Transplantation in the EU: From the waiting lists to post-transplantation journey

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Medical technology innovation and policy advancements are improving the transplantation experience for thousands of people in the European Union.

At the same time, issues such as organ shortages and long waiting lists need political action, as well as further steps in cross-border coordination and differences among different member states not only on transplantation but also on a post-transplantation journey.

In this series of articles, Euractiv is looking at the state of solid organ and stem cell transplantation in the EU.
EU lacks cross border cooperation in access to transplants, experts warn

With such extended waiting times, clear and reliable information must be made available, Professor Thomas Mueller of Zürich Hospital said during a hybrid event organised by the Spanish presidency of the EU Council on Thursday and Friday (9-10 November).

“The access and the allocation of transplants on the waiting list of patients should be very transparent. There should be a clear procedural process for how a patient is put on the waiting list, how a patient is treated, and there should be traceability,” Mueller said.

Shortages mainly concern kidneys. At the end of 2021, almost 10,000 patients from Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, and Slovenia were waiting for a kidney transplant, according to Eurotransplant data. However, fewer than 3,000 kidneys were transplanted that year across the countries mentioned.

Mueller highlighted the need for more cooperation between EU countries, insisting that “cross-border collaboration” would facilitate transplants and help patients find available organs.

According to him, every country should be self-sufficient and match the needs of its own population.

Spain: EU and world leader

Regarding access to transplants, Spain stands out as an exception, with the country currently leading in both world and European metrics in the transplant sector.

In 2020, there were around 37 organ donors per million inhabitants in Spain. By way of comparison, in 2019, this figure was 11 donors per million inhabitants for Germany, 25 for Italy and less than 30 for France, according to Esanum, a social network for doctors and scientists.

One of the reasons for this success is the number of doctors trained and skilled for realising transplants.

“More than 10,000 emergency professionals and nearly 2,000 ICU residents have been trained in the last 15 years,” said Daniel Gallego, from the European Kidney Patients’ Federation and the European Kidney Health Alliance, at the event organised by the Spanish presidency.

In total, Spain has nearly 200 medical centres in which organ donation is available. But there is a wide range of disparities between the different regions of the country, as is the case in other member states – and some regions only have minor centres.

As such, Spain has also developed mobile teams of doctors to make donations possible in all minor centres around the country. The teams are composed of “a surgeon, a transplant coordinator, and a perfusionist”, Gallego said.

The mobile teams have reduced the waiting list from six months in 2016 to approximately three months in 2023.

Support from the Commission

Despite organ donation and transplants being specific to each member state and depending on their health system, the European Commission is seeking ways to support European countries at the EU level.

“The European Commission is supporting national competent authorities (NCAs) by facilitating the sharing of information between them, including guidance from the European Centre for Disease Prevention and Control (ECDC), particularly during the COVID-19 crisis,” the EU executive said in a press release.

For example, the ECDC draws up plans for managing epidemic outbreaks where blood, tissues, cells and organs are detected. Recently, its latest assessments have focused on the Ebola virus, West Nile virus, Zika virus and hepatitis A.

The Commission and EU lawmakers are also working on the revision of safety and quality standards for substances of human origin (SoHO). The Spanish EU Council Presidency hopes to find a provisional deal before the presidency ends on 31 December.

All transplantations should have standards of care "as high as possible in every country" without "any compromise", Mueller concluded.
Stem cell transplant risks mitigated with stem cell therapies

By Marta Iraila | Euractiv.com

Languages: Deutsch

While stem cell transplants can save the lives of people living with different life-threatening conditions, they also entail risks for both donors and recipients, but new stem cell therapies might offer solutions.

Stem cell transplants treat conditions such as leukaemia, myeloma and lymphoma – in which the bone marrow is damaged and can no longer produce healthy blood cells. The replacement cells can either come from a patient’s body or a donor.

Every year, around 40,000 stem cell transplants take place in Europe, which continues to grow thanks to medical advances despite the slowdown during the COVID-19 pandemic in 2020.

