**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2021

Autologous hematopoietic stem cell transplantation in multiple sclerosis: a global approval and availability review

Stathopoulos, P ; Léger, K ; Foege, M ; Lutterotti, A ; Müller, A ; Schanz, U ; Jelcic, I ; Martin, R

DOI: <https://doi.org/10.1038/s41409-021-01276-z>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-208591>

Journal Article

Accepted Version

Originally published at:

Stathopoulos, P; Léger, K; Foege, M; Lutterotti, A; Müller, A; Schanz, U; Jelcic, I; Martin, R (2021). Autologous hematopoietic stem cell transplantation in multiple sclerosis: a global approval and availability review. Bone Marrow Transplantation, 56(7):1754-1756.

DOI: <https://doi.org/10.1038/s41409-021-01276-z>

Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis: A global Approval- and Availability Review.

Stathopoulos P^{1*}, Leger K¹, Foege M¹, Lutterotti A¹, Müller A², Schanz U², Jelcic I¹, Martin R^{1*}.

1. Department of Neuroimmunology and Multiple Sclerosis Research Section, Department of Neurology, University Hospital Zurich

2. Department of Medical Oncology and Hematology and Stem Cell Transplant, University Hospital Zurich

*co-corresponding authors (panos.stathopoulos@usz.ch; roland.martin@usz.ch)

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disorder of the central nervous system. With a prevalence of approximately 100 per 100,000 population in Europe, it is one of the most common and severe neurologic disorders of young adults(1). The majority (80-90%) of patients present initially with a relapsing-remitting (RRMS) and later secondary progressive (SPMS) course, while a minority present with a primary progressive course (PPMS)(2). Disability accumulation over the years has enormous consequences and causes significant impairment of quality of life and ability to work. In the last two decades, efficient therapies that drastically reduce relapses and alter the course of the disease with significant impact on prognosis have been developed and approved(3)(4), however progression of disability is often not prevented. A novel concept, the status of no evidence of disease activity (NEDA or NEDA-3, characterized by absence of relapses, new MRI lesions, and disability accrual), has therefore emerged as a metric of therapeutic efficacy(5), with the goal to achieve a sustained, prolonged, and perhaps permanent NEDA status. In addition, employing an induction treatment strategy (as opposed to an escalation strategy) to block disease activity as early and completely as possible is increasingly discussed(6). Despite great reduction and in many cases elimination of relapses and MRI activity with newer approved therapies, 2-year-pooled NEDA is maximally 48%(7). Moreover, a minority of patients with aggressive MS remains clinically and/or radiologically active despite use of approved high-efficacy treatments and shows rapid disability accrual. Similarly, in a subset of patients transitioning from RRMS to SPMS, the progression cannot be halted with current high-efficacy treatments. It is in meticulously selected cases of aggressive, high-efficacy treatment-refractory RRMS or early PP- and SPMS with an inflammatory component that autologous hematopoietic stem cell transplantation (aHSCT) has emerged over the last two decades as a treatment option(8). Although aHSCT is intensive and until 2000 had shown significant mortality(9), it is increasingly safe with mortality reported to the European Blood and Marrow Transplantation Society from 2012-2016 of 0.2% in MS(7) and, importantly, it is presently the most effective immunotherapy with 2-year pooled NEDA ranging from 70-92%, in comparison to 32-48% with ocrelizumab, natalizumab, alemtuzumab or cladribine(7)(9)(8). Several studies from different countries across several continents have demonstrated the high efficacy of aHSCT (reviewed in(10)). Further, the use of aHSCT is currently rapidly increasing(8), and the main premise, establishment of a new adaptive immune system, particularly of CD4+ T cells, has been demonstrated(11).

Based on a) the growing evidence of high efficacy, b) the fact that aHSCT is safe, well-established and approved for several indications including another autoimmune disease, systemic sclerosis,

