1. Introduction

Myelin is a lipid-rich insulating substance made of multiple layers of compacted cell membranes. Oligodendrocytes of the central nervous system (CNS) ensheath the axons to form myelin that insulates segments of an axon for faster action potential conduction and to provide trophic support (Griffiths et al., 1998; Nave, 2010; Simons and Nave, 2015). Oligodendrocytes are required for the proper functioning and survival of the neuron. Improper development of myelin or damage to the existing myelin leads to interrupted signal propagation over the axon and disrupted metabolic support, resulting in failure of neuronal function followed by atrophy of the neuron (Siegel, 2006; Peru et al., 2008; Nave, 2010; Miron et al., 2011). Thus, strategies to activate and protect the oligodendrocyte progenitor cells (OPCs) residing in the CNS to replace the damaged myelin and to supply exogenous myelination-capable cells when endogenous OPCs are inadequate to remyelinate have been in the spotlight to treat demyelination diseases (Peru et al., 2008; Miron et al., 2011; Potter et al., 2011; Gupta et al., 2012). In this review, such therapeutic approaches taken against Pelizaeus–Merzbacher disease (PMD), adrenoleukodystrophy (ALD), multiple sclerosis (MS), and subacute sclerosing panencephalitis (SSPE) are discussed. Human clinical trials for all four diseases are summarized. Additionally, stem cell transplantation therapy for spinal cord injury is investigated as demyelination of axons is one of the main symptoms of the injury.

In recent years, a new tool has emerged to investigate neurodegenerative diseases in vitro. iPSCs carry the genotype of the person they are derived from. Hence, iPSCs derived from patients have the ability to reflect the cellular pathophysiology of the disease and are increasingly being used to study neurodegenerative diseases (Marchetto et al., 2008, 2010; Havlicek et al., 2014; Marchetto and Gage, 2014). Advances have been made to use mouse ESCs derived from oligodendrocytes and neurons as a model of myelin formation in vitro and test drug candidates to treat demyelination diseases (Deshmukh et al., 2013; Kerman et al., 2015). The techniques can be adapted to use human iPSCs. Patient iPSCs can be differentiated into oligodendrocytes and neurons to monitor defects in myelin formation (Figure). Additionally, these models are ideal platforms to test candidate drugs on human cells before clinical trials. This review discusses such potential uses of iPSCs as in vitro models of myelination and myelin disorders.
2. Pelizaeus–Merzbacher disease

PMD is an X-linked recessive disorder involving mainly the CNS with minor effects in the peripheral nervous system (Hobson and Garbern, 2012; Han et al., 2013). Mutations in the proteolipid protein 1 gene (PLP1) are responsible for PMD. One in 200,000 to 500,000 live births has PMD (Gupta et al., 2012; Torii et al., 2014). Individuals suffering from PMD have deficiencies of intellectual functions and motor skills involving walking, muscle stiffness, problems with movement and balance (ataxia), and involuntary jerking, with an average life span of approximately 30 years (Hobson and Garbern, 2012; Han et al., 2013).

Studies using transgenic mice and cells transfected with the PLP1 gene suggest that accumulation of the excess or misfolded PLP protein in the secretory pathway revealed the cellular basis of the disorder (Readhead et al., 1994; Gow and Lazzarini, 1996; Karim et al., 2010; Saher et al., 2012). The PLP is not delivered to the myelin membrane in sufficient amounts. Additionally, accumulated PLP triggers the unfolded protein response and attenuates delivery of cholesterol and maybe other cargo to the cell membrane. The oligodendrocyte metabolism is disrupted, resulting in abnormal differentiation, failure to form typical myelin structure, and apoptosis. A human iPSC-based model of PMD also supports this mechanism (Numasawa-Kuroiwa et al., 2014). iPSCs derived from two PMD patients were differentiated into oligodendrocytes and neurons. Cellular phenotypes of oligodendrocytes were investigated in detail and defects in myelin morphology were recorded for human cells, allowing the study of correlations among oligodendrocyte biology, genetic mutations that people carry, and the pathophysiology of PMD (Figure).

