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Norwegian health service should offer stem cell therapy for multiple sclerosis

PERSPECTIVES

GRO OWREN NYGAARD

uxgryg@ous-hf.no

Gro Owren Nygaard, specialist in neurology, senior consultant at the Department of Neurology, Oslo University Hospital, and researcher at the University of Oslo. She is a member of the core group in the Norwegian Quality and Competence Network and the Hospital Procurement Specialist Group for Multiple Sclerosis. She also heads the expert group for stem cell therapy for MS at Oslo University Hospital. She is project manager of the NOR-MS clinical trial and NevroVAX, the national vaccine study. She is a partner in the EU project EBV-MS.

The author has completed the ICMJE form and declares no conflicts of interest.

TRYGVE HOLMØY

Trygve Holmøy, specialist in neurology, head senior consultant at Akershus University Hospital and a professor at the University of Oslo. He is a member of the core group in the Norwegian Quality and Competence Network and the Hospital Procurement Specialist Group for Multiple Sclerosis and the expert group for stem cell therapy for MS at Oslo University Hospital. He participated in the working group that developed the National Clinical Guidelines for the Diagnosis and Treatment of Multiple Sclerosis, and has contributed as an expert in the field to the Norwegian Institute of Public Health's method assessments for MS therapy.

The author has completed the ICMJE form and declares the following conflicts of interest: he has received lecture fees from Merck, Biogen, Genzyme, Sanofi, Novartis and Roche, and participated in clinical trials organised by Biogen, Merck and Roche. He has assessed the scientific

basis for stem cell therapy for the Multiple Sclerosis Association in Norway. He is involved in the RAM-MS study and serves on the steering group for the ENSEMBLE study of ocrelizumab in multiple sclerosis.

Many Norwegian patients with multiple sclerosis choose to travel abroad for stem cell therapy at their own expense and risk. Based on the current knowledge base, selected patients should now be offered this therapy in Norway.

High-dose chemotherapy with autologous stem cell support (HDT) is not part of the standard treatment for multiple sclerosis (MS) in Norway, but it is available as part of an ongoing clinical trial. Many Norwegian neurologists have been sceptical of the treatment, while the media has described it as highly effective (1). Estimates from patient groups on social media indicate that approximately 400 MS patients in Norway have sought treatment abroad at their own expense and risk, with around 200 in Russia, 150 in Mexico and 50 in other countries.

Patients with relapsing-remitting MS are generally offered highly effective immunomodulatory therapy (2). This is effective for most patients, but some still experience relapses and disease progression (3, 4). Recent research shows that stem cell therapy is safe and, in our opinion, at least as effective as established treatments for certain patients (5, 6). We therefore believe that this treatment should be available in the Norwegian health service.

Stem cell therapy changes the immune system

The goal of stem cell therapy is to achieve long-term remission by resetting the patient's pathogenic adaptive immune system. Originally developed for malignant haematological diseases, this therapy has also been used for the past 25 years in severe autoimmune disorders (7). Close collaboration is required between neurologists and haematologists, and the procedure is carried out in specialised haematological departments. A hospital stay of two to four weeks is needed, during which the patient is isolated for part of the time.

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In short, the treatment involves mobilising and harvesting haematopoietic stem cells, followed by chemotherapy that, to a greater extent than other immunosuppressive treatments, kills the body's immune cells. The patient's stem cells are then reintroduced in order to rebuild the immune system (Figure 1).

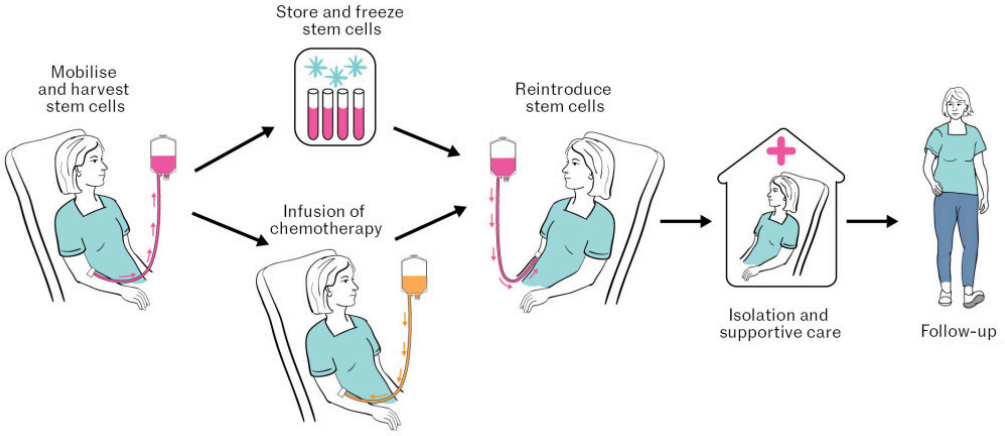

Figure 1 Stem cell therapy in multiple sclerosis

Stem cell therapy in Norway

Neurologists, haematologists and immunologists in Oslo sought approval back in 1997 to treat MS with stem cell therapy, but this was denied (Torstein Egeland, personal communication, 1 November 2023). It was not until 2015 that the first patient was treated at Haukeland University Hospital. A subsequent methods assessment led the Decision Forum to conclude that there was insufficient documentation to introduce the method, and they recommended that a clinical trial be initiated (8). An international clinical trial was therefore started at Haukeland University Hospital in 2017. In the trial, patients who have experienced relapses while receiving other MS treatment are randomised to receive either stem cell therapy or conventional therapy. As of November 2023, the trial has included 88 out of the 100 planned patients in Norway and internationally. The patients will be followed for two years, and the results are unlikely to be available before the second half of 2026. In addition, an estimated 40 patients have been treated on an individual basis at Haukeland University Hospital and Oslo University Hospital outside of the trial.

