Hematopoietic Cell Transplantation for Autoimmune Diseases and Miscellaneous Indications

Number: 0606

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers hematopoietic cell transplantation (autologous or allogeneic) experimental and investigational for any of the following autoimmune diseases (not an all-inclusive list) because its effectiveness for these indications has not been established.

- Anti-phospholipid syndrome
- Autoimmune cytopenia (e.g., autoimmune hemolytic anemia, Evans syndrome, and idiopathic thrombocytopenic purpura)
- Autoimmune diseases-induced cirrhosis
- Celiac disease
- Chronic inflammatory demyelinating polyradiculopathy
- Crohn's disease
Dermatomyositis
Inflammatory bowel disease
Juvenile rheumatoid arthritis
Multiple sclerosis
Neuromyelitis optica
Pemphigus
Polymyositis
Rheumatoid arthritis
Systemic lupus erythematosus
Systemic vasculitis
Ulcerative colitis

II. Aetna considers hematopoietic cell transplantation (autologous or allogeneic) experimental and investigational for any of the following miscellaneous conditions (not an all-inclusive list) because its effectiveness for these indications has not been established.

- Age-related macular degeneration
- Amyotrophic lateral sclerosis
- Diabetes mellitus (type I)
- Essential thrombocythemia
- Polycythemia vera
- Recessive dystrophic epidermolysis bullosa
- Retinitis pigmentosa
- Thrombotic thrombocytopenic purpura

III. Aetna considers the use of mesenchymal stem cells in hematopoietic stem cell transplantation experimental and investigational for the treatment of autoimmune diseases and selected indications listed in policy statement II.

IV. Aetna considers autologous hematopoietic cell transplantation medically necessary for the treatment of adults (18 to 69 years of age) with rapidly progressive scleroderma (systemic sclerosis) at risk of organ failure when
either of the following is met:

Active interstitial lung disease (as determined by broncho-alveolar cell composition or ground-glass opacities on computed tomography of the chest) plus either a forced vital capacity (FVC) or a diffusing capacity of the lung for carbon monoxide (DLCO) of less than 70 % of the predicted value; or

Previous scleroderma-related renal disease.

and the member meets the transplanting institutions' selection criteria, or in the absence of such criteria, the member does not have any of the following exclusion criteria:

Poor renal function (creatinine clearance of less than 40 ml/min)
Severe lung disease (diffusing capacity of the lung for carbon monoxide (DLCO) of less than 40 % of the predicted value; or forced vital capacity (FVC) of less than 45 % of the predicted value)
Pulmonary arterial hypertension
Poor lung function (left ventricular ejection fraction (LVEF) of less than 50%)

Background

Autoimmune diseases (ADs) include a heterogeneous group of immune-mediated disorders that are responsive to suppression or modulation of the immune system. Some common ADs are multiple sclerosis (MS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). The prevalence of ADs in the United States is estimated to be approximately 2 %. In particular, MS afflicts about 350,000 people in the United States, while RA and SLE affects 0.5 to 1.0 % and 0.05 % of Americans, respectively. These diseases are often characterized
by chronic, painful and debilitating courses that warrant aggressive therapy. For some patients with severe, relapsing/refractory cases, conventional therapy may not be satisfactory.

High-dose chemotherapy (HDC) and bone marrow/peripheral stem cell transplantation (autologous or allogeneic) has been studied for the treatment of severe ADs. The notion of employing HDC and bone marrow/peripheral stem cell transplant to treat AD is based on encouraging results in experimental animals and from serendipitous reports of patients with both ADs and malignancies who were allotransplanted for the latter. High-dose chemotherapy and bone marrow/peripheral stem cell transplant has been tried for patients with ADs who are refractory to standard therapies and are at high-risk of subsequent morbidity and mortality. Multiple sclerosis, RA, SLE, and systemic sclerosis are the ADs that have been most commonly treated by this procedure. Although early findings are promising, the number of patients treated is limited, and only short-term follow-up is available. Furthermore, the mechanism of improvement or stabilization is unclear, and the procedure has the potential for life-threatening toxicity.

**Systemic Sclerosis (Scleroderma):**

A review (Bingham et al, 2000) stated that autologous stem cell transplantation is starting to be examined as a potential therapy for severe, refractory ADs including neurological, rheumatological, and hematological diagnoses. Increasing numbers of cases are now reported in the scientific literature. Data from all transplanted patients are being collated in a centralized register by the European Group for Blood and Marrow Transplantation and the European League against Rheumatism to ensure effective assessment of the safety and effectiveness of this promising procedure. Thus far, results have been encouraging; however, they need to be confirmed by well-designed randomized, controlled studies in view of the well-known difficulty of judging objectively the effect of a treatment.
in patients with these diseases. Optimization of mobilization, conditioning regimen, as well as graft manipulation is needed to maximize effectiveness without increasing mortality and morbidity. The use of maintenance therapy after autologous stem cell transplantation to prevent relapse needs to be investigated. Furst (2000) noted that stem cell transplantation for the treatment of systemic sclerosis is showing some apparent effectiveness, but its use is only in the pilot stages.

Witkowska et al (2014) stated that autoimmune connective tissue diseases (ACTDs) are heterogeneous disorders associated with different manifestations, clinical course of disease and prognosis among patients. Although recent advances in understanding the pathogenesis have led to major progress in target-oriented therapy, they still remain incurable. Novel biological drugs, cellular therapy and HSCT are real hopes for treatment development in the future. The concept of both autologous and allogeneic HSCT in children with autoimmune diseases is developing energetically since 1996, when the first HSCT was performed. Nowadays, after 17 years of clinical experience, both types of HSCT remain attractive and powerful salvage methods of treatment. However, there are still many doubts and unclear issues, which need further investigation. These investigators provided an overview of the knowledge concerning actual data on HSCT in a pediatric group of patients with different ACTDs, focused on juvenile idiopathic arthritis (JIA), SLE and systemic sclerosis.

Cipriani et al (2015) stated that the presence of autoimmune diseases, including systemic sclerosis (SSc), suggest failure of the normal immune regulatory processes leading to activation and expansion of auto-reactive effector immune cells. Recently, stem cell transplantation emerged as a novel rescue therapy for a variety of refractory autoimmune diseases. The therapeutic strategy involves the ablation of the aberrant self-reactive immune cells by chemotherapy and the regeneration of a new self-tolerant immune system formed by the transplanted stem cells. In the last few years, thousands of patients worldwide have received HSCT, mostly autologous, as treatment for severe
irreversible autoimmune diseases, with promising results. These investigators reviewed the results of published small series of SSc patients treated with allogeneic and autologous HSCT, as well as 3 randomized trials, exploring the safety and effectiveness of autologous HSCT in SSc. The authors concluded that although the results are encouraging, nonetheless, the correct application of stem cell transplantation remains an area of active investigation; results of larger randomized, double-blind clinical trials, will certainly improve the knowledge of the appropriate clinical use of stem cell therapy in SSc patients.

Host et al (2017) stated that autologous hematopoetic stem cell transplantation (AHSCT) has emerged as a therapeutic option for patients with refractory, severe autoimmune disease. This is a systematic review of the current literature on AHSCT in adult patients with systemic sclerosis (SSc). Original articles published between 2005 and 2016 that evaluated the use of AHSCT in patients with SSc were reviewed with respect to the primary outcomes of overall and transplant related mortality (TRM) rates, and secondary outcomes of changes in mRSS, FVC, progression-free survival (PFS)/EF and quality of life (QOL) measures. These researchers also focused on patient characteristics, the AHSCT conditioning and mobilization regimens used, and their relationship to patient outcome in each study. Of the 155 articles found, only 9 articles were suitable for review. There were 2 randomized controlled trials (RCTs), ASTIS and ASSIST, and 7 observational and cohort studies. In general, patients undergoing AHSCT had diffuse SSc with mRSS greater than 14, and interstitial lung disease (ILD). The 2 RCTs showed a benefit in PFS/EFS (80 to 81 %), FVC and QOL measures in AHSCT compared to monthly cyclophosphamide. All the studies showed an improvement in mRSS; TRM rates varied among studies, from 0 to 23 %, with a trend to higher mortality rates in studies using higher doses of cyclophosphamide or myeloablative conditioning regimens. The authors concluded that AHSCT is beneficial in some patients with SSc and that patient selection and conditioning regimens are critical determinants of prognosis and mortality post-ASCT.
Del papa et al (2017) retrospectively evaluated the efficacy of AHSCT in 18 patients with rapidly progressive diffuse cutaneous systemic sclerosis (rp-dcSSc), and compared their disease outcomes with those of 36 demographically- and clinically-matched patients treated with conventional therapies. Cutaneous involvement, by performing mRSS, lung diffusion capacity, by measuring diffusing capacity of lung for carbon monoxide (DLCO), and disease activity, by applying the European Scleroderma Study Group (ESSG) scoring system, were the outcome variables measured at the baseline time and then every 12 months for the following 60 months in both the AHSCT-treated patients and the control group. In the AHSCT group, TRM was 5.6%. In this group, both mRSS and ESSG scores showed a significant reduction 1 year after AHSCT (p < 0.002); and these results were maintained until the end of follow-up. Conversely, DLCO values remained stable during the whole period of follow-up. Survival rate of AHSCT group was much higher than that observed in the whole control group (p = 0.0005). The probability that the ESSG score and mRSS would remain at a high level, and DLCO could decrease, was significantly higher in the control group as a whole and in the subgroup of control patients treated with cyclophosphamide than in the AHSCT group. The authors concluded that the findings of this study confirmed that the AHSCT was effective in prolonging survival, as well as in inducing a rapid reduction of skin involvement and disease activity, and preserving lung function in patients with rp-dcSSc.

The experts from the European League against Rheumatism (EULAR, 2017) recommended that hematopoietic stem cell transplantation (HSCT) should be considered for the treatment of selected patients with rapidly progressive SSc at risk of organ failure. To reduce the risk of treatment-related side effects, HSCT should be performed in selected centers with experience in this kind of treatment. Careful evaluation of the benefit to risk ratio in individual patients with SSc selected for HRCT should be done by experts. Further studies should help to identify subgroups of patients with SSc in whom HSCT would be
In a prospective, observational study, Nair and colleagues (2018) evaluated long-term outcomes in a cohort of patients with SSc treated with HSCT. A total of 4 SSc patients who underwent HSCT at a tertiary care center in India between 2008 to 2012 were included in this study. The selection criteria included young individuals with rapidly progressive disease and at least one major organ involvement. These researchers used granulocyte colony-stimulating factor for peripheral blood stem cell mobilization, pre-transplant conditioning with fludarabine, cyclophosphamide and rabbit anti-thymocyte globulin followed by re-infusion of autologous stem cells as per standard institute protocol. A total of 4 patients (1 male and 3 females) underwent autologous HSCT for SSc. Patients had heterogeneous disease manifestations including severe Raynaud's phenomenon with vasculopathic ulcers, gastrointestinal (GI) problems and mild ILD. Patients were followed-up for a mean duration of 7 years. There was significant sustained improvement in skin score, vasculopathy and GI manifestations; ILD did not show any deterioration. The QOL indices showed remarkable improvement in all subjects. No complications related to transplant were noted. The authors concluded that in the absence of an effective pharmacotherapy for SSc, autologous HSCT has a huge potential in management of cutaneous and internal organ manifestations.

