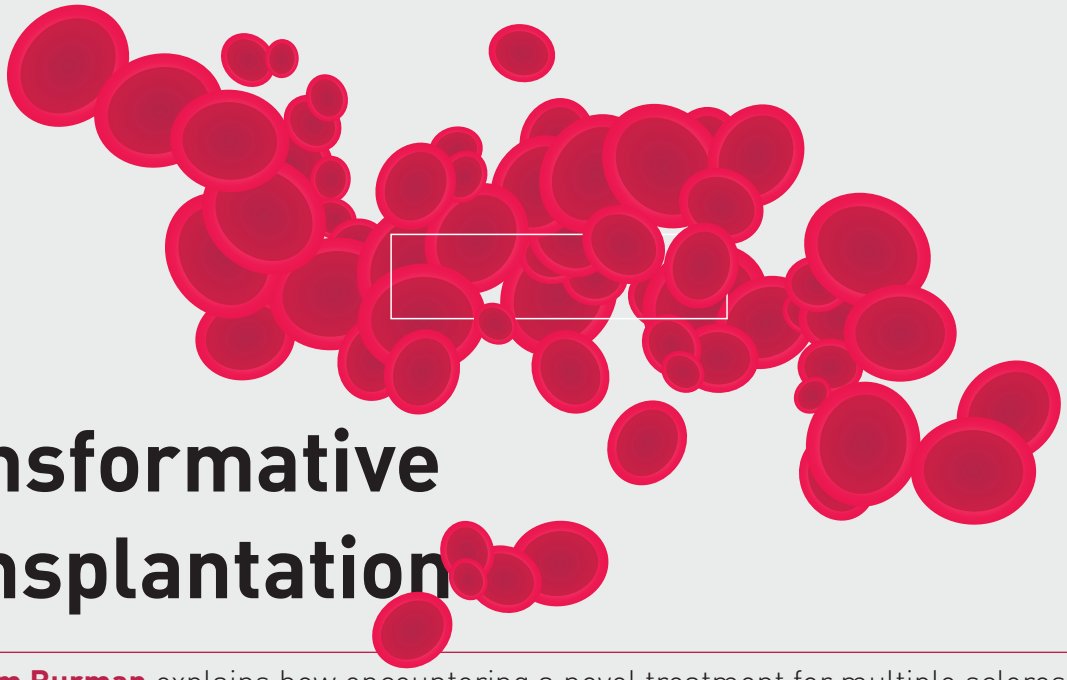


Transformative transplantation

Dr Joachim Burman explains how encountering a novel treatment for multiple sclerosis during his medical residency led him to dedicate his career to the technique's advancement

Could you outline the focus and main objectives of your study into haematopoietic stem cell transplantation (HSCT) and its use in treating multiple sclerosis (MS)?

The ultimate goal of my research is to establish HSCT as a treatment available to patients in routine healthcare. We have been undertaking transplants for MS in Uppsala, Sweden, for over 10 years. During this time, we have gained a very clear clinical impression that this procedure leads to long-term remission in the majority of patients. Even if some individuals have residual disease, it tends to be very mild. Many patients also improve in terms of disability, which has never been seen with conventional treatment. On the whole, HSCT is far superior to all other available therapies for MS in terms of efficacy. As a serious disease that gives rise to physical and mental disability as well as premature death, it would be unethical not to pursue this line of research.

How has your professional background prepared you for this type of research?

I came into research during my residency in neurology. At the time, I was not particularly attracted by it and was aiming for a career in clinical medicine. However, I was intrigued by autoimmune diseases and, when we started to see the outstanding results of the early transplants for MS, I was absolutely stunned. As I had learnt a great deal about MS during my clinical training, I immediately realised that this could be a highly promising avenue to pursue. By that stage, I was convinced I had to go into research.

What makes HSCT such an effective treatment for inflammatory active MS?

MS is an autoimmune disease in which a patient's immune system attacks the brain and spinal cord. While most drugs used in the treatment of MS try to calm the immune system or impede its ability to penetrate into the nervous system, HSCT fixes the underlying problem by removing the erroneous immune system and replacing it with a healthy new one. This transplantation is somewhat similar to a solid organ transplantation. If you have faulty kidneys you can get a replacement from another person and live a perfectly normal life; the main difference with HSCT is that we can use the patient's own haematopoietic stem cells – which is much safer. Those stem cells will rebuild a new immune system and, if everything works out, that immune system will no longer contain the components that give rise to MS.

More patients per capita undergo transplantation in Sweden than anywhere else in the world; why is this?