Stem cell therapy is safe, but challenging

The first attempt at stem cell therapy for MS was in 1995, and more than 50 observational studies and two randomised clinical trials documenting safety and efficacy have been published (Table 1) (6, 9–12). The first studies involved patients with advanced disease. As younger patients with a shorter disease duration were included, and the intensity of immunosuppression was reduced, research has shown the therapy to have a good effect and an acceptable risk profile (6).

Table 1

Effect of stem cell therapy in MS

Study	Randomised clinical phase 2 trial 2015 (10)	Randomised clinical phase 3 trial 2019 (11)	Meta-analysis of observational studies 2022 (6)	Registry study 2023 (12)
Population	21 patients with secondary progressive disease and increasing functional impairment and at least one contrast-enhancing MR lesion in the past year	110 patients with relapsing-remitting MS and signs of disease activity despite conventional therapy in the past year	50 studies/4831 patients, most with relapsing-remitting MS	3915 patients with relapsing-remitting MS
Treatment	Stem cell therapy (n = 9), mitoxantrone (n = 21)	Stem cell therapy (n = 55), conventional therapy (n = 55)	Stem cell therapy	Stem cell therapy (n = 167) fingolimod (n = 2 558), natalizumab (n = 1 490) ocrelizumab (n = 700)
Follow-up period	4 years	Median 2 years, max. 5 years	0.5–11.3 years	Stem cell therapy 4 years, fingolimod 2.8 years, natalizumab 2.5 years, ocrelizumab 1.5 years
Effect	Stem cell therapy reduced the number of new MR lesions by 79 % compared with mitoxantrone.	Average functional impairment reduced by 10.0 % with stem cell therapy, increased by 6.7 % with conventional therapy.	73 % with preserved or improved function level, 81 % experienced no new attacks, and 68 % showed no signs of disease progression	The function level with stem cell therapy was the same as for ocrelizumab and natalizumab, and better than with fingolimod. The relapse rate with stem cell therapy was the same as with ocrelizumab, and better than with natalizumab and fingolimod.

Data from just over 3000 patients show that treatment-related mortality for autoimmune disorders in Europe decreased from 1.3 % in the early 2000s to 0.2 % in the last decade. This is probably due to a combination of more experience, less intense immunosuppression, and younger and healthier patients (5).

Stem cell therapy can be challenging for patients. Most experience hair loss, and all require in-patient supportive care during the acute phase. The most common complications are lymphopenia with fever (30 %), infection and electrolyte disturbances (30 %), and many need blood products (77 %) (13). However, the risk of infection is transient and low after three months. A total of 10–20 % of patients develop secondary autoimmunity, most frequently thyroid disorders, and up to 40 % of women experience premature menopause and infertility (5, 13).

The most common conventional therapy for relapsing-remitting MS today is rituximab or other immunosuppressive therapies. These medications also increase the risk of infections, which, unlike with stem cell therapy, increases with time (14).

Stem cell therapy is effective for some

A large meta-analysis of observational studies on stem cell therapy published in 2022 showed a considerable reduction in neurological disability, relapse rate and new MR lesions in white matter in the central nervous system (Table 1). The effect was most convincing for younger patients with relapsing-remitting MS and/or lesions showing signs of active inflammation (6).

The results of two randomised clinical trials have been published and several trials are ongoing. The first, in 2015, showed that patients treated with stem cell therapy had fewer new MR lesions than patients who had received potent immunosuppressive therapy in the form of mitoxantrone (Table 1) (10). This phase 2 trial was important because it documented that stem cell therapy inhibited inflammatory activity. In 2019, results were published from a large-scale randomised clinical trial of patients who had experienced relapses despite conventional therapy. After one year, the trial showed a significantly improved average neurological function level with stem cell therapy and deterioration with conventional therapy. The difference between the groups persisted five years after treatment. Although many patients in the control group did not receive one of the most effective conventional MS drugs, the trial confirmed that stem cell therapy has a good effect in relapsing-remitting MS (11), and observational studies support the finding that this effect is maintained for many years (6).

A European observational study on stem cell therapy as the initial treatment for highly aggressive relapsing-remitting MS found a dramatic improvement after one year in all 28 patients (15). The experiences from the first 30 patients treated in Norway align with international results, demonstrating improved function levels and increased capacity to work (13).

