



Letter to the Editor

Is it time to use hematopoietic stem cell transplantation for severe and refractory crohn's disease?

Dear Editor

Autoimmune diseases affect 3% of the world's population. In the United States, it is estimated that 20 million people are affected by one of the 80 known autoimmune diseases, including Crohn's Disease (CD).¹

The CD is a heterogeneous, unpredictable, severe, chronic, remitting-relapsing disease that can affect any part of the digestive tract. Diarrhea, abdominal pains and complications resulting from fistulas and perianal disease are frequent in affected individuals and exert an impact on the quality of life. The therapy includes anti-inflammatory, immunomodulating or immunosuppressant drugs, or glucocorticoids. At the present time, the gold standard treatment for most patients is the use of the biologic agents, such as tumor necrosis alpha factor antagonists, integrin alpha 4 beta 7 inhibitors or interleukin 12/23 blockers, such as Ustekinumab. All these biological agents are available in Brazil and none are considered superior to the others. Moreover, there is no defined criterion for the indication of any of these agents when one has failed. Both primary and secondary failed responses are described, along with unacceptable immediate and long-term side effects in many patients. Therefore, although biological agents have had positive results regarding the control of CD, the cure is far from being achieved and many patients remain without a treatment option.¹

The background for hematopoietic stem cell transplantation (HSCT) for CD occurred in patients who had concomitant neoplastic disorders, such as lymphoma or leukemia.² The first two patient reports of HSCT treatment for CD alone were published in 2003.³ These were followed by a number of case series and a randomized study involving 45 patients, which was published by the European group ASTIC, with the initial conclusions that HSCT is a beneficial procedure for CD.^{4–6}

The first case report in Brazil was published in 2015 and gave rise to a clinical project for CD with autologous unselected HSCT (US Clinical Trials NCT 03000296) involving 40 patients.⁷ In a sample of 14 patients, significant improvements

were found 30 days after the procedure, with the normalization of the CD activity index, low toxicity and improvements in quality of life.⁸

Clinical, relapse-free survival is higher than 90% one year after the procedure and 57% after three years. Survival free of glucocorticoids, medications and surgical procedures after five years is 70, 80 and 60%, respectively.⁴

These data lead us to claim that there is a place for HSCT in the treatment of CD, for which the death rate is low and the morbidity stemming from the procedure can be controlled. Based on the literature and data cited, it is evident that HSCT has benefits in the remission of symptoms without the long-term use of medications for patients with CD and other autoimmune diseases that are refractory to conventional treatment.⁹ However, in order to achieve success in the treatment and avoid severe outcomes, the procedure should be performed at experienced centers. Furthermore, the patient selection should be judicious. The HSCT is not indicated, depending on the patient's overall health status and existing comorbidities.⁶ A gastroenterologist is fundamental in the selection and management of patients, who should be referred as soon as possible after they become refractory to conventional treatments.⁹

Thus, we consider it urgent that experienced centers in Brazil work together in making new studies to perform the procedure, under careful patient selection and using unified protocols and prospective data collection.

REFERENCES

1. Lichtenstein GR, Loft EV, Isaacs KL, Regueiro MD, Gerson LB, Methodologist MG, et al. ACG clinical guideline: management of crohn's disease in adults. *Am J Gastroenterol*. 2018;113(4):481–517.
2. Kashyap A, Forman SJ Autologous bone marrow transplantation for non-Hodgkin's lymphoma resulting in long term remission of coincidental Crohn's disease. *Br J Haematol*. 1998;103:651–2.

3. Burt RK, Traynor A, Oyama Y, Craig R. High dose immune suppression and autologous haematopoietic stem cell transplantation in refractory Crohn's disease. *Blood*. 2003;101(5):2064–6.
4. Burt RK, Craig RM, Milanetti F, Quigley K, Gozdziak P, Bucha J, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. *Blood*. 2010;116(26):6123–32.
5. Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, et al. Autologous hematopoietic stem cell transplantation for refractory crohn disease. *JAMA*. 2015;314(23):2524–34.
6. Lindsay JO, Allez M, Clark M, Labopin M, Ricart E, Rogler G, et al. ASTIC trial group; European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party; European Crohn's and Colitis Organisation Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial. *Lancet Gastroenterol Hepatol*. 2017;2(6):399–406.
7. Ruiz MA, Kaiser Junior RL, Gouvêa Faria MA, De Quadros LG. Remission of refractory Crohn's disease after autologous hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter*. 2015;37(2):136–9.
8. Ruiz MA, Kaiser RLJ, De Quadros LG, Piron-Ruiz L, Peña-Arciniegas T, Faria MA, et al. Low toxicity and favorable clinical and quality of life impact after non-myeloablative autologous hematopoietic stem cell transplant in Crohn's disease. *BMC Res Notes*. 2017;10(1):495.
9. Snowden JA, Sharrack B, Akil M, Kiely DG, Lobo A, Kazmi M, et al. Autologous Haematopoietic stem cell transplantation (aHSCT) for severe resistant autoimmune and inflammatory disease—a guide for the generalist. *Clin Med*. 2018;18(4):329–34.

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