Currently available treatments for PMD are rather restricted and focus on alleviating the symptoms rather than curing the myelin deficit (Uchida et al., 2012; Torii et al., 2014). Thus, transplantation of cells capable of myelination has become a target as a treatment for PMD. Oligodendrocyte and Schwann cell transplantation to donor animals has been experimentally investigated since the 1980s (Table 1) (Duncan et al., 1981, 1988). Recently, animal models are being used to test the feasibility of transplantation of human cells (Table 1). For example, NSCs isolated from donated fetal brains (Uchida et al., 2012) and human glial progenitor cells (GPCs), either isolated from donated fetal brains or from surgical samples (Windrem et al., 2008), are transplanted into the dysmyelinated shiverer mouse model. These cells spread around the CNS and myelinated axons restore impulse transduction across the axons. Since fetal tissue as a transplantation material in the clinic may have several limitations, including availability as a constant source, moral objection of the recipient, and immune system complications due to the allogenic nature of the cells, iPSC-derived cells are being tested as an alternative. Human iPSC-derived OPCs have been shown to efficiently myelinate axons of shiverer mice (Wang et al., 2013). Importantly, neither of the transplanted progenitor cells showed any tumorigenic activity.

Human fetal NSCs that were not tumorigenic in mouse (Uchida et al., 2012) were tested for safety and efficacy in an open-label phase I clinical trial (Table 2) (Gupta et al., 2012). The 4 male patients involved in the trial had early-onset severe PMD due to amino acid substitution mutations in PLP1 and were between 14 months and 66 months of age. The NSCs were transplanted surgically into the frontal lobe white matter. Patients received immunosuppressants for 9 months after transplantation due to the allogenic nature of the NSCs. No severe adverse effects related to the transplantation procedure or to immunosuppression were observed. Twelve months after transplantation, the mental and physical functions of all four patients were stable or improved, such as the ability to self-feed. Neurological improvements such as reduced nightly continuous positive airway pressure requirements were observed. Consistently, MRI data indicated increased myelination in the regions of transplantation. A long-term follow-up of these four patients is currently ongoing (https://clinicaltrials.gov/ NCT01391637).

Umbilical cord blood (UCB) is a source of hematopoietic stem cells (HSCs) and has been successfully transplanted for treatment of many inherited metabolic diseases (Prasad et al., 2008). UCB transplantation can stabilize the disease progression if performed early. With this premise, Wishnew et al. (2014) transplanted UCB in two young boys with PMD (Table 2). One patient had a duplication of and the other had an aberrant splicing mutation in the PLP1 gene. At the ages of 9 months and 29 months, the patients underwent UCB transplantation after myeloablative chemotherapy as the cords came from an unrelated donor. Both patients showed improved disease phenotype and no severe complications related to the transplantation procedure after 7-year and 1-year follow-ups. Modestly improved motor skills and cognitive skills were reported. These may be associated with increase in myelination observed by MRI. However, due to lack of MRI data on the natural course of the disease, such a statement is not conclusive.

The outcomes of stem cell transplantation therapies for PMD are very encouraging as all patients show stable or improved motor skills and mental abilities. Increased myelination within the CNS suggests that these interventions are, at least in part, acting through an expected mechanism. All patients tolerated the allogenic cells even after removal of immunosuppression. It is especially noteworthy that one of the boys who received UCB transplantation has shown positive results for 7 years and can attend mainstream schooling with some extra support.
3. Adrenoleukodystrophy

ALD is caused by disruption of the ATP-binding cassette subfamily D member 1 gene (ABCD1) that is on the X chromosome (Kemp et al., 2001; Baarine et al., 2015). At least 517 different mutations disrupting the ABCD1 gene have been identified with a conservative incidence rate of 1 in 20,000, which may be as high as 1 in 14,000 (Kemp et al., 2001, 2010). The encoded protein (also known as ALDP) localizes to the peroxisomal membrane and is involved in transfer of very-long-chain fatty acids (VLCFAs) into peroxisomes, where VLCFAs are oxidized. Although ALD is characterized by accumulation of VLCFAs, the mechanism of myelin disruption is unknown. People with ABCD1 mutations can show a variety of phenotypes, the most devastating being childhood-onset cerebral ALD (ccALD). From 30% to 35% of ALD patients start showing demyelination within the cerebrum between the ages of 3 to 10 years (Kemp et al., 2001; Miller et al., 2011). The neurological and cognitive decline is very quick; usually total disability is evident within 3 years of diagnosis.
Table 1. A synopsis of the stem cell transplantation tests in animal models. This table is aimed at providing a small sample of studies involving transplantation of various stem cells into animal models with defective myelin in order to supplement human clinical trials.

