCT indicated a progression-free survival rate of 76% over 2 to 13 years, with no treatment-related mortality or severe side effect reported. However, some patients experienced relapses within five years, and the optimal conditioning regimen remains uncertain [26]. While allogeneic SCT may effectively eliminate autoreactive lymphocytes, its associated risks warrant caution. Currently, allogeneic SCT for NMOSD is classified as developmental and is not recommended [27]. Two clinical trials examining autologous HSCT for NMO were withdrawn without releasing data (*ATTEND; NCT03829566* and *HSCT-NMO; NCT01339455*). Further research is essential to establish safety, efficacy, and optimal protocols for both types of HSCT.

A novel cell-based therapy involves the development of genetically engineered receptors, particularly chimeric antigen receptors (CARs). These receptors are typically derived from the variable regions of an antibody, combined with key

intracellular signaling domains of a TCR. CAR-T cell therapy genetically modified T cells to express receptors that specifically target disease-associated antigens. Additionally, T cells are transfected with two or more costimulatory domains, to received intracellular signals to increase their T cell response. In the context of autoimmune diseases like NMOSD, this approach eliminates autoreactive immune cells, restore immune tolerance, and modulate pathological immune responses. For instance, $CD4^+$ T cells have been transduced to upregulate FoxP3, Treg cells differentiation [28]. Similarly, CAR-T cells have been engineered to target the B cell maturation antigen (BCMA; CT103A) in patients with refractory AQP4-IgG-seropositive NMOSD. Anti-BCMA CAR-T cells with enhanced chemotaxis and increased CXCR3 expression efficiently cross the blood-brain barrier, eliminating plasmablasts and plasma cells in the CSF, which contribute to neuroinflammation in NMOSD [29].

A trial assessing the safety and efficacy of CD19 and CD20 CAR-T cell therapy in NMOSD was withdrawn due to recruitment challenges (*NCT03605238*) [30]. A phase 1, open-label, single-arm trial assessed the safety and efficacy of CT103A, a BCMA-targeting CAR therapy, in 12 AQP4-IgG-seropositive NMOSD patients (83.3% women, median age 49.5). Seven patients (58%) developed infections (none grade 4), and all experienced cytokine release syndrome (grade 1–2), but the safety profile was manageable. After a median follow-up of 5.5 months, 11 patients had no relapses, and all reported improved disability and quality of life, with a downward trend in AQP4-IgG levels [31]. Currently, an open-label phase I trial is underway, evaluating B cell maturation antigen CAR-T cell therapy after lymphodepletion with cyclophosphamide and fludarabine in 12 patients with refractory AQP4-IgG^+ NMOSD (*NCT04561557*). Initial results are anticipated by 2027. Another single-arm, open-label, single-center, phase I study is ongoing. The primary objective is to evaluate the safety of CD19 CAR T therapy for patients with relapsed or refractory NMOSD, and to evaluate the pharmacokinetics of CD19 CAR-T cells (*NCT05828212*). An additional open-label, single-arm, dose-escalation study in up to 20 patients with refractory NMOSD will start in October 2024. The aim is to evaluate the safety and efficacy of the treatment with B cell activating factor receptor CAR-T therapy (*NCT06561009*).

4. Experts opinion

Immunotherapy for NMOSD is a field in constant evolution, driven by new insights into disease pathogenesis. While continuous immunosuppression has been a standard approach, the field is now facing the challenges of achieving lasting disease control without ongoing immunosuppression. Despite encouraging pre-clinical results, antigen-specific immunotherapies are still not approved for autoimmune diseases, with very few tested beyond Phase I or II clinical trials. The potential for epitope spreading complicates successful antigen-specific tolerance induction. Furthermore, NMOSD patients who test negative for AQP4-IgG and MOG-IgG pose significant diagnostic and therapeutic challenges. These patients require the identification of novel antigens for targeted treatment without inadvertently inducing bystander tolerance. Genetic heterogeneity further complicates immune tolerance induction, particularly since such induction often occurs after periods of subclinical disease, which can lead to substantial tissue damage and trigger local inflammation. Thus, the identification of effective biomarkers for patient stratification and treatment personalization remains an important need for antigen-specific immunotherapy. Three main active research areas in immune tolerance hold potential for clinical application. First, tolerogenic vaccines aim to establish robust, lasting autoantigen-specific immune tolerance. Second, T cell therapies using Tregs (either polyclonal, antigen-specific) or CAR-T cells aim to establish active dominant immune tolerance or eliminate pathogenic immune cells. Third, IL-2 therapies aim to expand immunosuppressive regulatory T cells in vivo. While various therapeutic strategies are being explored, many of these methods are quite invasive, expensive, and demand a high level of expertise. These factors should be considered when evaluating the feasibility and broader application of these treatments in clinical practice. In NMOSD, the most promising alternatives to induce immune tolerance may include Treg cells therapy or antigen-specific tolerance (e.g. AQP4 peptides). However, further investigations are needed to understand their efficacy and potential clinical use fully.

Declaration of interest

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