

# THE STEM CELL TRANSPLANT PROGRAM FOR AUTOIMMUNE DISEASES

## Autoimmune Diseases (ADs)

These are a group of illnesses that all have an altered reactivity of the immune system where it reacts against its own organism. The clinical course is usually chronic and varies depending on the organs involved and the clinical evolution for each individual patient. Immunosuppression (suppressing the immune system) is the conventional therapy that the majority of patients with a relatively benign state respond well to, whereas more aggressive forms of the disease are poorly controlled by subsequent lines of therapy. It should be remembered that organ damage caused by the disease maybe associated with the side effects of long-term immunosuppression.

## Stem Cell Transplantation for Autoimmune Diseases

Bone marrow transplantation is a procedure commonly used for the treatment of serious blood diseases, including leukaemias and lymphomas. According to data from the Registry of the European Society for the Blood & Marrow Transplantation about 20,000 procedures are carried out every year in Europe, for a total of more than 250,000 transplants practiced from the late 1970's to today.

The efficacy of the transplant was seen both in the experimental model and in patients who had a transplant for a haematological disease and who were also suffering from an autoimmune disease.

The data reported in the literature show that the transplant is able to provide a clinical response in the majority of patients suffering from autoimmune diseases (AD's) resistant to conventional treatments; the duration of the response is variable, above all depending on the diagnosis. (see reference 1)

The transplant is confirmed to be however, a useful therapeutic option in patients with poor prognosis. The role of the transplant must be established by prospective trials that are currently being carried out or are in the planning stages. The European Society of Blood & Marrow Transplantation has recently issued guidelines for the use of transplantation in autoimmune diseases (see reference 2).

## Case studies

To date, approximately 1,500 transplants have been performed in Europe for Autoimmune Diseases, in particular neurological (multiple sclerosis) , rheumatologic (Scleroderma and Lupus) and gastroenterological diseases (Crohn's disease). In the majority of cases, the patient's own stem cells have been used (autologous transplantation), and more rarely those of a healthy donor (allogeneic transplantation) (see reference 1).

A series of data shows that the immune system regenerates extensively after transplantation, correcting the alterations that had resulted in the onset of autoimmune disease ("reset" of the immune system) (see reference 3).

Post-transplantation, the majority of patients achieve disease stabilization and in most of the diseases are able to suspend immunosuppressive treatments.

The likelihood of a recurrence depends on the disease and the transplantation technique used. In principle, success is more likely in the early stages of the disease and in patients of a younger age. In the more advanced stages, there is a reduction of the effectiveness

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and increased toxicity related to the procedure.

In a retrospective analysis by the European Society for Blood & Marrow Transplantation performed on 900 patients, transplant-related mortality was mainly linked to the diagnosis (certain diseases lead to damage on the organism that increases procedure-related toxicity) and to the centre's experience, very probably due to the équipe having greater knowledge and to a better selection of eligible patients (see reference 1). It follows that this selection must be carried out by trained personnel and in accordance with the guidelines of the international scientific societies and the laws in force, in order to ensure that every patient receives a therapeutic proposal in which they are properly assessed for the risks and benefits.

Equally important is the correct information given to the patient, who must have full access to information on the treatment so that he/she is able to sign our consent form approved by our local Ethics Committee in full awareness.

## The transplantation technique

The autologous transplantation consists of three phases:

**1) Mobilization phase:** the stem cells from the bone marrow in the blood are mobilized by a combination of chemotherapy and hormone treatment that regulates the production of the blood cells. At the end of this phase, the stem cells are collected through a procedure of extracorporeal circulation, subject to strict biological controls and then frozen at -196°C.

**2) Conditioning therapy:** chemotherapy drugs are administered again to reset the immune system. One side effect of the conditioning therapy is a transient toxicity on the bone marrow, resulting in a drop of blood cells (White Blood Cells, Red Cells and Platelets), see below.

**3) Transplantation:** immediately after the conditioning therapy, the patient's stem cells are thawed and infused intravenously, like a normal transfusion. The stem cells return to the bone marrow (homing) and restore the normal bone marrow function in about two weeks after transplantation; in this period the patient must remain in a sterile environment to prevent immunosuppression complications and to be assisted by personnel who are specifically trained and skilled to assist these patients.

The patient can be discharged when the blood cell values have returned to normal.