<table>
<thead>
<tr>
<th>Model</th>
<th>Study</th>
<th>Outcomes</th>
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| Quaking mouse (CNS hypomyelination)        | Cells: Rat Schwann cells Transplantation: Injection into the spinal cord Parkin and PACRG genes mutated (Duncan et al., 1981) | - Lysolecithin induced demyelination  
- Immunosuppression administered  
- Myelination of spinal neurons by Schwann cells  
- Minimal to no migration of Schwan cells |
| Myelin-deficient rat (proteolipid protein gene mutated) | Cells: Rat CNS cells (mixture) and Schwann cells Transplantation: Injection into the spinal cord (Duncan et al., 1988) | - Cells migrated away from injection site  
- Transplanted oligodendrocytes myelinated axons of the spinal cord  
- Transplanted Schwann cells also myelinated CNS axons |
| Shiverer mouse (MBP gene mutated)          | Cells: Fetal human glial progenitor cells Transplantation: Injection into brain at several locations Mice are also immunodeficient (rag2−/−) (Windrem et al., 2008) | - Human cells myelinated in the mouse brain  
- Restored conduction velocity and nodes  
- Increased neurological function  
- Increased survival and decreased seizures  
- Cells were nontumorigenic |
|                                            | Cells: Human neural stem cells (hNSCs) Transplantation: Injection into brain at several locations Mice are also immunodeficient (rag2−/−) (Uchida et al., 2012) | - hNSCs turned into oligodendrocytes preferentially  
- Robust myelination  
- Restored conduction velocity and nodes  
- Myelin detected by magnetic resonance imaging |
|                                            | Cells: Human iPSC-derived oligodendrocyte progenitor cells (hiPSC-OPCs) | - hiPSC-OPCs turned into oligodendrocytes and astrocytes |
|                                            | Transplantation: Injection into brain Mice are also immunodeficient (rag2−/−) (Wang et al., 2013) | - Robust myelination of the entire brain  
- Restored nodes of Ranvier  
- Increased survival  
- Cells were nontumorigenic |
Another common type of ALD is adrenomyeloneuropathy (AMN), which involves axonopathy of mostly spinal cord. AMN onset is at 28 ± 9 years of age and it progresses more slowly.

Correlation between ALD severity and either ABCD1 mutations or plasma VLCFA levels has not been observed (Kemp et al., 2010; Jang et al., 2011). Reflecting such complexity, mice with mutated ABCD1 gene fail to replicate ALD phenotypes, especially that of ccALD. Therefore, iPSCs derived from patients offer an ideal platform to study the disease pathophysiology and test drug candidates. Indeed, VLCFA accumulation is observed in oligodendrocytes derived from ccALD and AMN iPSCs (Jang et al., 2011; Baarine et al., 2015). Consistent with the disease severity, ccALD oligodendrocytes accumulated more VLCFAs than AMN oligodendrocytes. The excess VLCFA was not observed in the undifferentiated iPSCs (Jang et al., 2011), but it was observed for a subset of the lines when differentiated into neurons (Jang et al., 2011; Baarine et al., 2015). Additionally, ccALD iPSC-derived astrocytes were more prone to inflammatory activity (Baarine et al., 2015). Jang et al. (2011) also tested effects of lovastatin and 4-phenylbutyrate, two compounds known to lower VLCFA levels in fibroblasts, on ccALD iPSC-derived oligodendrocytes. Intriguingly, both drugs lowered the VLCFA level, though only lovastatin's effect was statistically significant. These results demonstrate the utility of iPSCs for studying complex disease phenotypes and testing candidate drugs for ALD and, more generally, other demyelinating diseases in vitro (Figure).

