An updated review on the utility of hematopoietic stem cell transplant in the treatment of refractory myasthenia gravis

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Abstract

INTRODUCTION: Hematopoietic stem cell transplantation (HSCT) has been shown to be an effective treatment in many severe autoimmune diseases. There have been a number of reported cases of successful HSCT in severe, refractory myasthenia gravis (MG).

OBJECTIVE: To review and summarize the current literature on the role of HSCT in the management of refractory MG.

METHODS: Databases including PubMed, clinical trials.gov, and Cochrane Reviews were searched for research articles containing "hematopoietic stem cell transplantation," "stem cell," and "myasthenia gravis." Articles were excluded if they were not written in English.

RESULTS: A total of 16 patients across 8 publications were identified as having undergone HSCT in the setting of MG. Following HSCT, all patients had significant improvement in their MG status, with 11 achieving complete stable remission. Common adverse effects were mostly infection-related and included neutropenic fever, cytomegalovirus viremia or reactivation, mucositis, and upper respiratory tract infection.

CONCLUSION: HSCT has the potential to provide sustained benefit for patients with MG who are refractory to conventional treatment. A large-scale prospective study is warranted to better define its role in the treatment of MG.

Introduction

Myasthenia gravis (MG) is an autoimmune neurological disorder that results from impaired transmission at the neuromuscular junction through the binding of antibodies to post-synaptic proteins.[1] Clinical manifestations include fluctuating muscle weakness affecting the ocular, bulbar, limb, and respiratory muscles. Myasthenic crisis is the most severe form of MG, requiring the use of mechanical or non-invasive ventilation. The most common antibodies are directed against the nicotinic acetylcholine receptor (AChR-Ab) or muscle-specific kinase (MuSK-Ab).[1]

The number of patients diagnosed with MG has increased in recent years. In 2021, the incidence and prevalence of MG in the USA were 37 per 100,000 and 3.7 per 100,000, respectively, both of which increased from the 1980s and 2000s.[2] The mainstay of treatment includes pyridostigmine as well as long-term immunosuppression with corticosteroids and corticosteroid-sparing agents such as azathioprine and mycophenolate mofetil. Other agents including complement inhibitors, neonatal fragment crystallizable receptor (FcRn) therapy, and anti-CD20 agents such as rituximab may be used. However, 10-15% of patients with MG continue to be treatment-refractory. Historically, this has been defined as failing to respond to adequate doses of conventional immunosuppression, experiencing side effects or comorbidities that preclude the use of typical agents, requiring excessive doses of potentially risky agents, or needing frequent rescue therapies.[3,4,5] The optimal treatment for this group of MG patients remains poorly defined. Therefore, there is a need to continuously identify alternative treatments for refractory MG patients.

Hematopoietic stem cell transplantation (HSCT)has emerged as a potential treatment modality for patients with refractory MG. Hematopoietic stem cells (HSCs) are collected from the patient or the donor in autologous and allogeneic transplants, respectively. HSCs are preserved with cryotherapy while the patient undergoes chemotherapy to ablate their innate immune system. The previously collected HSCs are then infused into the patient, leading to immune system reconstitution and recovery.[6] Studies have compared the effectiveness of autologous and allogenic transplants. For instance, between 1997 and 2014, European Society for Blood and Marrow Transplantation (EBMT) registry reported that most patients received autologous transplants, compared to fewer than 20 patients who had received allogenic transplants.[7] Since it has a better side effect profile, autologous HSCT has been preferred over allogeneic HSCT.

HSCT has been utilized in cases of refractory, autoimmune conditions including multiple sclerosis (MS), with good results.[8,9] There is mounting evidence supporting the safety and efficacy of HSCT in refractory MS, especially in cases of relapsing-remitting disease.[10,11] However, there is a paucity of data summarizing the use of HSCT in MG. This review aims to provide a summary of the reported cases of HSCT in patients with MG and the current evidence for using HSCT in this patient population.