More transplants mean that more patients receive the treatment they need. However, it also implies a greater need for post-transplant care and addressing diseases associated with the procedure.

One of the most tricky aspects of stem cell transplants is the need to find a suitable donor. For a person to be able to receive a transplant, there needs to be a match of human leukocyte antigens (HLA), which are proteins in most cells in your body that the immune system uses to see which cells belong in your body and which do not.

Tissue types are inherited, meaning the best chance to find a match is with a sibling from the same two biological parents. However, 70% of patients do not have a full match in their family, relying on external donors.

When this is the case, the probability of finding a match is not the same for everyone. There’s often a shortage of donors from diverse ethnic backgrounds, as patients from minority groups might have difficulty finding a suitable donor due to the genetic complexity of matching stem cells.

Another complex facet of donations is the possible complications after the procedure.

The most common side effect of a stem cell transplant is graft-versus-host disease (GVHD), a complication that occurs when the donor stem cells, the graft, attack healthy cells in the patient, the host.

Acute GVHD usually develops within the first 100 days after transplantation, and it affects approximately 30 to 60% of patients who undergo an allogeneic stem cell transplant.

Most of the risk factors that can contribute to GVHD are related to the donor – the older age of the donor, sex and whether there is an HLA mismatch.

And while recipients of a donation are exposed to risks, so are those who donate their stem cells.

Taking this into account and broadening the scope of donations, the European Parliament put forward an update on regulating substances of human origin (SoHO).

The text states that SoHOs should be obtained from individuals whose health status can guarantee that no adverse effects occur due to the donation.

The Parliament also adds that the regulation should include principles and technical rules to monitor and protect donors, which they consider “particularly important where the donation involves significant risk to the donor’s health”.

Stem cell transplants fall under this definition as there is a need for pre-treatment with medicinal products and a medical intervention to collect the substance.

“As different types of donation entail different risks for donors, with varying levels of significance, the monitoring of donor health should be proportionate to those levels of risk,” states the Parliament’s text.

The potential of new therapies

Anna Couturier, senior project manager at The European Consortium for Communicating Gene and Cell Therapy Information (EuroGCT), told Euractiv that the future of stem cell therapies moves away from traditional transplants to new advanced therapies (ATMPs) that will minimise the risks of donations and facilitate treatment.

“It cuts out the difficulties, this whole infrastructure that we have for donations, because you don’t have things like GVHD, you don’t have rejection from the body”, Couturier said.

These new therapies mean that the procedure won’t longer need an external donor as they will allow editing patient’s cells or genes without introducing any foreign actor.

According to the European Medicine Agency (EMA), stem cells are categorised as ATMPs when these cells undergo substantial manipulation or are used for a different essential function.

“We’re standing on an absolute precipice of approvals coming from the European Medicines Agency of new gene and cell therapies. In the next five years, it’s going to be unbelievable the differences in what treatments are available”, she said.

One of the examples of the potential of these therapies is Casgevy, a cell-based gene therapy medicinal product, which the EMA recommended for approval on 15 December.

This therapy is the first one that uses CRISPR/Cas9 technology, which allows editing of a patient’s blood stem cells.

Casgevy is indicated to treat transfusion-dependent beta-thalassemia and severe sickle cell disease, two inherited rare diseases caused by genetic mutations that affect the production or function of haemoglobin – the protein found in red blood cells that carries oxygen around the body. Both diseases are life-long, debilitating and life-threatening.

The EMA states that Casgevy is indicated for “patients 12 years of age and older for whom haemato-poietic stem cell transplantation is appropriate and a suitable donor is not available”.

Despite the big advances these therapies bring, Couturier added that “whether we are all up the task of making sure these new treatments reach patients safely, fairly, and accessibly is another question”.

She also worried about the need to stay cautious and the long way ahead in the next years to unleash these new treatments’ full potential.
Back to the future: Regenerating organs in the fight against shortages

By Amalie Holmgaard Mersh | Euractiv

Languages: Deutsch

With organs short in supply, we may have to rely on treatments for organ malfunctions, which are not dependent on human donors in the future. [Gorodenkoff/Shutterstock]

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In December 2022, around 52,000 patients were on waiting lists to receive a new organ, European Commission figures show. During 2022, a total of 27,952 patients had a transplant, the main ones being kidney, liver, heart, lung and pancreas.