We had some very positive early experiences with this procedure that prompted us to move on to the development of a clinical programme. In Sweden, all physicians can prescribe and use any approved drug with hardly any constraints. Since we use existing drugs that have been around for decades, we do not have to file a lot of paperwork and navigate through bureaucracy in order to use this treatment. In addition, healthcare in Sweden is publicly funded and not primarily based on individual performance. That means that I have nothing to lose by referring 'my' patients to the haematologists who perform the actual transplant. Therefore, I can have the patient's best interest at heart at all times. Over the years, we have been very lucky to collaborate with enthusiastic and open-minded haematologists, radiologists and laboratory personnel.

Why is HSCT still considered an experimental treatment? Could this alternative become a widespread therapeutic option in healthcare?

In order to gain acceptance, you have to perform a phase III trial, for which a great deal of financial support is required. As the drugs we are using are no longer protected by patents, there is no commercial potential in this treatment. Today we are relying purely on academic research, which is funded by anaemic research grants.

I think we will succeed in the end, but progress could be much faster. A phase III trial is currently in progress and, if it is positive, I believe HSCT will be accepted as a second-line treatment option that could benefit up to 30 per cent of MS patients. This could be a reality in five to 10 years.

A brighter future for multiple sclerosis patients

Pioneering research is underway at **Uppsala University**, Sweden, aimed at proving the efficacy and safety of haematopoietic stem cell transplantation as a treatment for multiple sclerosis

MULTIPLE SCLEROSIS (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) that affects an estimated 2.5 million people worldwide. It is the leading cause of physical disability in people of working age, predominantly appearing in individuals at around the age of 30. In the most severe cases, it leads to premature death; life expectancy in a person with MS is reduced by an average of 10 years.

These statistics correlate with the fact that currently available MS therapies do not cure the disease, but are rather aimed at halting its progression by reducing inflammation. A further limitation is that they are ineffective for a significant proportion of patients, particularly those who have progressed beyond the early stage of relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS), at which point neurodegeneration, CNS system atrophy and disability accumulation begin to take hold. There is also the risk of serious side effects, as well as the question of cost – approved MS therapeutics are expensive, and must be administered continuously if they are to be effective. As such, they represent a significant economic burden on healthcare systems across the world.

A BLAST FROM THE PAST

A solution may lie in a treatment strategy that has been used in medicine since the 1950s: haematopoietic stem cell transplantation (HSCT). Since its inception, HSCT has been performed over 1 million times across the globe, and today it is the treatment of choice for acute myeloid leukaemia and plasma cell disorders. The technique works by transplanting a new, healthy immune system into the patient, using haematopoietic stem cells from their own body. The results are permanent, and the treatment need only be performed once.

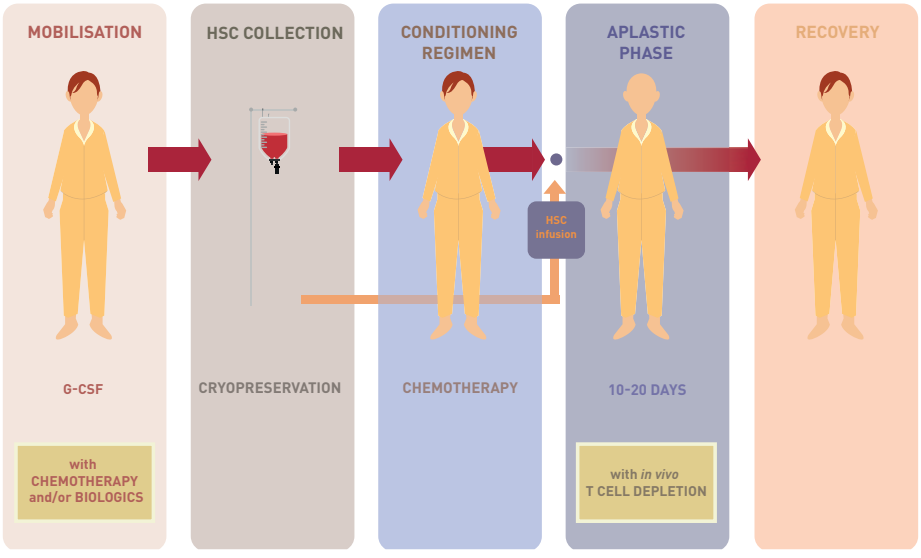
> Dr Joachim Burman is determined to bring haematopoietic stem cell transplantation into the mainstream as a routine treatment option for patients with multiple sclerosis.

Although not originally developed for use in MS, HSCT's application in this area can be traced back to the mid-1990s, when animal studies were used to test its efficacy in treating malignant RRMS. The positive findings produced here led to first-generation trials that, despite producing many important and positive findings, were also associated with high rates of treatment-related mortality. This was due to a combination of factors, including the use of heavy myeloablative transplantation regimens and the selection of participants with treatment-resistant and progressive forms of MS, for whom, it has since been established, HSCT is not effective. However, subsequent research has found HSCT to be very effective for treating RRMS, particularly highly aggressive cases – with two-thirds of treated patients achieving complete remission with no evidence of disease activity four to five years after the procedure. Furthermore, the development of less toxic conditioning regimens and improved patient selection has reduced treatment-related mortality to its current day low level (well below 1 per cent). Unfortunately, the misconception that HSCT is a high-risk strategy for MS treatment still lingers among some in medical field.