Methods

Databases including PubMed, clinical trials.gov, and Cochrane Reviews were searched for research articles describing the safety and effectiveness of HSCT in the treatment of MG. The search was completed using the terms "hematopoietic stem cell transplantation," "stem cell,"

and "myasthenia gravis." Articles not written in English were excluded. Patient characteristics included age, sex, disease duration, antibody status, prior MG treatments, and Myasthenia Gravis Foundation of America (MGFA) classification. Additional data collected included number of patients, comorbidities, HSCT type, MG outcomes, and reported side effects.

Results

A total of 16 patients (12 females and 4 males) from 8 publications were identified as having undergone HSCT for MG (Table 1). At the time of transplant, comorbid conditions included follicular lymphoma, familial Mediterranean fever, polymyositis, and aplastic anemia.[13,15,16] At the time of HSCT, MG disease duration ranged from 1 to 38 years (median 6 years). Patient ages ranged from 17 to 64 years (median 46 years). Fifteen patients underwent autologous HSCT while one underwent allogenic HSCT.[19]

Ten patients (62.5%) patients tested positive for AChR-Ab and 4 patients (25%) tested positive for MuSK-Ab. The remaining two patients tested negative for AChR-Ab, but they did not receive testing for MuSK-Ab.[13] Based on the MGFA classification, MG status was classified as follows: class IIIb in 2 patients (12.5%), IVa in 1 (6.3%), IVb in 5 (31.3%), and V in 6 (37.5%). MGFA status in 2 patients with generalized myasthenia gravis was unknown.[16,19] Before HSCT, all patients underwent various and numerous treatments for MG. The most common were prednisone in 14 patients (87.5%), plasmapheresis in 14 (87.5%), pyridostigmine in 13 (81.3%), intravenous immunoglobulin (IVIG) in 13 (81.3%), mycophenolate mofetil in 9 (56.3%), azathioprine in 8 (50%), rituximab in 8 (50%), and thymectomy in 8 (50%).

Follow-up duration ranged from 2 to 149 months post-transplant (median 38 months). All patients showed symptomatic improvement, with onset of improvement ranging from 2 weeks to 1 year after transplant (median 7 weeks). Fourteen patients (87.5%) were able to discontinue all MG medications. Eleven patients (68.8%) achieved a status of complete stable remission Of the patients who did not achieve complete stable remission, two had significant clinical improvement with minimal ocular symptoms and reduced AChR-Ab levels at their final follow-ups.[14,19] One patient originally classified as MGFA Class V prior to HSCT improved to Class IIa with discontinuation of all MG therapies.[12] One patient with coincident familial Mediterranean fever had to continue immunosuppression, but she experienced less frequent MG exacerbation after HSCT.[15] One patient with coexisting polymyositis and aplastic anemia showed improvement in muscle strength with some residual muscle weakness.[16]

Adverse effects related to HSCT included neutropenic fever in 7 patients (43.84%), cytomegalovirus viremia or reactivation in 5 (31.3%), mucositis in 4 (25%), upper respiratory tract infection in 2 (12.5%), oral herpetic infection in 2 (12.5%), bacteremia in 2 (12.5%), and rash in 2 (12.5%). One (6.3%) patient developed a secondary autoimmune disease of amegakaryocytic thrombocytopenia.[13] Three (18.8%) patients did not experience any notable adverse effects related to HSCT.[12,13,16] However, the patient with comorbid follicular lymphoma experienced a relapse of the lymphoma 12 months after HSCT and died 17 months later.[13] The authors of the study felt these complications were not related to HSCT.