Although it has been documented that stem cell therapy is effective in relapsing-remitting MS, it has been difficult to conclude whether it is more effective than conventional MS therapy. Some patients still experience relapses or impaired function levels after stem cell therapy (6). A recent registry study showed better efficacy of stem cell therapy compared to some of the most

effective conventional MS medications, while B-cell therapy with ocrelizumab was equally effective (12). It is therefore not certain that stem cell therapy is more effective than the best conventional therapy.

Experiences are more mixed for progressive MS without relapses. Studies indicate a stabilisation of function levels after treatment, but it is difficult to determine if this is due to the treatment or whether it reflects the natural course (6). Patients with progressive forms of MS should potentially be treated in a randomised clinical trial.

Stem cell therapy should be available in Norway

Stem cell therapy differs from conventional therapy in several aspects: the pharmaceutical industry has no incentive to conduct studies, the treatment requires significant hospital resources, and it is more risky and challenging in the acute phase. Whether cost, risk and treatment burden are greater over a lifespan is more uncertain.

Although more knowledge is still needed, we can conclude with reasonable certainty that stem cell therapy is highly effective for relapsing-remitting MS, and that the risk in younger patients with good neurological function is acceptable.

> ***«Although more knowledge is still needed, we can conclude with reasonable certainty that stem cell therapy is highly effective»***

Stem cell therapy has been incorporated into the standard treatment provision of the public health service in several European countries, including Sweden and Denmark, for selected patients with relapsing-remitting MS. It is also recommended by the European Society for Blood and Marrow Transplantation.

We believe that Norwegian patients with obvious inflammatory activity during conventional immunomodulatory therapy and patients with highly aggressive relapsing-remitting MS should be offered stem cell therapy by the Norwegian health service. As long as the clinical trial is ongoing, as many patients as possible should be included. Patients who exhibit inflammatory MS activity, such as relapses or new MR lesions indicating inadequate effect of conventional therapy, but do not meet the inclusion criteria for the clinical trial, should be considered outside the trial. We should ensure equal access throughout Norway, and the results should be recorded in national and international quality registers. All patients should feel confident that they are receiving good and appropriate treatment in Norway, eliminating the need for expensive trips abroad for treatment.

LITERATURE

1. Ystrøm T. Én sykdom – to helt forskjellige skjebner. NRK 11.11.2023. https://www.nrk.no/rogaland/xl/bade-tommy-herredsvela-ogline-flesjaa-

har-ms-_-men-line-har-tatt-stamcellebehandling-1.16610171 Accessed 23.11.2023.

2. Helsedirektoratet. Nasjonal faglig retningslinje. Multippel sklerose. https://www.helsedirektoratet.no/retningslinjer/multippelsklerose Accessed 15.10.2023.

3. Holmøy T, Nygaard GO, Myhr KM et al. Behandling som begrenser multippel sklerose. Tidsskr Nor Legeforen 2021; 141. doi: 10.4045/tidsskr.21.0155. [PubMed][CrossRef]

4. Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. Am J Med 2020; 133: 1380–1390.e2. [PubMed][CrossRef]

5. 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). 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; 55: 283–306. [PubMed][CrossRef]

6. Nabizadeh F, Pirahesh K, Rafiei N et al. Autologous Hematopoietic Stem-Cell Transplantation in Multiple Sclerosis: A Systematic Review and Meta-Analysis. Neurol Ther 2022; 11: 1553–69. [PubMed][CrossRef]

7. Muraro PA. Resetting tolerance in autoimmune disease. Science 2023; 380: 470–1. [PubMed][CrossRef]

8. Nasjonalt kunnskapssenter for helsetjenesten. Autolog hematopoietisk stamcelletransplantasjon ved multippel sklerose. https://nyemetoder.no/Documents/Rapporter/Rapport_2015_23_MS_Stamceller.pdf Accessed 15.10.2023.

9. Fassas A, Anagnostopoulos A, Kazis A et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. Bone Marrow Transplant 1997; 20: 631–8. [PubMed] [CrossRef]

10. ASTIMS Haemato-Neurological Collaborative Group On behalf of the Autoimmune Disease Working Party ADWP of the European Group for Blood and Marrow Transplantation EBMT. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology 2015; 84: 981–8. [PubMed][CrossRef]

11. Burt RK, Balabanov R, Burman J 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; 321: 165–74. [PubMed][CrossRef]

12. MSBase Study Group. Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis. JAMA Neurol 2023; 80: 702–13. [PubMed][CrossRef]

13. Kvistad SAS, Lehmann AK, Trovik LH et al. Safety and efficacy of autologous hematopoietic stem cell transplantation for multiple sclerosis in Norway. Mult Scler 2020; 26: 1889–97. [PubMed][CrossRef]

14. Luna G, Alping P, Burman J et al. Infection Risks Among Patients With Multiple Sclerosis Treated With Fingolimod, Natalizumab, Rituximab, and Injectable Therapies. JAMA Neurol 2020; 77: 184–91. [PubMed][CrossRef]

15. Das J, Snowden JA, Burman J et al. Autologous haematopoietic stem cell transplantation as a first-line disease-modifying therapy in patients with 'aggressive' multiple sclerosis. Mult Scler 2021; 27: 1198–204. [PubMed][CrossRef]

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