Sullivan and colleagues (2018) compared myeloablative CD34+ selected autologous hematopoietic stem-cell transplantation with immunosuppression by means of 12 monthly infusions of cyclophosphamide in patients with scleroderma. These researchers randomly assigned adults (18 to 69 years of age; had scleroderma for 5 years or less with pulmonary or renal involvement) with severe scleroderma to undergo myeloablative autologous stem-cell transplantation (36 participants) or to receive cyclophosphamide (39 participants). The primary end-point was a global rank composite score comparing participants with each other on the basis of a hierarchy of disease features assessed at 54 months: death,
event-free survival (EFS; survival without respiratory, renal, or cardiac failure), forced vital capacity (FVC), the score on the Disability Index of the Health Assessment Questionnaire, and the modified Rodnan skin score (mRSS). In the intention-to-treat population, global rank composite scores at 54 months showed the superiority of transplantation (67% of 1,404 pairwise comparisons favored transplantation and 33% favored cyclophosphamide, p = 0.01). In the per-protocol population (participants who received a transplant or completed greater than or equal to 9 doses of cyclophosphamide), the rate of EFS at 54 months was 79% in the transplantation group and 50% in the cyclophosphamide group (p = 0.02). At 72 months, Kaplan-Meier estimates of EFS (74% versus 47%) and overall survival (OS; 86% versus 51%) also favored transplantation (p = 0.03 and 0.02, respectively). A total of 9% of the participants in the transplantation group had initiated disease-modifying anti-rheumatic drugs (DMARDs) by 54 months, as compared with 44% of those in the cyclophosphamide group (p = 0.001).

Treatment-related mortality in the transplantation group was 3% at 54 months and 6% at 72 months, as compared with 0% in the cyclophosphamide group. The authors concluded that myeloablative autologous hematopoietic stem-cell transplantation achieved long-term benefits in patients with scleroderma, including improved EFS and OS, at a cost of increased expected toxicity. Rates of treatment-related death and post-transplantation use of DMARDs were lower than those in previous reports of non-myeloablative transplantation.

Inclusion criteria of this trial included pulmonary involvement (required active interstitial lung disease (as determined by broncho-alveolar cell composition or ground-glass opacities on computed tomography of the chest) plus either a forced vital capacity (FVC) or a diffusing capacity of the lung for carbon monoxide (DLCO) of less than 70% of the predicted value) as well as renal involvement required previous scleroderma-related renal disease. Key exclusion criteria included active gastric antral vascular ectasia, a DLCO of less than 40% of the predicted value, an FVC of less than 45% of the predicted value, a left ventricular ejection fraction (LVEF) of less than 50
%, a creatinine clearance of less than 40 ml/min, pulmonary arterial hypertension, or more than 6 months of previous treatment with cyclophosphamide.

**Age-Related Macular Degeneration:**

Du et al (2011) stated that there is currently no Food and Drug Administration-approved therapy for treating patients with geographic atrophy, a late stage of age-related macular degeneration (AMD). Cell transplantation has the potential to restore vision in these patients. These researchers discussed how recent advancement in induced pluripotent stem (iPS) cells provides a promising therapy for GA treatment. Recent advances in stem cell biology have demonstrated that it is possible to derive iPS cells from human somatic cells by introducing re-programming factors. Human retinal pigment epithelium (RPE) cells and photoreceptors can be derived from iPS cells by defined factors. Studies show that transplanting these cells can stabilize or recover vision in animal models. However, cell derivation protocols and transplantation procedures still need to be optimized. Much validation has to be done before clinical-grade, patient-derived iPS can be applied for human therapy. For now, RPE cells and photoreceptors derived from patient-specific iPS cells can serve as a valuable tool in elucidating the mechanism of pathogenesis and drug discovery for AMD.

Huang et al (2011) noted that retinal degenerative diseases that target photoreceptors or the adjacent RPE affect millions of people worldwide. Retinal degeneration is found in many different forms of retinal diseases including retinitis pigmentosa, AMD, diabetic retinopathy, cataracts, and glaucoma. Effective treatment for retinal degeneration has been widely investigated. Gene-replacement therapy has been shown to improve visual function in inherited retinal disease. However, this treatment was less effective with advanced disease. Stem cell-based therapy is being pursued as a potential alternative approach in the treatment of retinal degenerative diseases.
Schwartz et al (2012) stated that it has been 13 years since the discovery of human embryonic stem cells (hESCs). These researchers provided the first description of hESC-derived cells transplanted into human patients. They started 2 prospective clinical studies to establish the safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium (RPE) in patients with Stargardt's macular dystrophy and dry AMD -- the leading cause of blindness in the developed world. Pre-operative and post-operative ophthalmic examinations included visual acuity, fluorescein angiography, optical coherence tomography, and visual field testing. The authors concluded that hESC-derived RPE cells showed no signs of hyper-proliferation, tumorigenicity, ectopic tissue formation, or apparent rejection after 4 months. They stated that continued follow-up and future study is needed. The ultimate therapeutic goal will be to treat patients earlier in the disease processes, potentially increasing the likelihood of photoreceptor and central visual rescue.

Amyotrophic Lateral Sclerosis:

Glass et al (2012) advances in stem cell biology have generated intense interest in the prospect of transplanting stem cells into the nervous system for the treatment of neurodegenerative diseases. These researchers reported the results of an ongoing phase I trial of intra-spinal injections of fetal-derived neural stems cells in patients with amyotrophic lateral sclerosis (ALS). This is a first in-human clinical trial with the goal of assessing the safety and tolerability of the surgical procedure, the introduction of stem cells into the spinal cord, and the use of immunosuppressant drugs in this patient population. A total of 12 patients received either 5 unilateral or 5 bilateral (10 total) injections into the lumbar spinal cord at a dose of 100,000 cells/injection. All patients tolerated the treatment without any long-term complications related to either the surgical procedure or the implantation of stem cells. Clinical assessments ranging from 6 to 18 months after transplantation demonstrated no evidence of acceleration of disease progression due to the intervention. One patient has shown
improvement in his clinical status, though these data must be interpreted with caution since this trial was neither designed nor powered to measure treatment efficacy. These results allow the authors to report success in achieving the phase I goal of demonstrating safety of this therapeutic approach. Based on these positive results, the authors can now advance this trial by testing intra-spinal injections into the cervical spinal cord, with the goal of protecting motor neuron pools affecting respiratory function, which may prolong life for patients with ALS.

Martinez et al (2012) stated that ALS is characterized by the selective death of motor neurons. Stem cells have been proposed as a potential therapeutic strategy. These researchers described the safety of stem cell transplantation into the frontal motor cortex to improve upper motor neuron function. A total of 67 patients with definite ALS were included. After giving their informed consent, the patients underwent magnetic resonance imaging, functional rating, pulmonary function test, and laboratory tests. Their bone marrow was stimulated with daily filgrastim (300 μg) given subcutaneously for 3 days. Peripheral blood mononuclear cells were obtained by leukapheresis. Isolated CD133+ stem cells were suspended in 300 μl of the patient's cerebrospinal fluid and implanted into the motor cortex. Adverse events were recorded at each step of the procedure and were classified according to the Common Terminology Criteria for Adverse Events v3.0. The survival at 1 year was 90% after transplantation with a mean long-term survival rate of 40.17 months from diagnosis. The most common adverse events were in grades I to II and involved transient skin pain (19.5% of patients) attributed to the insertion of the Mahurkar catheter into the subclavian vein, minor scalp pain (15.9%), and headache (12.2%) from the surgical procedure. Several patients (1.5% to 4.5%) reported diverse grade I adverse events. There were 2 deaths, 1 considered to be associated with the procedure (1.5%) and the other associated with the disease. Autologous stem cell transplantation into the frontal motor cortex is safe and well-tolerated by patients. Moreover, they stated that further controlled studies are needed to define the efficacy of this
procedures.

Thomsen et al (2014) noted that while the genetics of ALS are becoming more understood in familial cases, the mechanisms underlying disease pathology remain unclear and there are no effective treatment options. Without understanding what causes ALS it is difficult to design treatments. However, in recent years stem cell transplantation has emerged as a potential new therapy for ALS patients. While motor neuron replacement remains a focus of some studies trying to treat ALS with stem cells, there is more rationale for using stem cells as support cells for dying motor neurons as they are already connected to the muscle. This could be through reducing inflammation, releasing growth factors, and other potential less understood mechanisms. Prior to moving into patients, stringent pre-clinical studies are required that have at least some rationale and effectiveness in animal models and good safety profiles. However, given the poor understanding of what causes ALS and whether stem cells may ameliorate symptoms, there should be a push to determine cell safety in pre-clinical models and then a quick translation to the clinic where patient trials will show if there is any effectiveness. The authors provided a critical review of current clinical trials using either MSCs or neural stem cells to treat ALS patients. Pre-clinical data leading to these trials, as well as those in development were also evaluated in terms of mechanisms of action, validity of conclusions and rationale for advancing stem cell treatment strategies for ALS.

In an open-label, phase II study, Glass and colleagues (2016) tested the safety of spinal cord transplantation of human stem cells in patients with ALS with escalating doses and expansion of the trial to multiple clinical centers. This trial included 15 participants at 3 academic centers divided into 5 treatment groups receiving increasing doses of stem cells by increasing numbers of cells/injection and increasing numbers of injections. All subjects received bilateral injections into the cervical spinal cord (C3 to C5). The final group received injections into both the lumbar (L2 to L4) and cervical cord
through 2 separate surgical procedures. Subjects were evaluated for adverse events (AEs) and progression of disease, as measured by the ALS Functional Rating Scale-Revised, forced vital capacity, and quantitative measures of strength. Statistical analysis focused on the slopes of decline of these phase II trial participants alone or in combination with the phase I participants (previously reported), comparing these groups to 3 separate historical control groups. Adverse events were mostly related to transient pain associated with surgery and to side effects of immunosuppressant medications. There was 1 incident of acute post-operative deterioration in neurologic function and another incident of a central pain syndrome. These researchers could not discern differences in surgical outcomes between surgeons. Comparisons of the slopes of decline with the 3 separate historical control groups showed no differences in mean rates of progression. The authors concluded that intra-spinal transplantation of human spinal cord-derived neural stem cells can be safely accomplished at high doses, including successive lumbar and cervical procedures. The procedure can be expanded safely to multiple surgical centers. This study provided Class IV evidence that for patients with ALS, spinal cord transplantation of human stem cells can be safely accomplished and did not accelerate the progression of the disease. This study lacked the precision to exclude important benefit or safety issues.