Discussion

Literature supports an expanded usage of HSCT as an emerging therapy for various autoimmune neurological disorders such as multiple sclerosis, neuromyelitis optica, and chronic inflammatory demyelinating polyneuropathy.[20,21]

The treatment of refractory MG cases has remained a significant challenge for clinicians. These patients do not typically respond to many traditional immunotherapies such as corticosteroids, azathioprine, mycophenolate mofetil, IVIG, or plasmapheresis. While the newer generation therapies such as complement inhibitors or FcRn therapy may provide benefits in a portion of patients, such treatments do not lead to disease remission. Our above summary of the current literature suggests that HSCT could has provide significant and sustained benefits in a selection of refractory MG cases. All patients who underwent HSCT responded positively. Fourteen (87.5%) of 16 patients were able to stop all MG medications and eleven (68.8%) achieved complete stable remission. Our summary seems to suggest that HSCT is equally effective for both AChR-Ab and MuSK-Ab positive MG patients. For patients refractory to traditional MG treatments, HSCT appears to be an effective option.

However, HSCT is different from traditional immunotherapy in that it requires hospital admission. Its associated temporary but profound immunosuppression may have both short-term and long-term implications on the body's immune system. So far the most notable side effects of HSCT are infections or infection related events including neutropenic fever, CMV viremia or reactivation, mucositis, and upper respiratory tract infection. In addition to HSCT side effects, HSCT also requires a conditioning regimen to provide sufficient immunoablation to reduce the risk of rejection and graft-versus-host-disease (GVHD) prior to HSCT which can also lead to further immune system weakening, rendering patients to risk of infections, new autoimmunity and malignancy in the long term. With an increased use of HSCT, there will be a better understanding of its indications, efficacy, and complications.

Our review had some limitations. The included studies were all retrospective, either case reports or case series. Retrospective studies are prone to bias in data collection, patient recall, and patient reporting. Even though HSCT

has been a promising treatment for the refractory MG cases we investigated, the sample size is relatively small, and the patients may not be representative of all patients with refractory disease. The case series in our review with the greatest number of MG patients had seven, which was the largest case series of MG patients known to date.[13] To better understand the role of HSCT in MG treatment, a randomized prospective study of a larger sample size is needed.

Conclusion

HSCT has been shown to provide sustained benefit in a small sample of cases of refractory MG. Large-scale, prospective studies are needed to further investigate the role of HSCT in the treatment of MG.

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Table 1: Summary of Reported Cases of HSCT in Patients with MG

Study	Age at HSCT/ Sex	Disease duration at HSCT (yrs)	MG features (disease type/ worst MGFA class/Ab status)	MG treatment prior to HSCT	HSCT type	HSCT related complications	Follow-up duration and outcome of MG	Notes
Beland et al., 2023[12]								
Patient #1	62/F	4	MGFA class V, MuSK-Ab (+)	Prednisone, methotrexate, rituximab, plasmapheresis	Autologous	URTIs, venous catheter related infection	66 months, MG improved (MGFA class IIa), off all MG medications	Improvement by 3 months
Patient #2	55/F	3	MGFA class IVb, MuSK-Ab (+)	Prednisone, azathioprine, rituximab, plasmapheresis	Autologous	None	42 months, CSR, off all MG medications	Improvement by 4 months
Patient #3	38/F	3	MGFA class IVb, MuSK-Ab (+)	Prednisone, rituximab, plasmapheresis	Autologous	Herpetic stomatitis, bacteremia, URTI, premature menopause	36 months, CSR, off all MG medications	Improvement by 2 months
Bryant et al., 2016[13]								
Patient #1	43/F	5	MGFA class V, AChR-Ab (-)	Pyridostigmine, prednisone, azathioprine, mycophenolate mofetil, cyclosporine, IVIG, plasmapheresis, thymectomy	Autologous	none	149 months, CSR, off all MG medications	Improvement by 7 weeks
Patient #2	55/M	11	MGFA class IIIb, AChR-Ab (+)	Pyridostigmine, prednisone, mycophenolate mofetil, IVIG, plasmapheresis	Autologous	Mucositis, CMV viremia	91 months, CSR, off all MG medications	Improvement by 3 weeks
Patient #3	49/F	14	MGFA class IVb, AChR-Ab (+)	Pyridostigmine, prednisone, azathioprine, IVIG, plasmapheresis, thymectomy	Autologous	Mucositis, VZV dermatitis	40 months, CSR, off all MG medications	Improvement by 6 weeks
Patient #4	24/F	7	MGFA class IIIb, AChR-Ab (+)	Pyridostigmine, prednisone, mycophenolate mofetil, IVIG	Autologous	Neutropenic fever, Mucositis, CMV viremia	33 months, CSR, off all MG medications	Improvement by 4 months
Patient #5	42/F	7	MGFA class IVa, AChR-Ab (-)	Pyridostigmine, prednisone, azathioprine, mycophenolate mofetil, cyclosporine, IVIG, plasmapheresis, thymectomy	Autologous	Neutropenic fever, CMV viremia, BK virus hemorrhagic cystitis, oral HSV	32 months, CSR, off all MG medications	Improvement by 2 weeks