The numbers speak for themselves. To accommodate this enormous demand, scientists are working hard to find solutions.

One of the potential solutions is animal-to-human transplantation, or xenotransplantation, with two transplants in the US involving genetically modified pig hearts.

Another future solution is artificial organs, which is still quite some way off. Researchers cannot grow whole organs in laboratories yet, said Micha Drukker, professor of stem cell biology, models and regenerative medicine at Leiden University.

What is showing promising developments, however, is the extraction and reprogramming of human stem cells, which can then be coaxed into specialised types of cells and inserted into a patient to regenerate fully or partially failing organs.

"Pluripotent stem cells are the beginning of everything. Basically, they can make all the cell types in the body," Drukker told Euractiv.

Scientists can get hold of those in two ways. One is to extract them directly from early human embryos to get what is called embryonic stem cells.

The second method, discovered by scientist Shinya Yamanaka in 2006 and earning him the Nobel Prize in 2012, works by taking mature cells from humans and reprogramming them to become induced pluripotent stem (IPS) cells – immature cells that can develop into all types of cells in the body.

Essentially, this means reversing time for the cells so scientists can reshape them into, for instance, pancreatic cells or heart cells.

"Stem cells are actually time machines," Drukker said, referencing the film Back to the Future.

By taking a little blood or a small piece of skin, mature cells can be reversed to a pluripotent state through a process called cellular reprogramming. Following this, scientists can guide them to become a pancreas cell or brain cell by using a process called differentiation.

"That’s why the notion of back to the future is important. You start from any age, go back to day one, and then you go back to the future and run the embryonic development again to make a liver or pancreatic cell," Drukker explained.

Promising trials for type 1 diabetics

How far science has come depends on the type of organ.

For type 1 diabetics, for whom the insulin-producing cells in the pancreas do not work, results in clinical trials so far are "extremely promising," said Drukker.

One US man with type 1 diabetes, who received an infusion with insulin-producing pancreatic islet cells, was even reportedly cured and the disease has so far not returned.

When it comes to other organs, success varies. For kidneys, for example, which are the most demanded organs, there is still a long way to go. Particularly because of their large, complex structure with many different types of tissue.

Essentially, this means reversing time for the cells so scientists can reshape them into, for instance, pancreatic cells or heart cells.

"You can make specific cell types of the kidney, but not the whole kidney yet. What we are good at now is re-making cells that are dysfunctional in specific organs," Drukker said, adding that kidney tissues are still in the early development stage.

"It’s not easy to repair. Typically the whole organ deteriorates as one. So the best approach is to replace everything, which is what people do today with kidney transplants," he added.

However, Drukker remains positive about the prospect of artificial organs as "just 15 years ago, none of this was possible."

Prioritising research

To continue development, scientists need the means to do it. While the field is moving forward in Europe, the process is significantly faster in the US and Japan, Drukker said, hinting that he would be happy to see the pace in Europe pick up.

Particularly investing more in automation and smart robotics, likely aided by artificial intelligence, would drive the research in a beneficial direction, he argued.

At the moment, scientists are working on induced pluripotent stem (IPS) cells from one person to treat the many, due to the extremely high cost of making the therapies in ultra-clean labs. This, however, can result in more immunological complications than providing patients with personalised treatment with their own cells.

But automated processes with the help of robots and AI could help upscale and drive the cost down to aid accessibility to the therapies – including the personalised ones.

"Ultimately, with more automation, you'll be able to offer better therapies, because they are basically your own cells," Drukker said.

With organs short in supply, we may have to rely on treatments for organ malfunctions, which are not dependent on human donors in the future. [Gorodenkoff/Shutterstock]
A new study shows that adverse effects in stem cell transplantation are less common when certain microbes are present in the patient’s gut, which opens possibilities to create better conditions synthetically and ensure safer outcomes.