ALD patients have been transplanted with HSCs in the form of bone marrow or UCB from either immunologically matched or mismatched sources since 1982 (Table 2) (Peters et al., 2004). A comparison of

<table>
<thead>
<tr>
<th>Experimental autoimmune encephalomyelitis (EAE)</th>
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<tbody>
<tr>
<td>Cells: Mesenchymal stem cells (MSCs) from the same strain of mice</td>
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<td>Transplantation: Intravenous injection immunized by myelin oligodendrocyte glycoprotein</td>
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<tr>
<td>(Zappia et al., 2005)</td>
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<tr>
<td>- Reduced demyelination of CNS</td>
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<tr>
<td>- Reduced immune cell infiltration to CNS</td>
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<td>- Not beneficial after disease stabilization</td>
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<tr>
<td>- MSCs migrated primarily to lymph nodes and spleen</td>
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<td>- T-cell activation was suppressed</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>(Zhang et al., 2005)</td>
</tr>
<tr>
<td>- Increased neurological function</td>
</tr>
<tr>
<td>- Reduced demyelination of CNS</td>
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<tr>
<td>- Reduced immune cell infiltration to CNS</td>
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<tr>
<td>- hBMSCs infiltrate brain</td>
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<tr>
<td>- Increased proliferation of oligodendrocyte lineage cells</td>
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<td>- Elevated BDNF levels in the brain</td>
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<tr>
<td>(Ryu et al., 2013)</td>
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<tr>
<td>- Serum IFN-β levels were elevated</td>
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<tr>
<td>- Reduced demyelination of CNS</td>
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<td>- Reduced immune cell infiltration to CNS</td>
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<tr>
<td>- Reduced levels of activating cytokines</td>
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<tr>
<td>- Elevated BDNF and NGF levels in the brain</td>
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<tr>
<td>- MSCs-IFN-β migrate into CNS</td>
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<tr>
<td>- Reduced blood–brain barrier permeability</td>
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<tr>
<td>(Hackett et al., 2014)</td>
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<tr>
<td>- lpr-NSCs exhibit increased survival and differentiation</td>
</tr>
<tr>
<td>- Increased neurological function</td>
</tr>
<tr>
<td>- Reduced immune cell infiltration to CNS</td>
</tr>
<tr>
<td>- NSCs migrated in the CNS</td>
</tr>
<tr>
<td>- NSCs remained as progenitors around the CNS lesions</td>
</tr>
<tr>
<td>- Both wt- and lpr-NSCs showed same effects</td>
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<tr>
<td>- Transplanted NSCs may have more of an immunomodulatory role</td>
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Table 1. (Continued).
Table 2. Clinical trials of stem cell transplantation to treat myelin disorders. The transplantation materials used in and the outcomes of the human clinical trials discussed in this review are summarized.