## The Transplant Program for Autoimmune Diseases at Careggi University Hospital

The activity of autologous hematopoietic stem cell transplantation in severe autoimmune diseases began at Careggi University Hospital in 1998, thanks to the creation of an interdisciplinary network of specialists (neurologists, rheumatologists and gastroenterologists) who joined together with the haematologists to implement the program.

Over the following 16 years, our Center has achieved considerable visibility for both the volume of activity (according to EBMT data, updated in January 2013, Careggi University Hospital is the number one European center for the number of transplants performed), as well as the number of publications in scientific journals (see references 3, 7).

The activity of the Centre is well integrated into the European and American scientific

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societies for bone marrow transplantations, collaborating and coordinating initiatives on an international level (see references 2, 8, 9).

The most frequently treated disease is multiple sclerosis, followed by scleroderma. The clinical features of autoimmune diseases require the development of specific skills both on the medical side as on the nursing side; this is an added feature of our Center, where the special care and needs of the patients is of fundamental importance to us.

## Screening Process for HSC Transplant

The possibility of being included on the transplant program is evaluated by a team which includes a haematologist of the Transplant Center (TC) and a medical specialist in the patient's illness (Neurologist, Rheumatologist or Gastroenterologist).

This evaluation is carried out on the basis of the documentation sent by the patient to the administrative secretary and contact point ([bmtms-firenze@dmsc.unifi.it](mailto:bmtms-firenze@dmsc.unifi.it)). The request together with the documentation can also be sent by the patient's referring specialist.

The team may subsequently request additional test results for a better assessment as to the feasibility of the transplant. The patient will also be informed as to the economic aspects of the transplant and payment schedule.

Patients who are at this stage considered to be potential candidates will be invited to make an appointment at the Transplant Centre (Medical Assessment Team Consultation – see below).

In the case of patients who live far away (outside of Europe), the evaluation can be carried out by a Skype call only if full clinical documentation is available. The tests to be performed may vary based on the patient's pathology and will be communicated individually to the patient via email. The patient will also be informed as to the economic aspects of the transplant and payment schedule.

## Medical Assessment Team Consultation

The Medical Specialist of the illness for which the transplant is being evaluated (Neurologist, Rheumatologist, Gastroenterologist), the Haematologist physician and trial nurse of the program will all be present at this appointment.

During the screening consultation, the indication for the transplantation of haematopoietic stem cells for the patient in question will be evaluated and discussed fully with the patient. Only if the patient proves to be a candidate for the procedure, will the trial nurse arrange for any tests required to complete the screening and she will check for venous access.

A preliminary program for the mobilisation and transplantation procedures will be arranged together with the patient. Closer to these pre-arranged dates, the patient will be contacted to confirm the dates, to send any additional test results by email or fax to the contact point and for any additional information that the patient may require.

## Second Visit

This second appointment is made just before the patient is admitted to the transplant center for mobilization, and the TC specialist together with the trial nurse will be present who will carry out any final checks and tests. On this occasion, a bone marrow biopsy will be performed and the overall picture of the patient including lab will be evaluated along with any other specific tests that were carried out at the screening stage. This visit is usually arranged for about two weeks before admission for mobilization; if the patient

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lives a long way from the TC, the interval between this last visit and mobilization therapy will be reduced.

## Publications

1. Farge D, Labopin M, Tyndall A, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. *Haematologica* 2010;95:284-92.
2. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012;47:770-90.
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4. Saccardi R, Di Gioia M, Bosi A. Haematopoietic stem cell transplantation for autoimmune disorders. *Curr Opin Hematol* 2008;15:594-600.
5. Saccardi R, Kozak T, Bocelli-Tyndall C, et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. *Mult Scler* 2006;12:814-23.
6. Mancardi G, Saccardi R. Autologous haematopoietic stem-cell transplantation in multiple sclerosis. *Lancet Neurol* 2008;7:626-36.
7. Saccardi R, Mancardi GL, Solari A, et al. Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life. *Blood* 2005;105:2601-7.
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9. Pasquini MC, Griffith LM, Arnold DL, et al. Hematopoietic stem cell transplantation for multiple sclerosis: collaboration of the CIBMTR and EBMT to facilitate international clinical studies. *Biol Blood Marrow Transplant* 2010;16:1076-83.