At Uppsala University in Sweden, Dr Joachim Burman is determined to bring HSCT into the mainstream as a routine treatment option for patients with MS. At present, although an estimated 30 per cent of the country's 20,000 MS patients could benefit from the treatment, only 1 per cent are offered it. However, even with this low figure, Sweden is a trailblazer in this regard; more HSCTs are performed per capita in Sweden than in any other country, with the treatment being undertaken in all University Hospitals nationwide. Nevertheless, HSCT is still considered an experimental treatment by many, and a number of challenges must be overcome if the treatment is to be rolled out significantly.

LOOKING FOR ANSWERS

In order to advance HSCT as a treatment for MS, Burman's group and its collaborators



Autologous haematopoietic stem cell transplantation (HSCT) for autoimmune diseases.

are currently engaged in a number of studies. Firstly, to elucidate the biological mechanism(s) underlying the treatment's efficacy, a combination of established and novel immunological techniques are being employed, including flow cytometry, antigen recognition assays and the multiplex protein analysis of serum and cerebrospinal fluid. "Multiplex assays provide an opportunity to measure a multitude of proteins simultaneously in a small sample volume. Ten years ago, studies were limited to analysing one or a few proteins in every sample – but now we can analyse up to 100," Burman enthuses.

The second aim is to accurately characterise the treatment's risk/benefit ratio in different subgroups of patients. This will be achieved using information gathered through a nationwide clinical follow-up programme (which is currently underway), together with data provided by the European Group for Blood and Marrow Transplantation Registry.

Thirdly, the researchers wish to establish whether or not it can be conclusively proven beyond reasonable doubt that HSCT can be curative. Over the next two years, therefore, the team will perform a positron emission tomography (PET) study on MS patients who were treated using HSCT 10 years ago and still show no evidence of disease activity. If a complete cure can be demonstrated, this will set a new standard for the treatment of autoimmune diseases.

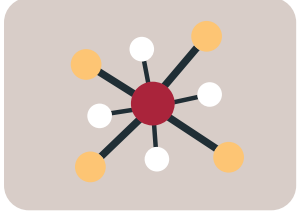
The fourth and final aim is to complete a phase III clinical trial of HSCT versus the best available alternative therapy. This is necessary in order to obtain regulatory approval, as well as foster wider trust in the procedure. So far, two-thirds of the 120 patients required for this study have been recruited. "We put safety first, so we select our patients very carefully, trying to find individuals that can go through the procedure with minimal risk while having a great deal to gain," elucidates Burman.

OVERCOMING OBSTACLES

This work is not without its challenges. Securing funding is difficult, as HSCT provides no opportunity for commercial profit; as such, Burman's research is dependent entirely on academic research grants. In addition to this, awareness-raising efforts are required in order to overcome the widespread misconception that HSCT is a high-risk procedure.

However, Burman is determined to lead these efforts, no matter the work ahead. "My experience working with HSCT has convinced me that we are on the right path," he states. Given that HSCT offers benefits from both an individual and societal perspective – HSCT has the power to prevent and even reverse disability and bring about long-term remission in patients, while providing a cost-effective solution for healthcare systems – it seems highly probable that Burman shall succeed in seeing HSCT's widespread acceptance and implementation sooner rather than later.





HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE TREATMENT OF MULTIPLE SCLEROSIS

OBJECTIVE

To establish haematopoietic stem cell transplantation as a routine treatment option for patients with multiple sclerosis.

KEY COLLABORATORS

Dr Kristina Carlson; **Dr Helene Hallböök**; **Dr Ulla Olsson-Strömberg**; **Dr Elisabeth Ejerblad**; **Dr Hans Hägglund**, Department of Hematology, Uppsala University Hospital, Sweden

Professor Elna-Marie Larsson, Department of Radiology, Uppsala University, Sweden

Professor Richard K Burt, Northwestern University Feinberg School of Medicine, USA

Professor Henrik Zetterberg, the Sahlgrenska Academy at the University of Gothenburg, Sweden, and University College London's Institute of Neurology, UK

PARTNERS

Uppsala PET Centre

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DR JOACHIM BURMAN is Senior Consultant Neurologist at Uppsala University Hospital and Vice President of the Swedish Multiple Sclerosis Society. He received his medical degree from Uppsala University in 2001 and trained as a neurologist at the Hospital of Hudiksvall in Sweden. Since 2009, he has been working at Uppsala University Hospital where he has specialised in neuroinflammatory disases such as multiple sclerosis. At present, he is leading the Hematopoietic Stem Cell Transplantation for Neurological Diseases Program at Uppsala University Hospital.

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