<table>
<thead>
<tr>
<th>Myelin disorder</th>
<th>Study</th>
<th>Outcomes</th>
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| **PMD**         | Cells: Fetal nervous system stem cells  
                 Transplantation: Injection into the brain white matter  
                 n = 4 patients  
                 (Gupta et al., 2012) | - No severe complications  
- Stable or improved mental function  
- Improved neurological function  
- Increased myelination |
|                 | Cells: Allogenic umbilical cord blood  
                 Transplantation: Intravenous infusion  
                 n = 2 patients  
                 (Wishnew et al., 2014) | - No severe complications  
- Improved disease phenotype  
- Improved motor skills and cognitive skills  
- Increased myelination |
| **MS**          | Cells: Autologous mesenchymal stem cells (MSCs)  
                 Transplantation: Intrathecal injection  
                 n = 10 patients  
                 (Mohyeddin Bonab et al., 2007) | - No severe complications  
- Variable disability scores  
- Mostly stable plaques  
- Minimally improved neurological function |
|                 | Cells: Autologous mesenchymal stem cells  
                 Transplantation: Intrathecal only or intrathecal and intravenous injection  
                 n = 10 patients and 5 patients  
                 (Karussis et al., 2010) | - No severe complications for 25 months  
- Mostly decreased disability scores  
- Increased neurological function  
- No new demyelinating plaques  
- Suppressed activated lymphocytes  
- MSCs disseminated from injection site |
|                 | Cells: Autologous mesenchymal stem cells  
                 Transplantation: Intravenous injection  
                 n = 10 patients; 8 controls  
                 (Connick et al., 2011) | - No severe complications  
- Improved clinical trial strategy to evaluate MS therapies |
|                 | Cells: Lymphocyte-depleted autologous hematopoietic stem cells (HSCs)  
                 Transplantation: Intravenous infusion with high-dose immunosuppressive therapy  
                 n = 26 patients  
                 (Bowen et al., 2012) | - 1 death due to infection  
- 2 severe adverse effects with worsening disability scores  
- Mild complications  
- Stable or worsened disability scores |
transplanted versus nontransplanted ccALD patients (n = 94 and n = 283, respectively) showed that hematopoietic cell transplantation (HCT) is very effective when performed at the early stages of the disease with increased survival; however, at later stages of disease, the benefit of HCT was minimal due to complications arising from the HCT procedure (Mahmood et al., 2007). A more recent study involving 60 ccALD patients who underwent HCT in a single institution reiterated similar findings (Miller et al., 2011). Patients receiving HCT with lower cerebral disease component benefit more in terms of survival and neurological function (Table 2). For patients that are not eligible for allogenic HCT, correction of the ABCD1 gene within their own HSCs is also being explored (Cartier et al., 2009). Transplantation of these genetically engineered HSCs offers similar benefits to HCT (Table 2). Thus, ALD patients without a matched donor or older patients who show severe adverse reaction to allogenic HSCs may soon benefit from HCT.

All of these studies underline the importance of early diagnosis of ccALD. Neonatal mutation screening will significantly improve outcomes of transplantation. Despite years of clinical application, the mechanism of the positive effect of transplanted cells is not known. More studies comparing pathophysiology before and after transplantation are required.

4. Multiple sclerosis
MS is a demyelinating disorder with a significant inflammatory component (Compston and Coles, 2008;
Constantinescu et al., 2011). Myelin loss disrupts the ability of the nervous system to efficiently communicate, resulting in physical, mental, and psychiatric problems (Compston and Coles, 2008). The immune cells invade the CNS to remove myelin debris and are involved in the death of neurons and oligodendrocytes. There is no cure for this disease that affects over 2.3 million people worldwide (www.nationalmssociety.org). Most, if not all, of the current therapies for MS target the immune system (Compston and Coles, 2008). Although immunotherapies slow down or inhibit further demyelination and lessen the progression of the disease, they usually are not sufficient to enhance remyelination.

Experimental autoimmune encephalomyelitis (EAE) is an animal model used to investigate inflammatory demyelinating diseases of the CNS including MS (Constantinescu et al., 2011) (see also Duncan et al. (2011) for a review of animal models of leukodystrophies). The animal models, mostly those of rodents but also nonhuman primates, are immunized with CNS tissue homogenate or peptides of specific myelin proteins to induce the immune system of the animal and initiate EAE. Activated T cells targeting myelin enter the brain and spinal cord and induce inflammation leading to demyelination and cell death. EAE is being used to study many aspects of MS, including the T cell-mediated autoimmune component of MS (Carbayal et al., 2015). Many of the current therapies for MS have been investigated with EAE models, including stem cell transplantation approaches (Table 1) (Constantinescu et al., 2011).

Despite its many benefits, EAE fails to reflect the complexity and heterogeneity of MS (Hartley et al., 2014). Patient-derived iPSCs may close the gap between animal models and MS pathophysiology. A total of five iPSC lines from MS patients have been published; however, no clear phenotype specific to MS has been recognized so far (Song et al., 2012; Douvaras et al., 2014). This may be due to several reasons: 1) MS is a complex disease with both genetic and environmental components; 2) in these studies oligodendrocytes but not the myelin was investigated; and 3) the immune component was missing in the in vitro models. Future studies comparing MS patient-derived myelin to controls in a controlled in vitro environment are required for better understanding of the disease.