Patient #6	42/F	5	MGFA class IVb, AChR-Ab (+)	Pyridostigmine, prednisone, azathioprine, mycophenolate mofetil, IVIG, plasmapheresis, thymectomy	Autologous	Amegakaryocytic thrombocytopenia	41 months, CSR, off all MG medications	Improvement by 5 weeks
Patient #7	53/F	1	MGFA class V, AChR-Ab (+)	Pyridostigmine, prednisone, IVIG, plasmapheresis	Autologous	Neutropenic fever	29 months, CSR, off all MG medications	HSCT for follicular lymphoma with coincident active MG. MG improvement by 5 weeks
Håkansson et al., 2017[14]	64/F	38	MGFA class V, AChR-Ab (+)	Pyridostigmine, prednisone, methylprednisolone, azathioprine, mycophenolate mofetil, sirolimus, cyclosporine, cyclophosphamide, rituximab, eculizumab, terbutaline, bortezomib, IVIG, plasmapheresis	Autologous	Neutropenic fever, drug-related exanthema	24 months, significantly improved, off all MG medications	Improvement by 3 weeks
Inan et al., 2022[15]	27/F	1	MGFA class V, AChR-Ab (-), MuSK-Ab (+)	Pyridostigmine, methylprednisolone, rituximab, IVIG, plasmapheresis	Autologous	Urinary tract infection, Neutropenic fever, immunoglobulin deficiency	30 months, improved, still requiring intermittent rituximab, plasmapheresis and IVIG	Coexisting familial Mediterranean fever, MG improvement after 4 months
Mitsumune et al., 2018[16]	54/M	27	GMG, AChR-Ab (+)	Pyridostigmine, prednisone, cyclosporine, cyclophosphamide, IVIG, thymectomy	Autologous	none	2 months, improved	Coexisting polymyositis, aplastic anemia, thymoma
Schlatter et al., 2023[17]	33/F	14	MGFA class IVb, AChR-Ab (+)	Pyridostigmine, prednisone, mycophenolate mofetil, cyclophosphamide, rituximab, eculizumab, IVIG, plasmapheresis, thymectomy	Autologous	Neutropenic fever, rash, EBV reactivation	26 months, CSR, off all MG medications	Improvement by 3 weeks

Sossa Melo et al., 2019[18]	60/M	4	MGFA class V, AChR-Ab (+), MuSK-Ab (-)	Pyridostigmine, prednisone, azathioprine, cyclosporine, mycophenolate mofetil, rituximab, IVIG, plasmapheresis, thymectomy	Autologous	Neutropenic fever, CMV reactivation	65 months, CSR, off all MG medications	Improvement by 9 weeks
Strober et al., 2009[19]	17/M	16	GMG, AChR-Ab (+)	Pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, IVIG, plasmapheresis, thymectomy	Allogeneic	Mucositis, *Staphylococcus epidermidis* bacteremia, CMV reactivation	40 months, improved, off all MG medications	Improvement within first year

Abbreviations: Ab, antibody; AChR, acetylcholine receptor; CMV, cytomegalovirus; CSR, complete stable remission; EBV, Epstein Barr virus; F, female; GMG, generalized myasthenia gravis; HSCT, Hematopoietic stem cell transplantation; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; M, male; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific kinase; URTI, upper respiratory tract infection; VZV, varicella zoster virus.