In an editorial that accompanied the afore-mention study, Appel and Armon (2016) stated that these are clearly early stages of evaluating the risks and benefits of transplanting neural progenitor stem cells in patients with ALS

**Chronic Inflammatory Demyelinating Polyradiculopathy:**

Snowden et al (2012) provided revised and updated guidelines of the European Group for Blood and Marrow Transplantation (EBMT) for both the current application and future development of HSCT in ADs in relation to the benefits, risks and health economic considerations of other modern treatments. These investigators listed sibling donor and well-
matched unrelated donor as generally not recommended for chronic inflammatory demyelinating polyradiculopathy and neuromyelitis optica, among many ADs. They emphasized a need for prospective interventional and non-interventional studies, where feasible, along with systematic data reporting, in accordance with EBMT policies and procedures.

Press et al (2014) noted that only 70 to 80 % of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) respond satisfactorily to the established first-line immunomodulatory treatments. Autologous HSCT (AHSCT) has been performed as a last treatment resort in a few therapy-refractory cases with CIDP. These researchers described the results of AHSCT in 11 consecutive Swedish patients with therapy-refractory CIDP with a median follow-up time of 28 months. Case data were gathered retrospectively for AHSCT treatments in 11 patients with CIDP refractory to the first-line immunomodulatory treatments, intravenous high-dose immunoglobulin, corticosteroids and plasma exchange and to 1 or more second-line treatments used in 10 of the 11 patients. The median Inflammatory Neuropathy Cause and Treatment (INCAT) score within 1 month prior to AHSCT was 6 and the Rankin score 4. Total INCAT and Rankin scores improved significantly within 2 to 6 months after AHSCT and continued to do so at last follow-up. The motor action potential amplitudes (CMAP) improved already within 4 months (median) after AHSCT; 3 of the 11 patients relapsed during the follow-up period, requiring re-transplantation with AHSCT in 1; 8 of the 11 patients maintained drug-free remission upon last follow-up. Autologous HSCT was safe but on the short-term associated with a risk of cytomegalovirus (CMV) and Epstein-Barr virus re-activation, CMV disease, hemorrhagic cystitis and pancreatitis. The authors concluded that these findings though hampered by the limited number of patients and the lack of a control group suggested AHSCT to be effective in therapy-refractory CIDP, with a manageable complication profile. They stated that confirmation of these results is needed through randomized controlled trials (RCTs).
Crohn's Disease:

Leung and associates (2006) reviewed the evidence regarding the use of hematopoietic cell transplantation (HCT) for the treatment of Crohn's disease (CD). A Medline search (1970 to 2005) was performed using the keywords -- bone marrow transplant, stem cell, hematopoietic cell, Crohn's disease and inflammatory bowel disease. These researchers identified 1 case in which a patient developed CD following an allogeneic HCT from a sibling suffering with CD. Evidence for transfer of the genetic predisposition to develop CD was also identified with report of a patient that developed severe CD following an allogeneic HCT. Following HCT it was found that the donor (that had no signs or symptoms of CD) and the recipient had several haplotype mismatches in HLA class III genes in the IBD3 locus including a polymorphism of NOD2/CARD15 that has been associated with CD. A total of 33 published cases of patients with CD who underwent either autologous or allogeneic HCT were identified. At the time of publication 29 of these 33 patients were considered to be in remission. The median follow-up time was 7 years, and 20 months for allogeneic and autologous HCT, respectively. For patients who underwent HCT primarily for treatment of their CD there have been no mortalities related to transplant complications. The authors concluded that these preliminary data suggested that both allogeneic and autologous HCT may be effective in inducing remission in refractory CD. This supports the hypothesis that the hematolymphatic cells play a key role in CD and that re-setting of the immune system may be a critical approach in the management or cure of CD.

Al-toma et al (2007) reported on the feasibility, safety, and effectiveness of ASCT in patients with refractory celiac disease with aberrant T cells (RCD type II). A total of 13 patients with RCD type II were evaluated. Seven patients (3 women, 4 men, mean age of 61.5 years [range of 51 to 69 years]) underwent transplantation. After conditioning with fludarabine and melphalan, ASCT was performed. Patients were monitored for response, adverse effects, and hematopoietic reconstitution.
All 7 patients completed the mobilization and leukapheresis procedures successfully and subsequently underwent conditioning and transplantation. Engraftment occurred in all patients. No major non-hematological toxicity or transplantation-related mortality was observed. There was a significant reduction in the aberrant T cells in duodenal biopsies associated with improvement in clinical well-being and normalization of hematological and biochemical markers (mean follow-up of 15.5 months; range of 7 to 30 months). One patient died 8 months after transplantation from progressive neuro-cesiak disease. The authors concluded that these preliminary results showed that HDC followed by ASCT seems feasible and safe and might result in long-term improvement of patients with RCD type II whose condition did not respond promptly to available drugs.

Kotlarz et al (2012) examined heterogeneity among patients with very early onset inflammatory bowel disease (IBD), its mechanisms, and the use of allogeneic hematopoietic stem cell transplantation (HSCT) to treat this disorder. These investigators analyzed 66 patients with early onset IBD (younger than 5 years of age) for mutations in the genes encoding IL-10, IL-10R1, and IL-10R2. IL-10R deficiency was confirmed by functional assays on patients' peripheral blood mononuclear cells (immunoblot and enzyme-linked immunosorbent assay analyses). They assessed the therapeutic effects of standardized allogeneic HSCT. Using a candidate gene sequencing approach, these researchers identified 16 patients with IL-10 or IL-10R deficiency: 3 patients had mutations in IL-10, 5 had mutations in IL-10R1, and 8 had mutations in IL-10R2. Refractory colitis became manifest in all patients within the first 3 months of life and was associated with perianal disease (16 of 16 patients). Extra-intestinal symptoms included folliculitis (11 of 16) and arthritis (4 of 16). Allogeneic HSCT was performed in 5 patients and induced sustained clinical remission with a median follow-up time of 2 years. In-vitro experiments confirmed reconstitution of IL-10R-mediated signaling in all patients who received the transplant. The authors concluded that they identified loss of function
mutations in IL-10 and IL-10R in patients with very early onset IBD. These findings indicated that infantile IBD patients with perianal disease should be screened for IL-10 and IL-10R deficiency and that allogeneic HSCT can induce remission in those with IL-10R deficiency.

In an editorial that accompanied the study by Koltarz et al, Muise and colleagues (2012) explained that the short-term results of this small series should be interpreted with caution. The editorialists noted that “This study also reports the outcomes of 5 patients after hematopoietic stem cell transplantation (HSCT) with 2-year follow-up on 4 patients. The authors used a highly immunosuppressive conditioning regimen that also resulted in depletion of myeloid cells including dendritic cells in conjunction with intense gut decolonization. HSCT in this patient population was remarkably well tolerated and led to complete clinical remission in 4 out of 5 patients. Although successful, it will be interesting to determine whether HSCT will result in a permanent “cure” for the colonic, joint, and skin disease in patients with IL-10RB mutations, because this receptor is widely expressed in these tissues and presumably the deficiency would persist after HSCT. Variable results in HSCT ability to establish long-term remission in adult-onset IBD patients (reviewed by Anderson et al) points to cautious interpretation of these promising short-term HSCT results. This study also leads to another important question regarding the role of HSCT in all infantile IBD. As the authors correctly point out, there is a strong possibility that some infant and VEO-IBD patients may have gene defects in the non-hematopoietic cells, including epithelial barrier genes and, therefore, HSCT for all infantile IBD cannot be recommended at this time, unless a hematopoietic gene mutation that is functionally linked to disease can be identified”.

The National Institute for Health and Clinical Excellence’s clinical guideline on “Crohn’s disease: Management in adults, children and young people” (NICE, 2012) does not mention the use of stem cell transplantation as a therapeutic option. Furthermore, a RCT on the use of autologous stem cell
transplantation for CD is currently underway.

Al-toma et al (2014) stated that both, autologous and allogeneic HSCT can be used to cure or ameliorate a variety of malignant and non-malignant diseases. The rationale behind this strategy is based on the concept of immunoablation using HDC, with subsequent regeneration of naive T-lymphocytes derived from re-infused hematopoietic progenitor cells. In addition, the use of HSCT allows for the administration of HDC (whether or not combined with immunomodulating agents such as anti-thymocyte globulin) resulting in a prompt remission in therapy-refractory patients. These researchers provided an update of the major areas of successful uses of HSCT in non-malignant gastro-intestinal disorders. A Medline search has been conducted and all relevant published data were analyzed. Hematopoietic stem cell transplantation has been proved successful in treating refractory CD. Patients with refractory celiac disease type II and a high risk of developing enteropathy associated T-cell lymphoma have shown promising improvement. Data concerning HSCT and mesenchymal SCT in end-stage chronic liver diseases are encouraging. In refractory autoimmune gastro-intestinal diseases HDC followed by HSCT seems feasible and safe and might result in long-term improvement of disease activity. Moreover, they stated that mesenchymal SCT for a selected group of CD is promising and may represent a significant therapeutic alternative in treating fistulas in CD.

Hawkey et al (2015) evaluated the effect of autologous HSCT on refractory CD. This was a parallel-group randomized clinical trial conducted in 11 European transplant units from July 2007 to September 2011, with follow-up through March 2013. Patients were aged 18 to 50 years with impaired quality of life from refractory CD not amenable to surgery despite treatment with 3 or more immunosuppressive or biologic agents and corticosteroids. All patients underwent stem cell mobilization before 1:1 randomization to immune-ablation and HSCT (n = 23) or control treatment (HSCT deferred for 1 year [n = 22]). All were given standard CD treatment as needed. Primary
outcomes included sustained disease remission at 1 year, a composite primary end-point comprising clinical remission (Crohn Disease Activity Index (CDAI) less than 150 [range of 0 to 600]), no use of corticosteroids or immunosuppressive or biologic drugs for at least the last 3 months, and no endoscopic or radiological evidence of active (erosive) disease anywhere in the gastro-intestinal (GI) tract. Secondary outcomes were individual components of the primary composite outcome and other measures of disease activity, laboratory results, quality of life and functional status, and GI tract imaging. A total of 23 patients underwent HSCT and 22 received standard CD treatment (controls). Sustained disease remission was achieved in 2 patients undergoing HSCT (8.7 %) versus 1 control patient (4.5 %) (absolute difference, 4.2 % [95 % confidence interval [CI]: -14.2 % to 22.6 %]; p = 0.60); 14 patients undergoing HSCT (61 %) versus 5 control patients (23 %) had discontinued immunosuppressive or biologic agents or corticosteroids for at least 3 months (difference, 38.1 % [95 % CI: 9.3 % to 59.3 %]; p = 0.01); 10 versus 2 patients had a CDAI less than 150 (remission) at the final evaluation, 8 (34.8 %) versus 2 (9.1 %) for 3 or more months (difference, 25.7 % [95 % CI: 1.1 % to 47.1 %]; p = 0.052); 8 (34.8 %) versus 2 (9.1 %) patients were adjudicated free of active disease on endoscopy and radiology at final assessment (difference, 25.7 % [95 % CI: 1.1 % to 47.1 %]; p = 0.054). There were 76 serious adverse events in patients undergoing HSCT versus 38 in controls; 1 patient undergoing HSCT died. The authors concluded that among adult patients with refractory CD not amenable to surgery who had impaired quality of life, HSCT, compared with conventional therapy, did not result in a statistically significant improvement in sustained disease remission at 1 year and was associated with significant toxicity. These findings do not support the widespread use of HSCT for patients with refractory CD.