c) the fact that phase III clinical trials of aHSCT compared to best available therapy are difficult to perform due to the high cost and lack of support from commercial, private, and government entities, but also due to recruitment difficulties as aHSCT is indicated in a small number of patients with MS, d) a clear desire of patients with aggressive disease to have access to aHSCT, e) the fact that many patients with MS are willing to travel to countries where aHSCT is offered widely, and f) socioeconomic considerations that aHSCT as a one-time treatment will reduce overall disease cost long-term, we applied for approval of aHSCT in MS to the Swiss Health Authorities (Federal Office of Public Health, FOPH) early in 2018. As part of the arguments that were presented to the FOPH, we assessed the availability and approval status of aHSCT in other countries. With support from the MS International Federation (MSIF), we sent a questionnaire to national MS societies from 43 countries. The questionnaire asked whether 1. aHSCT in MS is available in the country in question, 2. guidelines for the application of aHSCT exist, 3. activities for the promotion of aHSCT in MS are performed, 4. the cost of aHSCT is reimbursed upon recommendation by an MS specialist or a general neurologist, 5. specific conditions need to be fulfilled for reimbursement, and 6. a formalized reimbursement policy exists (see Table). Twenty-nine of 43 (67.4%) countries responded. Nineteen of the 29 (65.5%) countries reported that aHSCT has been performed as treatment of MS, although it had been performed in just a few selected cases in 8 of the 19 (42.1%) countries. National guidelines for the application of aHSCT existed at the time of the questionnaire in 7 of the 19 (36.8%) countries where aHSCT has been applied for MS treatment; in another 4 (21.1%) countries, guidelines were center-specific. Activities for the promotion of aHSCT in MS were described in 8 of 19 (42.1%) countries performing the treatment in selected MS patients. In 14 of 19 (73.7%) countries performing aHSCT in MS, treatment was reimbursed upon recommendation by a specialized team comprised of MS experts and hematologists. Further, in 5 of 19 (26.3%) countries performing aHSCT in MS, treatment was also reimbursed upon recommendation by a general neurologist. As far as conditions for reimbursement are concerned, in 7 of 19 (36.8%) countries no particular conditions were specified for reimbursement, in the remaining 12 countries (63.2%) conditions were center-specific and/or relying on scientific consensus regarding aHSCT indications; of those, only 4 countries required participation in a aHSCT registry in addition. Finally, only in 5 of 19 (26.3%) countries was the reimbursement procedure formalized in a document.

In summary, the data led to the following conclusions: First, aHSCT in MS is a treatment that has been performed in the majority of countries that responded to our questionnaire, although in about half of those aHSCT has been administered only to a limited number of selected patients. Second, guidelines for performance of aHSCT in MS existed in only half of the countries where the treatment has been applied; in addition, guidelines were often center-specific and not national. Third, reimbursement most often relied upon treatment recommendation by a panel of experts, however, the process was, in most cases, not specified by a nation-wide protocol or formalized in a federal document. Overall, the questionnaire-generated data indicated that, among the countries surveyed, application of aHSCT was not universal, but in more than half the countries was in use as a therapeutic option for a specific subset of patients.

In Switzerland, our application for approval of aHSCT as a treatment for MS has been successful, and aHSCT is now available and reimbursed by the health care providers as long as patients agree to be enrolled in a registry study (BASEC-Nr. 2018-01854) that will run from 2018 to 2023;

at the end of this period, continuation of the registry along with potential wider application of aHSCT in MS will be evaluated. Enrolment criteria for patients with aggressive RRMS, SP- and PPMS are oriented along international recommendations(8), but are not as narrow as those of recent phase IIb/III clinical studies(12). In this pilot application of aHSCT, the treatment has been approved for only one center in Switzerland, namely the University Hospital Zurich. Candidate patients are discussed at regular joint board meetings of neurologists and hematologists before a decision is made. Registry study data are captured in electronic case report forms and reported annually. Ancillary studies about the mechanism/s of action of aHSCT, specifically aspects of immune reconstitution after aHSCT, alterations of microbiota and other questions are being addressed under separate protocols and funded by the Swiss National Science Foundation and Swiss MS Society. It is our hope and goal that through the present report and the Swiss aHSCT-in-MS registry we will be able to contribute to better defining procedures for this valuable treatment for selected MS patients and that the treatment will become available in more countries.

Acknowledgements: the authors would like to thank Prof. Xavier Montalban, Dr. Anna Helme, and Dr. Joanna Laurson-Doube for help with drafting and distributing the questionnaire, all those individuals who contributed questionnaire responses, and Dr. Clare Walton for valuable discussions. The questionnaire was sent to the MS societies of Argentina, Australia, Austria, Belgium, Brazil, Canada, Cyprus, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Guatemala, Iceland, India, Iran, Ireland, Italy, Japan, Latvia, Lebanon, Luxembourg, Malta, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, Tunisia, Turkey, United Kingdom, Uruguay, and United States of America. MS societies from Argentina, Australia, Austria, Belgium, Canada, Cyprus, Denmark, Finland, France, Germany, Guatemala, India, Iran, Ireland, Italy, Japan, Netherlands, New Zealand, Norway, Portugal, Russia, Spain, Sweden, Switzerland, Tunisia, Turkey, United Kingdom, Uruguay, United States kindly responded to our query.