Mesenchymal stem cells (MSCs) offer an easily accessible form of stem cells as they are present in many adult human tissues (Pountos and Giannoudis, 2005). They can differentiate into many cell types including bone, cartilage, fat, muscle, and tendon. It is hypothesized that MSCs can suppress the immune system, which can damage neurons and oligodendrocytes as discussed above (Darlington et al., 2011; Cohen, 2013). MSCs can also stimulate the neuronal repair mechanisms by secreting neuroprotective factors. These tissue protective and immunomodulatory characteristics of MSCs make them intriguing candidates for MS therapy. For instance, in one study, MSCs migrated to demyelinating regions of the inflamed CNS and inhibited the myelin-specific T cells in an EAE model and regulated the cytokines released from T helper 1 (Th1) and T helper 17 (Th17) (Bai et al., 2009). Engineered MSCs exhibit superior ability over naïve MSCs to treat MS. Interleukin-10 transfected into MSCs showed significant inhibitory activity on the proliferation of CD4+ T lymphocytes of EAE mice and significantly improved remyelination (Liao et al., 2016). Additionally, interferon-β-secreting MSCs reduced further injury to the blood–brain barrier permeability and also increased remyelination (Ryu et al., 2013).

As discussed above, NSC or OPC transplantation enhances myelination of axons in dysmyelinated mouse models (Uchida et al., 2012; Wang et al., 2013).Remarkably, NSCs have immunomodulatory effects as well. Chemokines secreted by NSCs impair recruitment of immune cells to the CNS (Ravanidis et al., 2015). Leukemia inhibitory factor produced by NSCs inhibits pathogenic Th17 cell differentiation resulting in amelioration of EAE (Cao et al., 2011). Transplantation of Fas-deficient NSCs decreases the inflammatory infiltration into the CNS by inducing apoptosis of Th1 and Th17 cells (Hackett et al., 2014). NSCs may exert their immunomodulatory effect without entering the CNS (Ben-Hur, 2008). When injected intravenously to an EAE mouse, NSCs traveled to the lymph nodes and spleen rather than migrating into the CNS. There, they attenuated T-cell activation and reduced inflammatory response to myelin. Similarly, transplantation of NG2+ progenitor cells, which can mature into oligodendrocytes but may also have other resident functions in the CNS, into EAE mice reduced immune cell infiltration and increased myelination (Bai et al., 2013).

To investigate the feasibility of MSC transplantation in humans, 10 MS patients received bone marrow-derived autologous MSCs intrathecally (Mohyeddin Bonab et al., 2007). Patients’ neurological functions improved slightly (Table 2). The Expanded Disability Status Scale (EDSS) is a tool for quantifying disability of MS. Posttransplantation EDSS scores of patients were too variable to be conclusive with both increased and decreased scores. Similarly, changes in demyelinating plaque numbers varied from patient to patient but were generally stable. In a phase I/II human clinical trial, the immunological effects of bone marrow-derived autologous MSCs were examined in 15 patients (Karussis et al., 2010). No major adverse reactions to the transplantation procedure were evident within the duration of study (25 months; Table 2). Neurological function either improved or was stable as measured by the
EDSS. No new plaques developed. Activated lymphocytes and antigen-presenting cells were suppressed after transplantation; however, the activated T-cell population (CD4- and CD25-double positive) increased. Intriguingly, MSCs, as traced by MRI, disseminated from the injection site within the CNS. A more recent study addressed the trial design features to better measure the benefits and risks of stem cell transplantation in MS patients (Connick et al., 2011). Ten patients and 8 controls were assessed both before and after transplantation to minimize the effect of variance observed between patients and for one patient throughout the disease course (Table 2). The safety of autologous MSC transplantation was reiterated. The authors suggested that assessing neuroprotection with specific methods rather than measuring wider neuronal functions is a more relevant evaluation of the intervention.