Stem cell transplantations can help cure many haematological conditions – such as leukaemia, myeloma, and lymphoma – in which the bone marrow is damaged and can no longer produce healthy blood cells.

However, there are still considerable risks associated with them, like graft-versus-host disease (GVHD) and transplant-related mortality (TRM).

GVHD can happen after a stem cell transplantation, when in some cases the donor stem cells, the graft, attack healthy cells in the patient, typically in the skin, the gut or the liver.

It affects up to 30% of patients and can be severe. In some cases, patients respond to steroids, but in many others, they are refractory, reducing the survival outcomes and setting the mortality rate as high as 50%.

Some previous studies have shown that the probability of developing GVHD is related to the recipient’s microbiome, the community of bacteria, fungi, and viruses that reside in patients’ guts.

“There’s been quite a bit of interest in the microbiome because a few landmark studies have shown a correlation between the microbiome and outcomes in stem cell transplantation,” Erik Thiele Orberg from TUM (Technical University of Munich) told Euractiv.

“We didn’t understand the mechanisms that underlie and confer this effect,” he explained.

Along with a team of researchers from the TUM and the Universitätsklinikum Regensburg (UKR), Thiele Orberg has tried to fill some of the knowledge gaps in a study.

According to Thiele Orberg, these findings will help identify individuals at risk of developing these adverse reactions during stem cell transplantation.

In the study, researchers analysed stool samples from a cohort of patients undergoing stem cell transplantation and confirmed that patients with a higher bacterial diversity had better outcomes, including reduced mortality, lower transplant-related mortality, and less relapse.

They aimed to identify metabolites – substances produced by gut bacteria during metabolism – that could influence immune responses in patients undergoing stem cell transplantation and identify the microbiome contributing to their production.

Thiele Orberg explained that they were able to find which consortia of protective bacteria, bacteriophages, and metabolites are highly associated with beneficial outcomes and are useful in identifying their lack in patients, creating a risk of developing GVHD and transplant-related mortality.

**New possibilities for future procedures**

The researcher’s next step is to figure out how to create this beneficial landscape in the recipient’s guts.

The study’s findings suggest that it may be possible to use synthetic bacteria consortia to produce the protective metabolites identified in the study to improve the transplantations’ outcomes.

All these new data, Thiele Orberg added, could also be used to improve other already established procedures, like faecal microbiota transplantation (FMT), the transplant of faecal matter from a donor into the intestinal tract of a recipient to change their microbiome.

“It is currently being researched in several advanced clinical trials, but we still have the same burning questions in that field, namely what makes a donor a good donor [for FMT] and why do some patients respond and others don’t,” he explained.

One of the current hypotheses, backed by early pilot experiments, is that the patients who respond to FMT are those able to kick-start their metabolite production after the procedure.

With these new findings, Thiele Orberg explained that a future standard procedure to ensure better outcomes could go as follows:

A patient undergoing stem cell transplantation would be continuously screened using the immune modulatory metabolite risk index. Once a patient is considered to be at risk, they could be prophylactically treated using metabolite cocktails or precision FMT products from donors that have been previously validated for robust metabolite production.

All these discoveries open new investigative paths not only for stem cell transplantation but also for new microbiome studies in other cell therapies.
**PROMOTED CONTENT**

Why a successful transplant is only half the patient journey

By Olivier Charmeil | Sanofi

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**By Olivier Charmeil | Sanofi**

People often think that the process of organ or stem cell transplantation ends once the patient receives the transplant. But this, in fact, is only half of the patient journey.

Olivier Charmeil is the Executive Vice President of General Medicines, Sanofi.

We’ve all probably heard about organ or stem cell transplants. Limited attention is being paid to what happens after a transplant has been performed. Yet, it is this period of so-called post-transplant care, which can last multiple years, that poses many challenges to transplant patients – both for their survival and quality of life. These challenges need greater attention and awareness across Europe, not only for solid organ but also for stem cell transplants.