Financial disclosures: R. M. received unrestricted grant support from Biogen and Novartis, and compensation for advice or lecturing by Biogen, Novartis, Sanofi Genzyme, Merck, Hoffmann La Roche, Teva, Neuway, CellProtect and Third Rock Ventures. He is a co-founder and co-owner of Cellerys, which pursues antigen-specific tolerization. Together with M. Sospedra, he is an inventor on a Univ. Zurich-held patent of target antigens GDP L-fucose synthase and RAS guanyl-releasing protein 2 for multiple sclerosis. IJ has received speaker honoraria or unrestricted grants from Biogen Idec and Novartis and has served as advisor for Neuway, Merck, Novartis and Sanofi Genzyme.

References

1. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. *Revue Neurologique*. 2016 Jan;172(1):3–13.
2. Weinshenker BG, Rice GP, Noseworthy JH, Carriere W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study. 4. Applications to planning and interpretation of clinical therapeutic trials. *Brain*. 1991 Apr;114 (Pt 2):1057–67.

3. Tintore M, Vidal-Jordana A, Sastre-Garriga J. Treatment of multiple sclerosis — success from bench to bedside. *Nat Rev Neurol*. 2019 Jan;15(1):53–8.
4. Brown JWL, Coles A, Horakova D, Havrdova E, Izquierdo G, Prat A, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. *JAMA*. 2019 Jan 15;321(2):175.
5. Giovannoni G, Tomic D, Bright JR, Havrdová E. “No evident disease activity”: The use of combined assessments in the management of patients with multiple sclerosis. *Mult Scler*. 2017 Aug;23(9):1179–87.
6. Stankiewicz JM, Weiner HL. An argument for broad use of high efficacy treatments in early multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2020 Jan;7(1):e636.
7. Muraro PA, Martin R, Mancardi GL, Nicholas R, Sormani MP, Saccardi R. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. *Nat Rev Neurol*. 2017 Jul;13(7):391–405.
8. for the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and EBMT (JACIE), Sharrack B, Saccardi R, Alexander T, Badoglio M, Burman J, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant*. 2020 Feb;55(2):283–306.
9. Sormani MP, Muraro PA, Schiavetti I, Signori A, Laroni A, Saccardi R, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. *Neurology*. 2017 May 30;88(22):2115–22.
10. Cohen JA, Baldassari LE, Atkins HL, Bowen JD, Bredeson C, Carpenter PA, et al. Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation. *Biology of Blood and Marrow Transplantation*. 2019 May;25(5):845–54.
11. Muraro PA, Douek DC, Packer A, Chung K, Guenaga FJ, Cassiani-Ingoni R, et al. Thymic output generates a new and diverse TCR repertoire after autologous stem cell transplantation in multiple sclerosis patients. *Journal of Experimental Medicine*. 2005 Mar 7;201(5):805–16.
12. Burt RK, Balabanov R, Burman J, Sharrack B, Snowden JA, Oliveira MC, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. *JAMA*. 2019 Jan 15;321(2):165.

177 **Table**

Question	N of countries	% of countries
Countries that responded	29 of 43	67.4%
Availability of aHSCT in MS	19 of 29	65.5%
• Established use	11 of 19	57.9%
• Only in a limited number of cases	8 of 19	42.1%
Guidelines for aHSCT in MS		
• National	7 of 19	36.8%
• Center-specific	4 of 19	21.1%
Activities for the promotion of aHSCT in MS	8 of 19	42.1%
Reimbursement of aHSCT cost		
• Based on recommendation by a team of experts	14 of 19	73.7%
• Based on recommendations by a general neurologist	5 of 19	26.3%
Specific conditions for reimbursement		
• No particular conditions	7 of 19	36.8%
• Center specific/relying on scientific consensus	12 of 19	63.2%
Formal reimbursement policy document	5 of 19	26.3%

178 aHSCT, autologous hematopoietic stem cell transplantation; MS, multiple
179 sclerosis

180
181