Diabetes Mellitus:

In a prospective phase I/II study, Voltarelli and co-workers (2007) examined the safety and metabolic effects of high-dose immunosuppression followed by autologous non-myeloablative
Hematopoietic stem cell transplantation (AHST) in newly diagnosed type 1 diabetes mellitus (T1DM). A total of 15 patients with type 1 DM (aged 14 to 31 years) diagnosed within the previous 6 weeks by clinical findings and hyperglycemia and confirmed with positive antibodies against glutamic acid decarboxylase were included. Patients with previous diabetic ketoacidosis were excluded after the first patient with diabetic ketoacidosis failed to benefit from AHST. Hematopoietic stem cells were mobilized with cyclophosphamide (2.0 g/m2) and granulocyte colony-stimulating factor (10 microg/kg per day) and then collected from peripheral blood by leukapheresis and cryopreserved. The cells were injected intravenously after conditioning with cyclophosphamide (200 mg/kg) and rabbit anti-thymocyte globulin (4.5 mg/kg). Main outcome measures were morbidity and mortality from transplantation and temporal changes in exogenous insulin requirements (daily dose and duration of usage). Secondary end points included serum levels of hemoglobin A1c, C-peptide levels during the mixed-meal tolerance test, and anti-glutamic acid decarboxylase antibody titers measured before and at different times following AHST. During a 7- to 36-month follow-up (mean of 18.8 months), 14 patients became insulin-free (1 for 35 months, 4 for at least 21 months, 7 for at least 6 months; and 2 with late response were insulin-free for 1 and 5 months, respectively). Among those, 1 patient resumed insulin use 1 year after AHST. At 6 months after AHST, mean total area under the C-peptide response curve was significantly greater than the pre-treatment values, and at 12 and 24 months it did not change. Anti-glutamic acid decarboxylase antibody levels decreased after 6 months and stabilized at 12 and 24 months. Serum levels of hemoglobin A(1c) were maintained at less than 7 % in 13 of 14 patients. The only acute severe adverse effect was culture-negative bilateral pneumonia in 1 patient and late endocrine dysfunction (hypothyroidism or hypogonadism) in 2 others. There was no mortality. The authors noted that high-dose immunosuppression and AHST were performed with acceptable toxicity in a small number of patients with newly diagnosed type 1 DM. With AHST, beta cell function was increased in all but 1 patient and induced prolonged insulin
independence in the majority of the patients. They stated that further follow-up is needed to confirm the duration of insulin independence and the mechanisms of action of the procedure. Furthermore, randomized controlled studies and more biological studies are needed to confirm the role of this procedure in changing the natural history of type 1 DM and to assess the contribution of hematopoietic stem cells to this change.

El-Badawy and El-Badri (2016) evaluated the clinical evidence on the safety and effectiveness of different types of stem cell therapy for both T1DM and T2DM. These investigators pooled participant-level data from 22 eligible clinical trials that satisfied inclusion criteria, with a total of 524 patients. There were significant differences in the outcome based on the type and source of the infused cells. Out of all T1DM patients who received CD34+ hematopoietic stem cell (HSC) infusion, 58.9 % became insulin-independent for a mean period of 16 months, whereas the results were uniformly negative in patients who received umbilical cord blood (UCB). Infusion of umbilical cord mesenchymal stem cells (UC-MSCs) provided significantly beneficial outcome in T1DM, when compared to bone-marrow mesenchymal stem cells (BM-MSCs) (p < 0.0001 and p = 0.1557). Administration of stem cell therapy early after DM diagnosis was more effective than intervention at later stages (relative risk [RR] = 2.0, p = 0.0008). Adverse events (AEs) were observed in only 21.72 % of both T1DM and T2DM stem cell recipients with no reported mortality. Out of all poor responders, 79.5 % were diagnosed with diabetic ketoacidosis. The authors concluded that: (i) remission of DM is possible following stem cell therapy; (ii) stem cell transplantation can be a safe and effective approach for therapy of DM; (iii) available data from these clinical trials indicate that the most promising therapeutic outcome was shown in mobilized marrow CD34+ HSCs; (iv) patients with previously diagnosed diabetic ketoacidosis are not good candidates for the applied approaches stem cell therapy; (v) stem cell therapy at early stages after DM diagnosis is more effective than intervention at later stages; and (vi) well-designed large scale randomized
studies considering the stem cell type, cell number, and infusion method in DM patients are urgently needed. This meta-analysis had several drawbacks: (i) some of the cases covered in this meta-analysis have been evaluated in a single study with low statistical power. In some studies, low number of patients enrolled, not sufficient for significant interpretation, (ii) the total sample size was not large and the follow-up time was not adequately long, and (iii) the number of trials was relatively small, and more accurate recommendations could be made when analyzing a larger cohort. Altogether, these limitations reflected the paucity of the available published data on this very important and much anticipated form of cell therapy and indicated the large gap between the pre-clinical and clinical studies.

**Multiple Sclerosis:**

A recent study (Mancardi et al, 2001) on autologous hematopoietic stem cell (ASCT) transplantation for the treatment of patients with rapidly evolving secondary progressive MS concluded that the final impact of this procedure on disease course remains to be established. In a study (Verburg et al, 2001) to evaluate the effectiveness of HDC followed by ASCT in the treatment of patients with refractory, progressively erosive RA, the authors concluded that there is a need for randomized clinical trials (RCTs). Tyndall (2001) stated that randomized, prospective controlled phase III trials are needed to ascertain the effectiveness of ASCT following immunoaiblation for the treatment of SLE, however, more phase I and II data is needed to plan the optimal protocol. An assessment by the BlueCross BlueShield Association Technology Evaluation Center (2001) concluded that there is insufficient evidence on health outcomes of the effect of stem cell transplant in autoimmune disease.

In a phase I/II study, Burt and colleagues (2009) examined the effects of autologous non-myeloablative hematopoietic stem cell transplantation in relapsing-remitting MS. Eligible patients had relapsing-remitting MS, attended Northwestern Memorial
Hospital, and despite treatment with interferon beta had had 2 corticosteroid-treated relapses within the previous 12 months, or 1 relapse and gadolinium-enhancing lesions seen on magnetic resonance imaging (MRI) and separate from the relapse. Peripheral blood hemopoietic stem cells were mobilized with 2 g/m2 cyclophosphamide and 10 microg/kg per day filgrastim. The conditioning regimen for the hemopoietic stem cells was 200 mg/kg cyclophosphamide and either 20 mg alemtuzumab or 6 mg/kg rabbit anti-thymocyte globulin. Primary outcomes were progression-free survival and reversal of neurological disability at 3 years post-transplantation. These researchers also investigated the safety and tolerability of autologous non-myeloablative hemopoietic stem cell transplantation. A total of 21 patients were treated. Engraftment of white blood cells and platelets was on median day 9 (range of day 8 to 11) and patients were discharged from hospital on mean day 11 (range of day 8 to 13). One patient had diarrhea due to clostridium difficile and 2 patients had dermatomal zoster. Two of the 17 patients receiving alemtuzumab developed late immune thrombocytopenic purpura that remitted with standard therapy. A total of 17 of 21 patients (81%) improved by at least 1 point on the Kurtzke expanded disability status scale (EDSS), and 5 patients (24%) relapsed but achieved remission after further immunosuppression. After a mean of 37 months (range of 24 to 48 months), all patients were free from progression (no deterioration in EDSS score), and 16 were free of relapses. Significant improvements were noted in neurological disability, as determined by EDSS score (p < 0.0001), neurological rating scale score (p = 0.0001), paced auditory serial addition test (p = 0.014), 25-foot walk (p < 0.0001), and quality of life, as measured with the short form-36 questionnaire (p < 0.0001). The authors concluded that non-myeloablative autologous hemopoietic stem cell transplantation in patients with relapsing-remitting MS reverses neurological deficits, but these results need to be confirmed in a randomized trial.

Tappenden and colleagues (2010) stated that therapeutic options for secondary progressive MS (SPMS) are limited.
Mitoxantrone is routinely used to stabilize disease progression; however, evolving evidence suggests clinical benefit from intensive treatment with autologous hematopoietic stem cell transplantation (HSCT). Given differences in cost and outcomes, preliminary cost-effectiveness studies are warranted if this approach is to be developed for more widespread application in SPMS. These researchers developed a decision-analytic Markov model to explore the potential cost-effectiveness of autologous HSCT versus mitoxantrone in SPMS, using patient-level data from registry sources. The model evaluates the lifetime costs and health outcomes associated with disability progression and relapse. Sensitivity analyses were undertaken to examine the uncertainty surrounding cost-effectiveness outcomes. In the absence of RCT evidence, conditions for comparative analysis were not ideal. Under optimistic assumptions, HSCT is estimated to cost below 3,000 pounds per quality adjusted life year gained. However, when a strict 6-month sustained progression rule is adopted, HSCT may be less effective and more expensive than mitoxantrone. The model results were sensitive to reducing procedural costs and HSCT-related mortality. The authors concluded that HSCT could potentially achieve an acceptable level of cost-effectiveness. However, caution should be exercised as large, high-quality RCTs comparing HSCT versus mitoxantrone are needed to validate these findings. Further analyses are necessary to examine the economic value of HSCT for the treatment of rapidly progressing, relapsing-remitting and aggressive forms of MS.

