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Review Article

# Autologous Hematopoietic Stem Cell Transplantation in Neuromyelitis Optica

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**Abstract**

Neuromyelitis Optica Spectrum Disorders (NMOSD) is an autoimmune astrocyte disease characterized by high recurrence rate and disability rate, symptoms of neurologic deficit are aggravated with the increase of recurrence times, and treatment for remission phase is of great importance. However, immunosuppressant's and targeted therapy used in remission phase have some disadvantages, such as off-label use, infection, need long time maintenance, patients with NMOSD may not response to those treatments and even relapse eventually. Highlighting the need for cell-based therapies bridge the gap of remission phase for refractory NMOSD, Hematopoietic Stem Cell Transplantation (HSCT) may precisely provide a potential approach as a promising therapy for refractory forms of NMOSD. Herein, we review clinical trials that implement HSCT on NMOSD in order to attract attention on this promising therapy that may induce long-term remission.

**Keywords:** Autologous hematopoietic stem cell transplantation; Immunotherapy; Neuromyelitis optica spectrum disorders; Longitudinal extended transverse myelitis; Optic neuritis

## Introduction

Neuromyelitis Optica (NMO) is an autoimmune astrocyte disease [1,2] characterized by Longitudinal Extended Transverse Myelitis (LETM) and Optic Neuritis (ON) [3], its pathogenic antibody is aquaporin-4-Immunoglobulin (AQP4-IgG) [4], one of most important aquaporin in CNS, where it is highly expressed on brain and lung tissue, also expressed on epithelial cells of the kidney ,stomach, airways, glands and skeleton muscle [5,6]. Since the milestone discovery of pathogenic antibody has been detected in patients of NMO made it distinct from Multiple Sclerosis (MS), disease definition has further broadened to NMO Spectrum Disorders (NMOSD) since 2007. While in year 2015 new criteria allow diagnosis with occurrence of one of six core characters with or without AQP4-IgG serologic status, but more restrict on clinical core characteristics and typical neuroimaging that includes ON, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic lesions on Magnetic Resonance Imaging (MRI), symptomatic cerebral syndrome with NMOSD-typical brain lesions [7].

The clinical course of NMOSD is relapsing and the symptom of neurologic deficit is accumulated with the attack. The aim to treat NMO in remission period is to prevent recurrent attack, reduce relapse rate and reduce neurological disability and mortality. Although patient with NMOSD has largely benefit from numerous effective therapies includes immunosuppressants and monoclonal antibody. However, disease progression cannot be halted by these agents including Disease Modifying Treatment (DMTs) and immunosuppressants or monoclonal antibodies, especially some patients with refractory course they may relapse soon after initial treatment [8]. meantime immunosuppressants and monoclonal antibody treatment for NMO have some disadvantages, such as off-label use [9], need life-long treatment , and patients may suffer serious side effects such as infection [10] and brings huge economic burden for patients. Even though NMO patient has benefited from these new immunotherapeutic approaches, disease cannot be cured to obtained a life-long remission. Therefore, making a room for explore profound and novel therapeutic approaches for NMO treatment. New evidence has demonstrated that Autologous Hematopoietic Stem Cell Transplantation (AHSCT) may play a promising and possibly curative strategies for NMO.

In this review, we will overview current knowledge on the potential mechanism of HSCT treatment, and then we will present up-to-date clinical analysis of the published evidence on the efficacy and adverse effect of hematopoietic stem cell transplantation on NMO. Then we will discuss outlook of Hematopoietic stem cell transplantation as a potential approach for patients with NMOSD, in order to provide an informative description of HSCT in NMO.

## Biological and Historical Rationale of HSCT in NMOSD

Hematopoietic-stem-cells are self-renewing and ability of giving rise to all mature cell types that comprise the blood-forming system [11]. Hematopoietic stem cell transplantation is a complex procedure that reconstitute host hematopoietic system through chemotherapy followed by a reconstruction of a new immune system. According to the donor of Hematopoietic Stem Cells (HSCs), HSCT procedures can be divided into autologous (auHSCT) or allogeneic (alHSCT). In auHSCT, the patitent plays both donor and recipient. alHSCT include a healthy allogeneic donor and the recipient (patient), however alHSCT has a higher risk of Graft-Versus-Host Disease (GVHD) [12] and transplant related motality [13]. European Bone Marrow Transplantation (EBMT) Autoimmune Disease Working




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Party (ADWP) recommends the use of AHSCT in NMOSD as a clinical option, with grade II evidence, in therapy-refractory patients [14]. In the treatment of severe autoimmune disease auHSCT have been preferred to prevent further transplantation related morbidity and mortality.

