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Julio VOLTARELLI, *et al.*
Bone Marrow Stem Cells vs Diabetes

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'Rebuilt' immune system shakes off diabetes
By Roxanne Khamsi

Diabetics appear to have been cured with a one-off treatment that rebuilds their immune system, according to a new study.

The technique, which uses patients' own bone marrow cells, has freed 14 of 15 patients with type 1 diabetes from their dependence on insulin medication.

So far, participants in the trial have gone 18 months without insulin therapy following the procedure, on average. One patient has lasted three years without needing such injections.

In patients with type 1 diabetes, which typically strikes in early childhood or adolescence, the immune system appears to erroneously attack cells in the pancreas that produce the hormone insulin. Without insulin, blood sugar levels in the body spiral out of control. People with diabetes receive insulin therapy, often in the form of self-injected shots, to keep their blood sugar levels under control.

Wipe out

Scientists have speculated that "resetting" the immune system might stop it from attacking the insulin-producing cells in the pancreas.

Julio Voltarelli, at the University of Sao Paulo in Brazil, and colleagues recruited 15 people aged 14 to 31 years who had recently been diagnosed with type 1 diabetes. Roughly 60% to 80% of these patients' insulin-producing cells had been destroyed by the time of their diagnosis, and all needed regular insulin shots.

The researchers removed bone marrow stem cells from the patients, who were then given drugs such as cytotoxan to wipe out their immune cells. Without an immune system, the patients were vulnerable to infection and so they were given antibiotics and kept in an isolation ward. They participants did not undergo radiation treatment – as leukaemia patients often do as part of a bone marrow transplant – and so had fewer side effects and less risk of organ damage.

Two weeks later, the patients received infusions of their own stem cells into their bloodstream via the jugular vein, which re-established their immune systems.

Throughout this time and following the stem cell transplant, the research team continued taking blood samples to assess how much insulin each patient required.

Free for life?

Of the 15 patients, 12 no longer needed insulin shots within a few days of undergoing the procedure. One patient from the group had a relapse and needed to take insulin for one year, before becoming insulin-independent again – and has remained this way for 5 months.

Of the remaining two participants, one stopped needing insulin shots for one year after the transplant but has spent the past two months back on the shots, and the final participant's diabetes did not respond to the stem cell treatment.

Those who responded to the treatment have not needed insulin shots – so far, for an average 18 months – and had not relapsed at the time of study publication. One patient had gone as long as 35 months without needing insulin therapy. "It may be that they become insulin-free for life. We don't know," says Voltarelli.

Exactly why some patients responded to the treatment and one did not remains a mystery. "It could be due to differences in genetic background or severity of the immune attack," Voltarelli suggests.

During the course of the trial, one patient developed pneumonia as a result of the immune-suppressing drugs used in the procedure. Two others developed complications, including thyroid dysfunction and early menopause, but it is not clear if these relate to the stem cell transplant

Honeymoon period

Jay Skyler, who heads the Diabetes Research Institute at the University of Miami in Florida, US, cautions that the trial did not include a control group. Skyler adds some people experience a remission of symptoms shortly after being diagnosed with type 1 diabetes, and the increase in insulin production seen among study participants might be related to this "honeymoon period".

Skyler also notes it is unclear exactly how the insulin production in the patients increased.

Still, he says that the trial has "shown some potentially promising results". And Voltarelli is hopeful that this type of approach could help patients with type 1 diabetes avoid some of the long-term complications that arise from the illness, such as kidney, eye and nerve damage, which result from chronically high levels of blood sugar.

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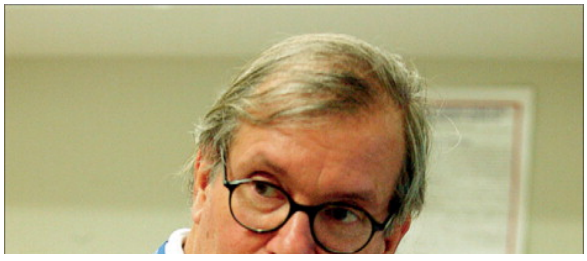
Julio Voltarelli



Leading expert in stem cell transplantation for the treatment of autoimmune diseases. Born on Dec 17, 1948, in Fernandópolis, Brazil, he died of complications of a liver transplant on March 21, 2012, in Blumenau, Brazil, aged 63 years.

Julio Voltarelli's passion and vision was to be able to modify the immune system in order to change a disease's course. As the coordinator of the Bone Marrow Transplant Unit at the Ribeirão Preto School of Medicine at the University of São Paulo in Brazil, Voltarelli was one of the first researchers in the world to use haemopoietic stem cells found in bone marrow to treat autoimmune diseases. “Julio was a pioneer driven by an internal compass, directed by uncanny intuition, steadied by intellect, and grounded by sincerity and honesty to improve this world through restoring to people what disease had extinguished”, says Richard Burt, associate professor and Chief of the Division of Medicine-Immunotherapy for Autoimmune Diseases at Northwestern University Feinberg School of Medicine in Chicago, USA. Since 2001, Voltarelli's team has undertaken almost 200 stem cell transplantations for autoimmune diseases, including type 1 diabetes, multiple sclerosis, systemic sclerosis, and lupus.