Atkin (2010) noted that MS is the leading autoimmune indication for autologous HSCT (aHSCT). Patient selection criteria and transplant interventions have been refined through a series of cohort and registry studies. High- and low-intensity chemotherapy-based conditioning regimens have been used, creating trade-offs between toxicity and effectiveness. Total body irradiation has been associated with greater toxicity and poor outcomes. Autologous HSCT stops MS relapses and lessens the disability in malignant MS, which otherwise rapidly incapacitates patients. Better responses occur in progressive...
MS earlier in the disease when it has a more inflammatory nature. Autologous HSCT prevents further disability in many patients, but some actually recover from their infirmities. Current regimens and supportive care result in very low morbidity and mortality. Patients with MS experience unique complications in addition to the expected toxicities. Cytokines used alone for stem-cell mobilization may induce MS flares but are safe to be used in combination with steroids or cytotoxic agents. Urinary tract infections, herpes virus reactivation and an engraftment syndrome may occur early after aHSCT. Rarely secondary autoimmune diseases have been reported late after HSCT. Increasing experience in caring for patients with MS has reduced the frequency and severity of toxicity. Conceived as an opportunity to "reboot" a tolerant immune system, aHSCT is successful in treating patients with MS that is refractory to conventional immunomodulatory drugs. It is noted that patients are unlikely to benefit from aHSCT if they have had longstanding MS or disabilities that have advanced to the point where they are wheelchair bound. Furthermore, previous MS treatments can potentially impact aHSCT (e.g., interferon may impair stem cell collection, natalizumab may increase the risk of opportunistic infections, and mitoxantrone could cause myelodysplasia). Moreover, the author stated that aHSCT for MS is still controversial. It has not entered widespread clinical use because of its perceived high mortality, high cost, and competition from new pharmaceutical agents. The author noted that a direct comparison of aHSCT with conventional treatments in multi-center randomized controlled trials and publication of 5 to 10 years long-term follow-up data from cohort studies and international registries are a necessary step in further defining the role of aHSCT in the management of MS.

At present, there are no well-designed randomized controlled clinical trials of stem cell transplantation in autoimmune diseases in the peer-reviewed published medical literature. Such studies are necessary to determine whether stem cell transplantation improves clinical outcomes of autoimmune diseases. In addition, where stem cell transplantation is used with myeloablative chemotherapy of autoimmune diseases, the
efficacy of stem cell transplantation in restoring hematopoiesis should be compared with administration of myelopoietic growth factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]).

The position statement from a National Institute of Allergy and Infectious Diseases and National Cancer Institute-Sponsored International Workshop on "Feasibility of allogeneic hematopoietic stem cell transplantation for autoimmune disease" (Griffith et al, 2005) concluded that "[a] rationale clearly exists for exploring the therapeutic and curative potential of allogeneic HCT for severe autoimmune disease [systemic sclerosis, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and autoimmune cytopenia]. Although safer allogeneic transplantation strategies have become available, experience is currently insufficient to allow reliable extrapolation of data on safety and risks from patients with malignancies to patients with autoimmune diseases. It is recommended that planning be initiated for clinical trials to generate safety and efficacy data for allogeneic HCT [hematopoietic stem cell transplant] in patients with severe autoimmune diseases".

Rice and colleagues (2013) stated that MS is incurable, but stem-cell therapy might offer valuable therapeutic potential. Efforts to develop stem-cell therapies for MS have been conventionally built on the principle of direct implantation of cells to replace oligodendrocytes, and therefore to regenerate myelin. Recent progress in understanding of disease processes in MS include observations that spontaneous myelin repair is far more widespread and successful than was previously believed, that loss of axons and neurons is more closely associated with progressive disability than is myelin loss, and that damage occurs diffusely throughout the central nervous system (CNS) in grey and white matter, not just in discrete, isolated patches or lesions. These findings had introduced new and serious challenges that stem-cell therapy needs to overcome; the practical challenges to achieve cell replacement
alone are difficult enough, but, to be useful, cell therapy for MS must achieve substantially more than the replacement of lost oligodendrocytes. However, parallel advances in understanding of the reparative properties of stem cells -- including their distinct immunomodulatory and neuroprotective properties, interactions with resident or tissue-based stem cells, cell fusion, and neurotrophin elaboration -- offer renewed hope for development of cell-based therapies. Moreover, the authors stated that these advances suggested avenues for translation of this approach not only for MS, but also for other common neurological and neurodegenerative diseases.

Burt et al (2015) determined the association of non-myeloablative HSCT with neurological disability and other clinical outcomes in patients with MS. This study included case series of patients with relapsing-remitting MS (n = 123) or secondary-progressive MS (n = 28) (mean age of 36 years; range of 18 to 60 years; 85 women) treated at a single US institution between 2003 and 2014 and followed-up for 5 years. Final follow-up was completed in June 2014. Treatment with cyclophosphamide and alemtuzumab (22 patients) or cyclophosphamide and thymoglobulin (129 patients) followed by infusion of un-manipulated peripheral blood stem cells. Primary end-point was reversal or progression of disability measured by change in the EDSS score of 1.0 or greater (score range of 0 to 10). Secondary outcomes included changes in the Neurologic Rating Scale (NRS) score of 10 or greater (score range of 0 to 100), Multiple Sclerosis Functional Composite (MSFC) score, quality-of-life Short Form 36 questionnaire scores, and T2 lesion volume on brain magnetic resonance imaging scan. Outcome analysis was available for 145 patients with a median follow-up of 2 years and a mean of 2.5 years. Scores from the EDSS improved significantly from a pre-transplant median of 4.0 to 3.0 (interquartile range [IQR]: 1.5 to 4.0; n = 82) at 2 years and to 2.5 (IQR, 1.9 to 4.5; n = 36) at 4 years (p < 0.001 at each assessment). There was significant improvement in disability (decrease in EDSS score of greater than or equal to 1.0) in 41 patients (50 %; 95 % CI: 39 % to 61 %) at 2 years and in 23 patients (64 %; 95 % CI: 46 % to 79 %) at
4 years. Four-year relapse-free survival was 80% and progression-free survival (PFS) was 87%. The NRS scores improved significantly from a pre-transplant median of 74 to 88.0 (IQR, 77.3 to 93.0; n = 78) at 2 years and to 87.5 (IQR, 75.0 to 93.8; n = 34) at 4 years (p < 0.001 at each assessment). The median MSFC scores were 0.38 (IQR, -0.01 to 0.64) at 2 years (p < 0.001) and 0.45 (0.04 to 0.60) at 4 years (p = 0.02). Total quality-of-life scores improved from a mean of 46 (95% CI: 43 to 49) pre-transplant to 64 (95% CI: 61 to 68) at a median follow-up of 2 years post-transplant (n = 132) (p < 0.001). There was a decrease in T2 lesion volume from a pre-transplant median of 8.57 cm³ (IQR, 2.78 to 22.08 cm³) to 5.74 cm³ (IQR, 1.88 to 14.45 cm³) (p < 0.001) at the last post-transplant assessment (mean follow-up of 27 months; n = 128). The authors concluded that among patients with relapsing-remitting MS, non-myeloablative HSCT was associated with improvement in neurological disability and other clinical outcomes. They stated that these preliminary findings from this uncontrolled study require confirmation in randomized trials.

The major drawbacks of this study were: (i) it was a single-center study, which may introduce the possibility of bias, (ii) a number of patients were treated on a compassionate basis, rather than on the study protocol, (iii) improvement in function in patients with MS may be in part a consequence of continuing recovery from earlier relapses, (iv) long-term follow-up (i.e., greater than or equal to 4 years) was not available for a substantial proportion of patients, and (v) this was an observational cohort study without a control group.

In an editorial that accompanied the afore-mentioned study, Hauser (2015) stated that (i) autologous HSCT does not appear to be effective against established progressive forms of MS and, absence of new data, additional trials of these protocols are probably not indicated for patients with progressive MS, (ii) immunosuppressive regimens that include HSCT appear to be effective against relapsing-remitting form of MS, at least over several years of observation. However, it is by no means clear that the beneficial effects result from the infusion of stem cells rather than from the conditioning regimen. Studies that
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delineate the role of HSCT specifically in improving outcomes relative to conditioning regimens alone are needed before this therapy should be deployed outside of the clinical research setting, (iii) the mechanism of action of autologous HSCT in MS needs to be clarified, and (iv) very long follow-up periods are needed to meaningfully assess the role of HSCT in the treatment of MS.

In a multi-center, phase II clinical trial, Mancardi et al (2015) examined the effect of intense immunosuppression followed by AHSCT versus mitoxantrone (MTX) on disease activity measured by MRI in patients with MS. Patients with secondary progressive or relapsing-remitting MS, with a documented increase in the last year on the EDSS, in spite of conventional therapy, and presence of 1 or more gadolinium-enhancing (Gd+) areas were included in this study. Patients were randomized to receive intense immunosuppression (mobilization with cyclophosphamide and filgrastim, conditioning with carmustine, cytosine-arabinoside, etoposide, melphalan, and anti-thymocyte globulin) followed by AHSCT or MTX 20 mg every month for 6 months. The primary end-point was the cumulative number of new T2 lesions in the 4 years following randomization. Secondary end-points were the cumulative number of Gd+ lesions, relapse rate, and disability progression. Safety and tolerability were also assessed; 21 patients were randomized and 17 had post-baseline evaluable MRI scans. Autologous HSCT reduced by 79 % the number of new T2 lesions as compared to MTX (rate ratio 0.21, p = 0.00016). It also reduced Gd+ lesions as well as the annualized relapse rate. No difference was found in the progression of disability. The authors concluded that intense immunosuppression followed by AHSCT is significantly superior to MTX in reducing MRI activity in severe cases of MS. They stated that these results strongly support further phase III studies with primary clinical end-points.

Stellmann et al (2015) noted that AHSCT is still not the standard treatment for highly inflammatory MS. Even though RCTs are lacking, predictors for treatment response have been
established. Since 2007, 10 patients have received AHSCT in Hamburg. These researchers presented observational data from patients treated in Hamburg and a review of the literature. Descriptive statistics were used for evaluating the course of the EDSS as a measure for clinical outcome, MRI and neuropsychology; new gadolinium and T2-MRI uptake lesions per scan were compared. In addition, a systematic review of the currently available literature was performed. The Hamburg series can be divided in 2 groups -- one group including 4 patients with chronic progressive MS with low inflammatory activity (median EDSS = 6.25, 0.5 relapses per year, no gadolinium-enhancing lesions) and the other group including 6 patients with mild-to-moderate disability, relapses and inflammatory activity (median EDSS = 4.25, 1 relapse per year, 2 gadolinium-enhancing lesions). The median follow-up was 2.4 years. While the 1st group did not seem to benefit from AHSCT, an improvement in 5 out of 6 patients was observed in the 2nd group. New T2 lesions occurred within the first 6 months but gadolinium-enhancing lesions were not observed (p < 0.05). A systematic literature search identified a higher efficacy of AHSCT in younger, less disabled MS patients with inflammatory activity, similar to the findings from Hamburg. The authors concluded that cohort reports described AHSCT as a safe and efficient therapeutic option in highly inflammatory MS. The authors concluded that based on these data AHSCT appeared to be a reasonable option in selected patients with highly inflammatory MS; however a RCT is needed.