Hematopoietic stem cell transplantation was initially been utilized to treat malignant disease [15], continually its role has emerged in the treatment of autoimmune disease including neurological ones [16]. In the early 1990s, the first report of HSCT for Experimental Autoimmune Encephalomyelitis (EAE) were conducted in rodent, which achieved effective response for both autologous and allogeneic HSCT [17]. And soon after a series of studies in SLJ mice or Lewis rats showed that HSCT could prevent symptom progression [18-22]. Based on the above studies from animal's models, the first HSCT was exploited for MS patient in 1995 by Fassas [23]. Gradually, it has been through a hard time for exploration for HSCT in MS, including the evidence of failure in HSCT for MS patient [24]. Soon after, more studies demonstrated that HSCT as a therapeutic strategy in MS is curative and cost-effective [25-28].

While in 2010, AHSCT was firstly been adopted in NMO is from Chinese scholars [29], using autologous peripheral hematopoietic stem cell transplantation to treat one single NMO patient, a 23-year-old woman who has achieved clinical remission for more than 12 months after transplantation. The first report of applying alHSCT in NMO is from Greco, two NMO patients has achieved durable clinical remissions after alHSCT, both achieved AQP4-IgG negative status and stability on MRI [30].

The rationale of HSCT is to destroy auto reactive immune cells (particularly T and B cells) and reconfigured it by hematopoietic stem cell infusion allowing the reconstitution of a new, self-tolerant immune system(naive cells replaced the memory T cells), as a result of inducing long-term disease remission instead of long-term immunosuppression [30,31].

## Clinical trials to date of HSCT in NMOSD

An overview of the latest studies in patients' demographics, clinical characters, serology and treatment response are shown in Table 1.A total of twelve studies, 61 patients were included, nine studies were auto-HSCT, only three studies underwent allo-HSCT. Most (9/12) studies are case or case series, except Greco [30] and Burt [28] conduct retrospective and prospective cohort study respectively. Median age at transplantation was 34.5.years (3-58). (53) 87% patients were female, which showed a female predominance. (32)52% patients were seropositive for anti-AQP4 antibody. EDSS scores showed decrease after HSCT in ten studies. The first three complications post HSCT most frequently recorded were febrile neutropenia (5/12), CMV reactivation (3/12), diarrhea(3/12). Among 61 patients, (32)52% suffered relapse after HSCT, the median follow up were 44 months (6-108), at last follow up period most majority studies achieved clinical remission or progression free or relapse-free survival.

## Discussion

Immunotherapy for NMOSD has been evolving since immunosuppression to targeted therapy (Anti-CD20 monoclonal antibody, etc), current immune approaches could prevent disease relapse but still remains therapy-resistance and inefficient for progressive forms of NMO. Compared to MS, the development of HSCT for NMOSD is relatively young, HSCT has been utilized in MS more than 5000 patients for over 2 decades, while for NMOSD, HSCT has just been applied to 61 patients for 10 years. limited clinical trials to date has provide evidence for its efficacy and safety in NMOSD, evidence reviewed above showed that HSCT may be a most promising immunotherapy for NMOSD in the future, as long as cell-based therapy has emerged in order to start a new era in treatment of neurological immune disorders. But still, questions are worth thinking while carry on studies of HSCT on NMOSD patients:

When is the best time to carry HSCT? How much disease activity should be appropriate to underwent HSCT? Whether regimens such as rituximab works or the restoration of immune tolerance works in the mechanism of HSCT treatment? How young should patients be? Based on the questions above, more multicenter studies and randomized controlled trials are warranted to evaluate the efficacy and long-term outcomes of HSCT on NMOSD.

## Declaration of Interest

No potential competing interest was reported by the authors.

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