Working with Burt, Voltarelli developed a protocol for transplanting stem cells in patients with type 1 diabetes. The researchers first removed cells from the bone marrow of patients and then treated the patients with radiation to destroy their immune systems, which were attacking the pancreatic ß cells responsible for producing insulin. Patients' stem cells were then injected back into their bone marrow in the hope of repopulating the pancreas with functioning ß cells. Voltarelli and his colleagues reported that 20 out of 23 patients who received the treatment no longer needed to inject insulin to control their blood sugar levels; for some, the treatment was effective for up to 3 years. It was, the researchers wrote in the Journal of the American Medical Association in 2009, “the only treatment capable of reversing type 1 DM [diabetes mellitus] in humans” at that time.

Voltarelli encountered doubt and resistance from colleagues who questioned why diabetes should be treated with a high-risk transplantation procedure, according to Maria Carolina Oliveira, a staff physician in the Department of Internal Medicine at the Ribeirão Preto School of Medicine, who worked closely with Voltarelli. But the improvement in patients' quality of life with treatment and the possibility that chronic complications, such as eye and kidney disease, would diminish as a result validated Voltarelli's efforts. His contribution in Brazil was important, says Oliveira: “He will definitely be remembered for his courage and audacity. He started something new in the country and worked against other people's opinion, especially concerning the type 1 diabetes stem cell transplantation protocol.”

Voltarelli graduated from the Ribeirão Preto School of Medicine at the University of São Paulo in 1972 and completed a residency in internal medicine and haematology there 2 years later. He received a doctorate in haematology and clinical immunology from the same institution in 1981 and then completed postdoctoral fellowships in the USA at the University of California, San Francisco, the Fred Hutchinson Cancer Research Center in Seattle, and the Scripps Research Institute in San Diego. In 1992, he returned to Brazil and established the Bone Marrow Transplant Unit at the

Ribeirão Preto School of Medicine.

Over the course of his career, Voltarelli published more than 130 articles and edited the first book in Portuguese on stem cell transplantation and clinical immunology; he was also on the editorial board of the journal Cell Transplantation. Shortly before his death, his colleagues elected him President of the Brazilian Society of Bone Marrow Transplantation. Voltarelli lobbied for the creation of a national transplant register in Brazil and for the certification of physicians who perform transplantations in the country. “He was the most loyal and correct scientist I ever worked with. He was extremely smart but extremely modest. He always discussed all of the protocols and projects with the whole group, taking into account all opinions”, remembers Belinda Simoes, who worked with Voltarelli for 20 years and who is the current coordinator of the Bone Marrow Transplant Unit. Voltarelli is survived by his wife and two daughters.

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Acute Response of Peripheral Blood Cell to Autologous Hematopoietic Stem Cell Transplantation in Type 1 Diabetic Patient

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Abstract

Objective

Autologous nonmyeloablative hematopoietic stem cell transplantation (AHST) was the first therapeutic approach that can improve ß cell function in type 1 diabetic (T1D) patients. This study was designed to investigate the potential mechanisms involved.

Design and methods

We applied AHST to nine T1D patients diagnosed within six months and analyzed the acute responses in peripheral blood for lymphocyte subpopulation as well as for genomic expression profiling at the six-month follow-up.

Results

We found six patients obtained insulin free (IF group) and three remained insulin dependent (ID group); C-peptide production was significantly higher in IF group compared to ID group. The acute responses in lymphocytes at six-month follow-up include declined CD3+CD4+, CD3+CD8+ T cell population and recovered B cell, NK cell population in both groups but with no significant differences between the two groups; most immune-related genes and pathways were up-regulated in peripheral blood mononuclear cell (PBMC) of both groups while none of transcription factors for immune regulatory component were significantly changed; the IF group demonstrated more AHST-modified genetic events than the ID group and distinct pattern of top pathways, co-expression network as well as ‘hub’ genes (eg, TCF7 and GZMA) were associated with each group.

Conclusions

AHST could improve the islet function in newly diagnosed T1D patients and elimination of the islet specific autoreactive T cells might be one of the mechanisms involved; T1D patients responded differently to AHST possibly due to the distinct transcriptional events occurring in PBMC.

Type 1 diabetes (T1DM) is an organ specific autoimmune disease, resulting from chronic immune attack against pancreatic beta cells [1]. Although it is thought to be mediated mainly by T helper 1 cells, a complex interaction of immune cells including CD4+T cell, CD8+Tcell and innate immune cell NK cell, B cell and antigen presentation cell is actually involved in the pathogenesis [2]. This course of immune-destruction is subclinical until approximately 60% to 80% of the beta-cell mass is destroyed, when the amount of beta-cell mass is insufficient to maintain glucose homeostasis and the clinical diagnosis of T1DM is established [3]. The best-established treatment is to tightly control the blood glucose by intensive insulin therapy [4]. However, long-term substitutive insulin therapy is still associated with major constraints and lack of effectiveness in preventing chronic vascular and neurological complications. Immunointervention therapy, which targets the causal pathogenic mechanism, therefore, may represent the only sensible strategy. Clinical trial of immunosuppression drugs (cyclosporine), antigen therapy (GAD) or immunoregulatory agents (anti-CD3 antibody) have obtained efficacy in patients with T1DM, however obstacles such as adverse effects, lack of long-lasting improvement and especially the exogenous insulin requirement remain still as a medical challenging [5].