Li and colleagues (2016) noted that HCT has been reported for a long time and can be used for MS; however, available data consisted of small samples and gave confusing results. In a systematic review and meta-analysis, these investigators estimated the effects of HCT for adults with MS. They searched the database of CNKI, PubMed, Embase, WEB of SCIENCE and the Cochrane Center Register of Controlled Trials to find initial studies and selected the appropriate researches included in the meta-analysis based on the inclusion and exclusion criteria; I2 was used to evaluate the heterogeneity and meta-regression was used for finding the source. Random effort model was
performed to pool the data and funnel plot was drawn to determine publication bias; 8 single-arm clinical trials studies were included. The I² value was 0.77 and 0.93, suggesting a heavy heterogeneity between studies. However, meta-regression analysis did not find the source of heterogeneity in which the publication country and follow up time were the influencing factors. Compared with baseline, the EDSS score of MS patients after HCT has a statistical decrease of 0.62 (95 % CI: 0.14 to 1.10) at the 12th month and 1.26 (95 % CI: 0.38 to 2.14) at the follow-up time ending point, respectively. The authors concluded that available evidence suggested that some clinical benefits of HCT when combined with immunotherapy on MS. However, as a consequence of wide CIs that were characteristics of small evidence bases, further investigations to provide enough baseline information according to the RCTs are needed for further analysis, such as subgroup analysis and meta-regression analysis.

Bakhuraysah and associates (2016) stated that HSCT is a treatment paradigm that has long been utilized for cancers of the blood and bone marrow, but has gained some traction as a treatment paradigm for MS. Success in the treatment of patients with this approach has been reported primarily when strict inclusion criteria were imposed that have eventuated a more precise understanding of MS pathophysiology, thereby governing trial design. Moreover, enhancing the yield and purity of hematopoietic stem cells during isolation along with the utility of appropriate conditioning agents has provided a clearer foundation for clinical translation studies. To support this approach, pre-clinical data derived from animal models of MS, experimental autoimmune encephalomyelitis, have provided clear identification of multipotent stem cells that can reconstitute the immune system to override the autoimmune attack of the CNS. These investigators discussed the rationale of HSCT to treat MS by providing the benefits and complications of the clinically relevant protocols, the varying graft types, and conditioning regimens. However, they emphasized that future trials based on HSCT should be focused on specific therapeutic strategies to target and limit ongoing neuro-degeneration and
demyelination in progressive MS, in the hope that such treatment may serve a greater catchment of patient cohorts with potentially enhanced efficiency and lower toxicity. Despite these future ambitions, a proposed international multi-center, randomized clinical trial of HSCT should be governed by the best standard care of treatment, whereby MS patients are selected upon strict clinical course criteria and long-term follow-up studies of patients from international registries are imposed to advocate HSCT as a therapeutic option in the management of MS.

In a multi-center, single-group, phase II clinical trial, Atkins and co-workers (2016) examined if near-complete immunoablation followed by immune cell depleted AHSCT would result in long-term control of MS. These researchers enrolled patients with MS, aged 18 to 50 years with poor prognosis, ongoing disease activity, and an EDSS of 3.0 to 6.0. Autologous CD34 selected hemopoietic stem-cell grafts were collected after mobilization with cyclophosphamide and filgrastim. Immunoablation with busulfan, cyclophosphamide, and rabbit anti-thymocyte globulin was followed by AHSCT. The primary outcome was MS activity-free survival (events were clinical relapse, appearance of a new or Gd-enhancing lesion on MRI, and sustained progression of EDSS score). Between diagnosis and AHSCT, 24 patients had 167 clinical relapses over 140 patient-years with 188 Gd-enhancing lesions on 48 pre-AHSCT MRI scans. Median follow-up was 6.7 years (range of 3.9 to 12.7). The primary outcome, MS activity-free survival at 3 years after transplantation was 69.6 % (95 % CI: 46.6 to 84.2). With up to 13 years of follow-up after AHSCT, no relapses occurred and no Gd enhancing lesions or new T2 lesions were seen on 314 MRI sequential scans. The rate of brain atrophy decreased to that expected for healthy controls; 1 of 24 patients died of transplantation-related complications; 35 % of patients had a sustained improvement in their EDSS score. The authors described the first treatment to fully halt all detectable CNS inflammatory activity in patients with MS for a prolonged period in the absence of any ongoing disease-modifying drugs. Furthermore, many of the patients had substantial recovery of
neurological function despite their disease's aggressive nature.

Nash and colleagues (2017) evaluated the safety, effectiveness, and durability of MS disease stabilization after high-dose immunosuppressive therapy (HDIT) and autologous HCT. High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) is a phase II clinical trial of HDIT/HCT for patients with relapsing-remitting MS (RRMS) who experienced relapses with disability progression (EDSS 3.0 to 5.5) while on MS disease-modifying therapy. The primary endpoint was event-free survival (EFS), defined as survival without death or disease activity from any one of the following: disability progression, relapse, or new lesions on MRI.

Participants were evaluated through 5 years post-transplant. Toxicities were reported using the National Cancer Institute Common Terminology Criteria for adverse events (AEs). A total of 25 subjects were evaluated for transplant and 24 participants underwent HDIT/HCT. Median follow-up was 62 months (range of 12 to 72); EFS was 69.2 % (90 % CI: 50.2 to 82.1); PFS, clinical relapse-free survival, and MRI activity-free survival were 91.3 % (90 % CI: 74.7 % to 97.2 %), 86.9 % (90 % CI: 69.5 % to 94.7 %), and 86.3 % (90 % CI: 68.1 % to 94.5 %), respectively; AE due to HDIT/HCT were consistent with expected toxicities and there were no significant late neurologic adverse effects noted.

Improvements were noted in neurologic disability with a median change in EDSS of -0.5 (IQR -1.5 to 0.0; p = 0.001) among participants who survived and completed the study. The authors concluded that HDIT/HCT without maintenance therapy was effective for inducing long-term sustained remissions of active RRMS at 5 years. Moreover, they stated that prospective clinical trials comparing HDIT/HCT to other approaches are needed; HDIT/HCT may represent a potential therapeutic option for patients with RRMS who fail conventional immunotherapy. This study provided Class IV evidence that participants with RRMS experienced sustained remissions with toxicities as expected from HDIT/HCT.

Casanova and associates (2017) described the long-term results of myeloablative AHSCT in the treatment of patients with MS.
Patients who failed to conventional therapies for MS underwent an approved protocol for AHSCT, which consisted of peripheral blood stem cell mobilization with cyclophosphamide and G-CSF, followed by a conditioning regimen of BCNU, etoposide, ara-C, melphalan IV, plus rabbit thymoglobulin. A total of 38 MS patients have been transplanted since 1999; 31 have been followed for more than 2 years (mean of 8.4 years). There were 22 RRMS patients and 9 SPMS patients; n death related to AHSCT. A total of 10 patients (32.3 %) had at least 1 relapse during post-AHSCT evolution, 6 patients in the RRMS group (27.2 %) and 4 in the SPMS group (44.4 %). After AHSCT, 7 patients (22.6 %) experienced progression of disability, all within SP form. By contrast, no patients with RRMS experienced worsening of disability after a median follow-up of 5.4 years, 60 % of them showed a sustained reduction in disability (SRD), defined as the improvement of 1.0 point in EDSS that sustained for 6 months (0.5 in cases of EDSS greater than or equal to 5.5). The only clinical variable that predicted a poor response to AHSCT was a high EDSS in the year before transplant. The authors concluded that AHSCT using the BEAM-ATG scheme is safe and effective to control the aggressive forms of RRMS.

In a meta-analysis, Sormani and co-workers (2017) summarized the evidence on immunoablative therapy followed by AHSCT to manage severe and treatment-refractory MS. These investigators collected all the published studies of AHSCT in any form of MS from 1995 to 2016, carefully excluding reports that were updated in subsequent studies. End-points were transplant-related mortality (TRM), rate of disease progression, and no evidence of disease activity (NEDA) status. A weighted meta-regression based on a Poisson model was run, assessing whether there were study-specific characteristics with an effect on TRM and progression. A total of 15 studies including 764 transplanted patients were pooled in the meta-analysis. The pooled estimate of TRM was 2.1 % (95 % CI: 1.3 % to 3.4 %); TRM was higher in older studies (p = 0.014) and in studies with a lower proportion of patients with RRMS (p = 0.028). A higher baseline EDSS (p = 0.013) was also significantly associated with
a higher TRM. Pooled rate of progression was 17.1% at 2 years (95% CI: 9.7% to 24.5%) and 23.3% (95% CI: 16.3% to 31.8%) at 5 years. Lower 2-year progression rate was significantly associated with higher proportions of patients with RRMS (p = 0.004). The pooled proportion of NEDA patients at 2 years was 83% (range of 70% to 92%) and at 5 years was 67% (range of 59% to 70%). The authors concluded that the emerging evidence on this therapeutic approach in MS indicated that the largest benefit/risk profile form this therapeutic approach can be obtained in patients with aggressive MS with a relapsing-remitting course and who have not yet accumulated a high level of disability.

In a large, multi-center, observational, retrospective cohort study, Murano and colleagues (2017) evaluated the long-term outcomes in patients who underwent autologous hematopoietic stem cell transplantation (AHSCT) for the treatment of MS. Eligibility criteria were receipt of AHSCT for the treatment of MS between January 1995 and December 2006 and the availability of a pre-specified minimum data set comprising the disease subtype at baseline; the EDSS score at baseline; information on the administered conditioning regimen and graft manipulation; and at least 1 follow-up visit or report after transplant. The last patient visit was on July 1, 2012. To avoid bias, all eligible patients were included in the analysis regardless of their duration of follow-up. Data analysis was conducted from September 1, 2014 to April 27, 2015. Demographic, disease-related, and treatment-related exposures were considered variables of interest, including age, disease subtype, baseline EDSS score, number of previous disease-modifying treatments, and intensity of the conditioning regimen. The primary outcomes were MS PFS and OS. The probabilities of PFS and OS were calculated using Kaplan-Meier survival curves and multi-variable Cox proportional hazards regression analysis models. Valid data were obtained from 25 centers in 13 countries for 281 evaluable patients, with median follow-up of 6.6 years (range of 0.2 to 16); 78% (218 of 281) of patients had progressive forms of MS. The median EDSS score before mobilization of peripheral blood stem cells was 6.5
(range of 1.5 to 9); 8 deaths (2.8 %; 95 % CI: 1.0 % to 4.9 %) were reported within 100 days of transplant and were considered transplant-related mortality. The 5-year probability of PFS as assessed by the EDSS score was 46 % (95 % CI: 42 % to 54 %), and OS was 93 % (95 % CI: 89 % to 96 %) at 5 years. Factors associated with neurological progression after transplant were older age (hazard ratio [HR], 1.03; 95 % CI: 1.00 to 1.05), progressive versus relapsing form of MS (HR, 2.33; 95 % CI: 1.27 to 4.28), and more than 2 previous disease-modifying therapies (HR, 1.65; 95 % CI: 1.10 to 2.47). Higher baseline EDSS score was associated with worse OS (HR, 2.03; 95 % CI: 1.40 to 2.95). The authors concluded that in this observational study of patients with MS treated with AHSCT, almost 50 % of them remained free from neurological progression for 5 years after transplant. Younger age, relapsing form of MS, fewer prior immunotherapies, and lower baseline EDSS score were factors associated with better outcomes. They stated that the findings of this study support the rationale for further randomized clinical trials of AHSCT for the treatment of MS.