The challenges of post-transplant care

Hematopoietic stem cell transplants, more commonly called bone marrow transplants, are a medical procedure for managing or curing life-threatening diseases such as lymphoma or leukaemia, as well as other debilitating diseases like multiple sclerosis. Leukaemia on its own accounts for a significant share of the 320,000 new blood cancer cases diagnosed every year in Europe, underlining just how large the patient population is that may eventually benefit from stem cell transplants.

As the number of stem cell transplants grow, there is an increasing need for post-transplant care, with many patients experiencing different complications. One of the most common of these complications is Graft-Versus-Host Disease (GVHD), where the recipient’s tissues and organs get inflamed or damaged because the donor’s immune system cells attack them.

Up to 50% of patients who received a donated stem cell transplant develop chronic GVHD, causing them significant physical discomfort and pain, joint stiffness, muscle weakness, fatigue, liver dysfunction, and difficulty breathing. These are only some of the symptoms of chronic GVHD, which can impact people’s ability to go about their everyday lives. The disease also leaves a mark on people’s mental wellbeing, with almost one-in-three patients experiencing depression and anxiety, further impacting their quality of life.

Beyond the individual impact, chronic GVHD places a significant long-term socioeconomic burden on healthcare systems, in particular specialised care resources, and on society through the loss of productivity due to sickness.

Low awareness of the diverse and evolving nature of GVHD symptoms among patients, relatives, and healthcare providers can lead to delays in diagnosis of chronic GVHD, making it treatment challenging and contributing to poor outcomes for transplant patients. Unfortunately, GVHD is one of the main causes of morbidity following stem cell transplants, with more than 30% of patients experiencing GVHD dying from this complication.

This may seem like a discouraging number, but I firmly believe that it is within our power to make sure that more people can benefit from life-saving stem cell transplants without suffering from GVHD as a consequence. Among others, I see two key areas of action to address this challenge: greater awareness and more effective treatments.

**Together for increased GVHD awareness**

It’s hard to effectively tackle a problem that only few people know about. Therefore, our first step is in limiting the effects of GVHD and ensuring that patients receive optimal post-transplant care needs to focus on making patients, their relatives, and healthcare providers more aware of the signs of the disease. This will help them recognise symptoms sooner, paving the way for more timely, effective, and comprehensive care.

Improving post-transplant care requires joint action by the whole GVHD community – and it’s promising to see that first steps in this direction are already being taken around the globe. The GVHD Alliance, which is celebrating its second anniversary this month, is one such joint initiative. Founded in the USA, the Alliance is making its way to Europe and works to improve the lives of people with GVHD through educational, advocacy, and awareness raising activities, including global GVHD Day. Taking place on 17 February every year, and for only the second time in 2024, this day unites people in their efforts to highlight GVHD patients’ needs and calls for change as well as better post-transplant care.

**Chasing the miracles of science to fight GVHD**

To ensure this better care for GVHD patients, effective treatments are needed. Stem cell transplant is a growing, but complex and often still underserved therapeutic area. Despite this, advances in scientific research over the past decades have already produced several medicines that help people fight GVHD and get back to living full lives post-transplant.

However, we cannot rest on our laurels. The mainstay treatment for chronic GVHD can have various side effects and more than 50% of patients eventually stop responding to it, leaving those living with GVHD with a need for new treatment options which can help improve their symptoms and long-term outcomes. This is why innovation and R&D efforts to produce medicines for GVHD should not only continue but intensify. This is what we are committed to at Sanofi. For over 40 years, we have been working to bring transformative therapies to transplant patients. We continue to chase the miracles of science and leverage our research expertise to bring more solutions to patients in need of stem cell transplants.

A brighter future for transplant patients

Through common efforts, we can help foster Europe’s leadership across the entirety of the patient’s transplant journey. This requires that European policymakers, healthcare providers, academia, regulators, and pharmaceutical companies join forces and lead cross-border collaboration to address the unmet needs of post-transplant care and the GVHD patient community.

Only by working together can we expand treatment options and ensure availability as well as timely patient access to life-saving solutions, so that no transplant patient is left behind.
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