In 2007, Julio C. Voltarelli's group reported the first clinical trial using AHST as a potential approach in cases of T1D [6]. Indeed, for the first time these studies demonstrated that AHST led to prolonged insulin independence coupled with a significant increase of c-peptide production. A follow-up study published two years later confirmed the insulin independence was due to improved ß cell function instead of a prolonged honeymoon [7]. Therefore, AHST has been the only T1D-related management shown to preserve ß cell function. However, AHST requires a relatively aggressive immune-intervention and complications such as pneumonia and endocrine dysfunction have been noted. Therefore, a need exists to be able to target those patients who will receive the most benefit from AHST and to further clarify the mechanisms involved in ß cell function recovery so that the strategy can be optimized and a broader patient population can benefit from this treatment approach.

In this study, we applied AHST therapy to a group of nine patients with newly diagnosed T1D and specifically investigated their immune reconstitution, as well as performed transcriptome profiling on their PBMC pre-treatment and six months post-treatment to identify the acute responsive events, which might give helpful insights to clarify the therapeutic mechanisms...

Results
We found six patients obtained insulin free (IF group) and three remained insulin dependent (ID group); C-peptide production was significantly higher in IF group compared to ID group. The acute responses in lymphocytes at six-month follow-up include declined CD3+CD4+, CD3+CD8+ T cell population and recovered B cell, NK cell population in both groups but with no significant differences between the two groups; most immune-related genes and pathways were up-regulated in peripheral blood mononuclear cell (PBMC) of both groups while none of transcription factors for immune regulatory component were significantly changed; the IF group demonstrated more AHST-modified genetic events than the ID group and distinct pattern of top pathways, co-expression network as well as ‘hub’ genes (eg, TCF7 and GZMA) were associated with each group.
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Voltarelli Nicholas Zavazava
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Immunological Applications of Stem Cells in Type 1 Diabetes

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Current approaches aiming to cure type 1 diabetes (T1D) have made a negligible number of patients insulin-independent. In this review, we revisit the role of stem cell (SC)-based applications in curing T1D. The optimal therapeutic approach for T1D should ideally preserve the remaining ß-cells, restore ß-cell function, and protect the replaced insulin-producing cells from autoimmunity. SCs possess immunological and regenerative properties that could be harnessed to improve the treatment of T1D; indeed, SCs may reestablish peripheral tolerance toward ß-cells through reshaping of the immune response and inhibition of autoreactive T-cell function. Furthermore, SC-derived insulin-producing cells are capable of engrafting and reversing hyperglycemia in mice. Bone marrow mesenchymal SCs display a hypoimmunogenic phenotype as well as a broad range of immunomodulatory capabilities, they have been shown to cure newly diabetic nonobese diabetic (NOD) mice, and they are currently undergoing evaluation in two clinical trials. Cord blood SCs have been shown to facilitate the generation of regulatory T cells, thereby reverting hyperglycemia in NOD mice. T1D patients treated with cord blood SCs also did not show any adverse reaction in the absence of major effects on glycometabolic control. Although hematopoietic SCs rarely revert hyperglycemia in NOD mice, they exhibit profound immunomodulatory properties in humans; newly hyperglycemic T1D patients have been successfully reverted to normoglycemia with autologous nonmyeloablative hematopoietic SC transplantation. Finally, embryonic SCs also offer exciting prospects because they are able to generate glucose-responsive insulin-producing cells. Easy enthusiasm should be mitigated mainly because of the potential oncogenicity of SCs.

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Stem cell therapy for type 1 diabetes mellitus: a review of recent clinical trials.

Couri CE, Voltarelli JC.

Abstract
Stem cell therapy is one of the most promising treatments for the near future. It is expected that this kind of therapy can ameliorate or even reverse some diseases. With regard to type 1 diabetes, studies analyzing the therapeutic effects of stem cells in humans began in 2003 in the Hospital das Clínicas of the Faculty of Medicine of Ribeirão Preto - SP USP, Brazil, and since then other centers in different countries started to randomize patients in their clinical trials. Herein we summarize recent data about beta cell regeneration, different ways of immune intervention and what is being employed in type 1 diabetic patients with regard to stem cell repertoire to promote regeneration and/or preservation of beta cell mass.The Diabetes Control and Complications Trial (DCCT) was a 7-year longitudinal study that demonstrated the importance of the intensive insulin therapy when compared to conventional treatment in the development of chronic complications in patients with type 1 diabetes mellitus (T1DM). This study also demonstrated another important issue: there is a reverse relationship between C-peptide levels (endogenous indicator of insulin secretion) chronic complications - that is, the higher the C-peptide levels, the lower the incidence of nephropathy, retinopathy and hypoglycemia. From such data, beta cell preservation has become an additional target in the management of T1DM 1.