The authors stated that the main drawback of this study was its partially retrospective nature. Although some of the data were obtained retrospectively from clinical records, these investigators took many steps to optimize the analysis. As with most database studies, the reported outcomes mirrored the practice for MS treatment in many countries. The raters of EDSS assessments were not masked to clinical information, and assessments were not systematically performed for the duration of follow-up in every patient. Therefore, these researchers limited the analysis of PFS to the large 85.1 % (239 of 281) subset of patients who had yearly EDSS assessments after transplant. The number of patients with enough data points for the different analyses was variable and sometimes low, which reduced statistical power. In a retrospective study, incomplete reporting and loss to follow-up may result in underestimating the frequency of late adverse events (AEs). Another limitation was that, although the analysis included 57.0 % (281 of 493) of the transplants registered with the CIBMTR and the EBMT during the study period, more than 1/3 of the activity
was not captured by this study. However, the reason for the 78.3 % (166 of 212) of unavailable cases was that the centers where the patients were treated declined to participate in the study; 74 % (43 of 58) of centers that did not join the study had performed fewer than 3 transplants, and lack of incentive for the clinicians to contribute few cases to a large study was stated in many centers’ responses. Based on this information, the authors do not expect that the unavailability of those cases could represent a significant source of bias.

Burman and colleagues (2017) noted that AHSCT is a promising therapy for MS, which has mainly been used in adults. These researchers examined the effectiveness and AEs of AHSCT in the treatment of children with MS using data from the European Society for Blood and Marrow Transplantation registry. A total of 21 patients with a median follow-up time of 2.8 years could be identified; PFS at 3 years was 100 %, 16 patients improved in EDSS score and only 2 patients experienced a clinical relapse. The procedure was generally well-tolerated and only 2 instances of severe transplant-related toxicity were recorded. There was no treatment-related mortality, although 1 patient needed intensive care. The authors concluded that AHSCT may be a therapeutic option for children with disease that does not respond to standard care.

**Polycythemia Vera:**

Polycythemia vera (PV) in children and adolescents is very rare. Data on clinical and laboratory evaluations as well as on treatment modalities are sparse. Cario and associates (2009) reported the long-term clinical course of a PV patient first diagnosed more than 40 years ago at age 12. In addition, after a systematic review of the scientific medical literature, clinical and hematological data of 36 patients (17 males and 19 females) from 25 previous reports were summarized. Three patients developed PV following antecedent hematological malignancies; Budd-Chiari syndrome was diagnosed in 7 patients indicating a particular risk of young patients of developing this disorder. One patient presented with ischemic
stroke, 1 patient with gangrene, and 3 patients with severe hemorrhage, 3 patients died from disease-related complications. Hematocrit levels and platelet counts were not correlated with disease severity. Leukocytosis greater than 15 x 10(9)/L was present in 9/35 patients and associated with a thromboembolic or hemorrhagic complication in 7 patients. The few available data on molecular genetics and endogenous erythroid colony growth indicate changes comparable to those detectable in adult patients. Treatment varied enormously. It included aspirin, phlebotomy, hydroxycarbamide, busulfan, melphalan, pyrimethamine, and interferon-alpha. Two patients successfully underwent stem cell transplantation. The authors stated that it is currently impossible to treat an individual pediatric PV patient with an evidence-based regimen.

Tefferi and Vainchenker (2011) updated oncologists on pathogenesis, contemporary diagnosis, risk stratification, and treatment strategies in BCR-ABL1-negative myeloproliferative neoplasms, including PV, essential thrombocythemia (ET), and primary myelofibrosis (PMF). Recent literature was reviewed and interpreted in the context of the authors' own experience and expertise. Pathogenetic mechanisms in PV, ET, and PMF include stem cell-derived clonal myeloproliferation and secondary stromal changes in the bone marrow and spleen. Most patients carry an activating JAK2 or MPL mutation and a smaller subset also harbors LNK, CBL, TET2, ASXL1, IDH, IKZF1, or EZH2 mutations; the precise pathogenetic contribution of these mutations is under investigation. JAK2 mutation analysis is now a formal component of diagnostic criteria for PV, ET, and PMF, but its prognostic utility is limited. Life expectancy in the majority of patients with PV or ET is near-normal and disease complications are effectively (and safely) managed by treatment with low-dose aspirin, phlebotomy, or hydroxyurea. In PMF, survival and quality of life are significantly worse and current therapy is inadequate. In ET and PV, controlled studies are needed to show added value and justify the risk of unknown long-term health effects associated with non-conventional therapeutic approaches (e.g., interferon-alfa). The authors stated that the unmet need for treatment in PMF
dictates a different approach for assessing the therapeutic value of new drugs (e.g., JAK inhibitors, pomalidomide) or allogeneic stem-cell transplantation.

Furthermore, Cancer Care Ontario's guidelines on the management of malignant thrombocytosis in Philadelphia chromosome-negative myeloproliferative disease (specifically ET or PV) (Matthews et al, 2008) as well as the National Health, Lung and Blood Institute's Diseases and Conditions Index on polycythemia vera (2011) do not list stem cell transplant as a therapeutic option.

**Recessive Dystrophic Epidermolysis Bullosa:**

Recessive dystrophic epidermolysis bullosa is an incurable, often fatal mucocutaneous blistering disease caused by mutations in COL7A1, the gene encoding type VII collagen (C7). On the basis of pre-clinical data showing biochemical correction and prolonged survival in col7−/− mice, Wagner et al (2010) hypothesized that allogeneic marrow contains stem cells capable of ameliorating the manifestations of recessive dystrophic epidermolysis bullosa in humans. Between October 2007 and August 2009, these researchers treated 7 children who had recessive dystrophic epidermolysis bullosa with immuno-myeloablative chemotherapy and allogeneic stem-cell transplantation. They assessed C7 expression by means of immunofluorescence staining and used transmission electron microscopy to visualize anchoring fibrils. These investigators measured chimerism by means of competitive polymerase-chain-reaction assay, and documented blister formation and wound healing with the use of digital photography. One patient died of cardiomyopathy before transplantation. Of the remaining 6 patients, 1 had severe regimen-related cutaneous toxicity, with all having improved wound healing and a reduction in blister formation between 30 and 130 days after transplantation. These researchers observed increased C7 deposition at the dermal-epidermal junction in 5 of the 6 recipients, albeit without normalization of anchoring fibrils. Five recipients were alive 130 to 799 days after transplantation;
1 died at 183 days as a consequence of graft rejection and infection. The 6 recipients had substantial proportions of donor cells in the skin, and none had detectable anti-C7 antibodies. The authors concluded that increased C7 deposition and a sustained presence of donor cells were found in the skin of children with recessive dystrophic epidermolysis bullosa after allogeneic bone marrow transplantation. They stated that further studies (with more objective methods to evaluate the frequency of blistering, larger patient cohorts, and longer follow-up periods) are needed to assess the long-term risks and benefits of such therapy in patients with this disorder.

**Retinitis Pigmentosa:**

Li et al (2012) stated that the U.S. Food and Drug Administration recently approved phase I/II clinical trials for embryonic stem (ES) cell-based retinal pigmented epithelium (RPE) transplantation, but this allograft transplantation requires life-long immunosuppressive therapy. Autografts from patient-specific induced pluripotent stem (iPS) cells offer an alternative solution to this problem. However, more data are required to establish the safety and effectiveness of iPS transplantation in animal models before moving iPS therapy into clinical trials. This study examined the effectiveness of iPS transplantation in restoring functional vision in Rpe65(rd12)/Rpe65(rd12) mice, a clinically relevant model of RP. Human iPS cells were differentiated into morphologically and functionally RPE-like tissue. Quantitative real-time polymerase chain reaction (RT-PCR) and immunoblots confirmed RPE fate. The iPS-derived RPE cells were injected into the subretinal space of Rpe65(rd12)/Rpe65(rd12) mice at 2 days post-natally. After transplantation, the long-term surviving iPS-derived RPE graft co-localized with the host native RPE cells and assimilated into the host retina without disruption. None of the mice receiving transplants developed tumors over their life-times. Furthermore, electroretinography demonstrated improved visual function in recipients over the life-time of this RP mouse model. The authors concluded that this study provided the first direct evidence of functional recovery in a clinically relevant
model of retinal degeneration using iPS transplantation and supports the feasibility of autologous iPS cell transplantation for retinal and macular degenerations featuring significant RPE loss.

**Rheumatoid Diseases:**

Liu et al (2014) noted that the clinical management of autoimmune rheumatic diseases (ARD) has undergone significant changes in the last few decades, leading to remarkable improvements in clinical outcomes of many patients with mild to moderate ARD. On the other hand, severe refractory ARD patients often have high morbidity and mortality. Extensive basic research and clinical evidence has opened the door to new encouraging perspectives, such as the establishment of a role of HSCT in the strategic management of ARD. Given the great heterogeneity of ARD, it is difficult to assign an optimal HSCT regimen to all ARD patients. The authors concluded that HSCT remains a challenging mode of therapy in ARD patients from the standpoints of both safety and effectiveness. As the clinical data of HSCT in ARD increases and as the understanding of stem cell biology and the downstream effects on the immune system increases, the future is promising for the development of optimal personalized HSCT regimens in ARD.

**Systemic Lupus Sclerosus:**

Loh et al (2007) stated that patients with cardiac dysfunction may be at increased risk of cardiac toxicity when undergoing HCT, which may preclude them from receiving this therapy. Moreover, cardiac dysfunction is common in SLE patients. While autologous HCT (auto-HCT) has been performed increasingly for SLE, its impact on cardiac function has not previously been evaluated. Thus, these investigators performed a retrospective analysis of SLE patients who had undergone auto-HCT to determine the prevalence of significant cardiac involvement, and the impact of transplantation on this. The records of 55 patients were reviewed, of which 13 were found
to have abnormal cardiac findings on pre-transplant 2-dimensional echocardiography or multi-gated acquisition scan: impaired left ventricular ejection fraction (LVEF) (n = 6), pulmonary hypertension (n = 5), mitral valve dysfunction (n = 3) and large pericardial effusion (n = 1). At a median follow-up of 24 months (8 to 105 months), there were no transplant-related or cardiac deaths. With transplant-induced disease remission, all patients with impaired LVEF remained stable or improved; while 3 with symptomatic mitral valve disease similarly improved. Elevated pulmonary pressures paralleled activity of underlying lupus. These data suggest that auto-HCT is feasible in selected patients with lupus-related cardiac dysfunction, and with control of disease activity, may improve. The authors stated that the findings of this study warrant a prospective study with a larger cohort of SLE patients. It is hoped that with further investigation, the selection of which patients with cardiac abnormalities would benefit from auto-HCT and justify the potential risk will be made clearer.