With the premise of generating a myelin-nonreactive immune system, patients' immune systems were almost completely ablated by high-dose immunosuppressive therapy followed by autologous HCT in 26 advanced MS patients (Bowen et al., 2012). Complications due to the transplantation procedure were more severe than in previous interventions (Table 2). Improvement of neurological functions of the patients was not significant. The benefits of transplantations in MS patients are minimal at best with worsening disability being common. The positive outcomes may be concealed due to the small group sizes and variable course of MS. iPSC models are also not able to replicate disease phenotype. More patient cell lines should be investigated.

5. Subacute sclerosing panencephalitis
SSPE is a rare, progressive neurological disorder of the CNS caused by persistent measles virus (MV) infection (Schonberger et al., 2013). It more commonly affects children and young adults in less developed countries. The SSPE incidence rate in the United States is reported to be 6.5–11 cases per 100,000 acute measles infections (Bellini et al., 2005), while the estimated number of SSPE patients in Turkey is approximately 3000 (www.sspedernegi.org/). It is predicted that MV accesses the CNS during primary infection by a hematogenous route, where it stays latent for on average 4 to 10 years (Schneider-Schaulies et al., 2003; Anlar and Yalaz, 2011). The survival period after onset of symptoms is typically between 1 and 3 years (Garg, 2008; Gutierrez et al., 2010).

The distinct processes leading to infection of cells in the brain are poorly understood and no cure for SSPE exists (Schneider-Schaulies et al., 2003; Anlar and Yalaz, 2011). As MSCs have been used in ALD with positive outcomes and in MS for their immunomodulatory characteristics, Kuskonmaz et al. (2015) transplanted five SSPE patients with autologous bone marrow-derived MSCs. One patient died of respiratory problems prior to evaluation and none of the remaining four patients showed any improvements (Table 2). Two patients remained stable; one patient deteriorated and one patient died due to disease progression. New inflammatory lesions developed in two of the patients. The variability of SSPE course and the small number of patients enrolled in the trial may mask any potentially gained benefits. Encouragingly, none of the patients developed any adverse effects to the transplantation procedure.

Currently, stem cell therapies for SSPE are in their infancy. New animal models have to be established for safety and efficacy testing of cells before human trials. Pretransplantation screenings of autologous stem cells for latent MV infection may have positive outcomes. Allogenic cells isolated from immunologically matched sources may also benefit patients, as was observed for other myelination disorders.

6. Spinal cord injury
Spinal cord injury (SCI) affects millions of people worldwide and constitutes a substantial health care burden (Salewski et al., 2015). The most common type of SCI, spinal contusion, causes permanent motor and sensory function loss due to major tissue death and cell damage to the injury site and its close proximity. The primary physical trauma to the spinal cord leads to vascular rupture, hemorrhage, and cell death. Oligodendrocytes and neurons are lost by necrosis. This initial injury is followed by the secondary injury, in which the lesion area grows gradually and chronic inflammation is present (Allison and Ditor, 2015). During this phase blood flow is reduced, resulting in ischemia, and free radical production increases, the blood–brain barrier breaks down, and immune cells infiltrate the injury site and the surrounding area. The secondary insults also contribute to necrosis of neurons and oligodendrocytes and demyelination (Almad et al., 2011).

Stem cells arise as a potential therapy to replace the lost cells, especially the oligodendrocytes to repair the myelin (Cummings et al., 2005; Barnabe-Heider and Frisen, 2008; Sharp et al., 2010; Li and Leung, 2015). Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), however, cannot be directly transplanted because these
cells can proliferate rapidly and turn tumorigenic. Rather, they are first converted into various cell types of the nervous system such as neural stem cells (NSCs), OPCs, and motor neurons and then transplanted. In animal SCI models, transplanted mouse or human NSCs and OPCs contribute to remyelination, axon regeneration, and functional recovery (Cummings et al., 2005; Barnabe-Heider and Frisen, 2008; Sharp et al., 2010; Li and Leung, 2015). Human NSCs transplanted into the injured spinal cord of mouse are more likely to become mature oligodendrocytes than NSCs transplanted into uninjured spinal cord (Sontag et al., 2014). This may be a feature of the injury highlighting a need to remyelinate axons in the injury site.