Song and colleagues (2011) examined the effectiveness and toxicity of autologous stem cell transplantation (auto-SCT) in patients with SLE (n = 17). Peripheral blood stem cells were mobilized with cyclophosphamide (Cy) and granulocyte colony-stimulating factor. After a conditioning regimen of Cy and antithymocyte globulin, stem cells was re-infused. The probabilities of overall survival (OS) and progression-free survival (PFS) were used to assess the efficacy and adverse experiences, to detect the toxicities of the treatment. The median follow-up time was 89 months (range of 33 to 110). Probabilities of 7-year OS and PFS were 82.4 % +/- 9.2 % and 64.7 % +/- 11.6 %, respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died due to severe pneumonia and heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their 7-year follow-up results suggested that auto-SCT seemed beneficial for SLE patients. Moreover, they stated that recruitment of more patients into multi-center, randomized, comparative studies versus conventional treatment of SLE is needed to evaluate the safety and
Hematopoietic Cell Transplantation for Autoimmune Diseases and Miscellaneous Conditions

Effectiveness of Auto-SCT.

Thrombotic Thrombocytopenic Purpura:

UpToDate reviews on “Treatment and prognosis of thrombotic thrombocytopenic purpura-hemolytic uremic syndromes in adults” (Kaplan and George, 2013) does not mention the use of transplantation as a therapeutic option.

Ulcerative Colitis:

UpToDate reviews on “Management of severe ulcerative colitis” (Peppercorn and Farrell, 2013) and “Treatment of ulcerative colitis in children and adolescents” (Bousvaros et al, 2013) do not mention the use of transplantation as a therapeutic option.

Mesenchymal Stem Cells:

Wu and colleagues (2013) stated that mesenchymal stem cells (MSCs) have been shown to be effective in the management of graft versus-host disease (GVHD) due to their immunomodulatory effects. In addition to prevention and treatment of GVHD, many studies have demonstrated that MSCs can promote hematopoietic engraftment, accelerate lymphocyte recovery, reduce the risk of graft failure, and repair tissue damage in patients receiving HSCT. Bone marrow (BM) has been considered as the traditional source of MSCs, and most of the knowledge concerning MSCs comes from BM studies. However, BM-derived MSCs have several limitations for their clinical application. Fetal-type MSCs can be isolated easier and proliferate faster in vitro as well as possessing a lower immunogenicity. Therefore, fetal-type MSCs, such as umbilical cord-derived MSCs, represent an excellent alternative source of MSCs. Mesenchymal stem cells play multiple important roles in HSCT. Nevertheless, several issues regarding their clinical application remain to be discussed, including the safety of use in humans, the available sources and the convenience of obtaining MSCs, the quality control of in vitro-cultured MSCs and the appropriate cell passages, the optimum
cell dose, and the optimum number of infusions. Furthermore, it is important to evaluate whether the rates of cancer relapse and infections increase when using MSCs for GVHD. The authors concluded that there are still many questions regarding the clinical application of MSCs to HSCT that need to be answered, and further studies are needed.

Batsali et al (2013) noted that in recent years there seems to be an unbounded interest concerning MSCs. This is mainly attributed to their exciting characteristics including long-term ex-vivo proliferation, multi-lineage potential and immunomodulatory properties. In this regard MSCs emerge as attractive candidates for various therapeutic applications. Mesenchymal stem cells were originally isolated from the BM and this population is still considered as the gold standard for MSC applications. However, the BM has several limitations as source of MSCs, including MSC low frequency in this compartment, the painful isolation procedure and the decline in MSC characteristics with donor’s age. Thus, there is accumulating interest in identifying alternative sources for MSCs. To this end MSCs obtained from the Wharton's Jelly (WJ) of umbilical cords (UC) have gained much attention over the last years since they can be easily isolated, without any ethical concerns, from a tissue which is discarded after birth. Furthermore WJ-derived MSCs represent a more primitive population than their adult counterparts, opening new perspectives for cell-based therapies. The authors provided an overview of the biology of WJ-derived UC-MSCs; and discussed the potential application of WJ-derived UC-MSCs for the treatment of cancer and immune mediated disorders, such as GVHD and SLE.

**Anti-Phospholipid Syndrome:**

Leone and colleagues (2017) noted that HSCT has been proposed as a therapeutic option for patients with SLE refractory to standard therapy. This therapeutic approach has been applied to other severe autoimmune diseases refractory to standard therapy with promising results. These investigators
systematically reviewed the literature and analyzed the available evidence on HSCT therapy in patients with SLE and anti-phospholipid syndrome (APS), with a focus on effectiveness and occurrence of AEs. A detailed literature search, applied to Ovid Medline, In-Process and Other Non-Indexed Citation and Ovid Medline 1986 to 2014, has been developed a priori to identify articles that reported findings from clinical and laboratory studies that investigated the effect of HSCT in patients with SLE. A total of 25 studies met all inclusion criteria, including a total of 279 SLE patients; of those, 54 patients also fulfilled the classification criteria of APS. The majority of the studies reported an improvement after HSCT in terms of diseases activity control (assessed with SLEDAI, or time-free from diseases) or OS. However, 1 study reported no net benefit of HSCT when compared to immunosuppression alone. One retrospective study reported an OS at 5 years of 81 % in 28 SLE patients. Of note, 5 cases (9.3 %) of aPL negativization were reported after HSCT in the APS patients. When combining these studies and analyzing these patients with APS, 32 out of 44 (73 %) were able to discontinue anti-coagulation after HSCT. These results also demonstrated a total of 86 infections in the pool of patients (30.8 %), 3 of which resulted in the death of the patient (1.3 %). These researchers observed an annual incidence of infection of 11.9 % with a mean follow-up of 36.2 months. The authors concluded that preliminary results of HSCT as a therapeutic option for SLE appeared promising. They stated that further studies are needed to evaluate the safety of the procedure for both the occurrence of secondary autoimmune disease and the rate of infection. However, the rate of AEs confines this option to very selected cases of SLE patients resistant or refractory to standard approaches.

**Autoimmune Diseases-Induced Cirrhosis:**

Liang and colleagues (2017) stated that there has been great interest in recent years to take advantage of MSCs to treat end-stage liver disease. These researchers evaluated clinical therapeutic effects of allogeneic MSC transplantation in liver cirrhosis caused by autoimmune diseases. The enrolled
patients with liver cirrhosis were assigned to receive allogeneic MSC infusions through a peripheral vein. The primary objective of this study was to assess the safety and effectiveness of MSCT in patients with autoimmune diseases-induced cirrhosis; secondary end-points were to assess changes in the Models of End Stage Liver Disease (MELD) scores and liver functions after the transplantation. A total of 26 patients were enrolled. Of these, 23 patients received umbilical cord MSCT, 2 received cord blood MSCT, and 1 received bone marrow MSCT; 3 patients died of the complications caused by cirrhosis and 2 patients received liver transplantation after MSCT; 4 patients were lost to follow-up. The mean of alanine transaminase values decreased 6 months, 1 and 2 years after the transplantation, but there were no statistical significance. The mean value of total bilirubin decreased at 6 months and 1 year follow-up. Average serum albumin levels improved at 6 months, 1 and 2 years follow-up. The mean value at 2 years increased significantly compared with the baseline value. A lowering of prothrombin time was seen at 6 months after MSCT; MELD score improved at 6 months, 1 and 2 years of follow-up. No serious AEs were observed during or 24 hours after infusions of MSCs in any of the 26 patients with liver cirrhosis. The authors concluded that based on this clinical trial, allogeneic MSCT through the peripheral vein probably is safe and seemingly has beneficial effect in patients with liver cirrhosis. Thus, they stated that allogeneic MSCT is a potential option for the treatment of liver cirrhosis caused by autoimmune diseases; further studies with higher numbers of patients are needed to better clarify the impact and mechanisms of MSCT in liver cirrhosis.

**Inflammatory Bowel Disease:**

Bakhtiar and associates (2017) stated that inflammatory bowel disease (IBD) in young children can be a clinical manifestation of various primary immunodeficiency syndromes. Poor clinical outcome is associated with poor quality of life and high morbidity from the complications of prolonged immunosuppressive treatment and malabsorption. In 2012,
mutations in the lipopolysaccharide-responsive beige-like anchor (LRBA) gene were identified as the cause of an autoimmunity and immunodeficiency syndrome. Since then, several LRBA-deficient patients have been reported with a broad spectrum of clinical manifestations without reliable predictive prognostic markers. Allogeneic HSCT (allo-HSCT) has been performed in a few severely affected patients with complete or partial response. These researchers presented a detailed course of the disease and the transplantation procedure used in a LRBA-deficient patient suffering primarily from infantile IBD with immune enteropathy since the age of 6 weeks, and progressive autoimmunity with major complications following long-term immunosuppressive treatment. At 12 years of age, allo-HSCT using bone marrow of a fully matched sibling donor -- a healthy heterozygous LRBA mutant carrier -- was performed after conditioning with a reduced-intensity regimen. During the 6-year follow-up, these investigators observed a complete remission of enteropathy, autoimmunity, and skin vitiligo, with complete donor chimerism. The genetic diagnosis of LRBA deficiency was made after allo-HSCT by detection of 2 compound heterozygous mutations, using targeted sequencing of DNA samples extracted from peripheral blood before the transplantation. The authors concluded that due to the lacking genotype-phenotype correlation in LRBA-deficient patients, further data are needed to establish predictive and prognostic biomarkers that would allow the reliable identification of candidates for early allo-HSCT. They stated that further studies on transplantation in LRBA deficiency are needed to evaluate the optimal conditioning regimen and determine the necessary level of chimerism for disease remission.

**Pemphigus:**

Wang and co-workers (2017) stated that pemphigus is a rare and fatal autoimmune disease for which the therapeutic options are limited. These researchers evaluated the effectiveness of autologous peripheral HSCT (APHSCT) for pemphigus. They conducted APHSCT for 12 pemphigus patients (7 males and 5 females, mean age of 23.8 years) with
life-threatening complications or who responded poorly to conventional therapy. Peripheral blood stem cells were mobilized with cyclophosphamide, G-CSF, and rituximab, and purified autologous CD34+ stem cells were infused; OS, PFS, and AEs were recorded. With a mean follow-up period of 80.3 months, OS and complete clinical remission rates were 92 % (11/12) and 75 % (9/12), respectively; AEs included pyrexia, allergy, infection, and elevation of enzymes. Only 1 patient died of severe sepsis and multiple organ failure 2 months after APHSCT. The authors concluded that APHSCT is a promising therapeutic option for pemphigus.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

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<th>Code Description</th>
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<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
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<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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<td>38207 - 38215</td>
<td>Bone marrow or stem cell services/procedures</td>
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<td>Code</td>
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<td>86920 - 86923</td>
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<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition</td>
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The above policy is based on the following references:


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128. Del Papa N, Onida F, Zaccara E, et al. Autologous hematopoietic stem cell transplantation has better


Hematopoietic Cell Transplantation for Autoimmune Diseases and Misce...
AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0606 Hematopoietic Cell Transplantation for Autoimmune Diseases and Miscellaneous Indications

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania revised 04/12/2018