The first clinical trial of stem cell therapy for SCI was run in 2009 by the Geron Corporation to test the safety of human ESC-derived OPCs (ir.geron.com; https://clinicaltrials.gov/ NCT01217008). The OPCs are derived from human ESC line WA01 (H1) using a protocol originally established by the Keirstead Lab (Sharp et al., 2010). Approximately 2 million cells were administered within 14 days of injury to 5 patients with complete thoracic SCI. The patients received immunosuppressants for 2 months. No adverse events were reported in the trial or by the follow-up studies ever since (ir.geron.com; www.biotimeinc.com) (Lebkowski, 2011). Additionally, the transplanted OPCs might have played a role in the reduction of the injury site in 4 of the patients (www.biotimeinc.com). Encouraged by these results, Asterias Biotherapeutics is undertaking a phase I/IIa human clinical trial (https://clinicaltrials.gov/ NCT02302157). OPCs derived by the same protocol will be transplanted to patients with cervical SCI in increased doses primarily to evaluate the safety of the treatment, but also the neurological function of the patients will be monitored (Priest et al., 2015).

In an ongoing phase I/IIa human clinical trial, Shin et al. (2015) transplanted human NSCs that were derived from human fetal telencephalon to 19 patients with cervical SCI. After approximately 2 months of injury, 2.0 × 10^6 cells were injected into the lesion area. Patients received an immunosuppressant for 9 weeks. Motor functions of 5 of the patients were improved 1 year after transplantation. None of the patients showed neurological deterioration, spasticity or tumor formation, or spinal cord damage due to transplantation procedure (Shin et al., 2015).

The limited number of human clinical trials demonstrates that SCI patients tolerate transplantation of allogenic cells either derived from human ESCs or from fetal tissue. Early outcomes of the trials suggest modest improvement of neurological function for the patients. These results are promising but to achieve significant clinical betterment of the patients the transplantation procedure needs to be optimized. More, a longer-term monitoring of the transplanted patients is required to evaluate the safety of transplanted cells for any adverse effects.

7. Concluding remarks
The studies discussed in this review demonstrate that stem cell transplantation offers a hope for incurable demyelination disorders (Table 2). Thus, there are several active studies registered in the National Institutes of Health clinical trials database. Out of the 14 studies targeting MS, 9 are currently recruiting patients. Three out of 5 of active ALD trials and 1 out of 3 active PMD trials also are recruiting volunteers. MSCs and HSCs from different sources are pretty much evenly split as transplantation material among trials. However, many challenges lie ahead of a readily available therapy. One of them is the type of stem cell to be used. MSCs and HSCs are easily accessible cells and have immunomodulatory effects, but they themselves do not participate in new myelin formation. NSCs and their derivatives with more restricted fates, OPCs and GPCs, can myelinate neurons while also suppressing lymphocytes. No tumorigenic activity associated with transplantation of these cells has been observed so far. Secondly, the source of cells is a key issue. Some patients may object to receiving fetal tissue-derived cells on moral grounds. Regardless, the requirement of immunosuppression for allogenic cells may also increase the risk that patients face. It may be possible to correct the genetic defect of patients’ own MSCs or HSCs for autologous transplantation for single-gene mutation diseases such as PMD and ALD. Additionally, iPSCs offer possibilities for autologous transplantations as they can be differentiated into specific cell types such as NSCs and OPCs. The investigations so far show that after sorting out undifferentiated cells within the population, these cells do not cause tumors after transplantation. For genetic diseases, iPSCs will also require gene correction before transplantation.

Patient-derived iPSCs are being used to study myelin biology in vitro (Figure). Thus far, cellular disease phenotypes of PMD and ALD but not of MS have been replicated using iPSCs. The difference may rise from the fact that more than one cell type is involved in MS without known mutations while both PMD and ALD iPSCs carry known mutations in a single gene. These observations underlie the importance of using myelination-in-a-dish approaches to study myelin formation.

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