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Stem Cell Transplantation for Refractory Crohn Disease

To the Editor The Autologous Stem Cell Transplantation International Crohn Disease (ASTIC) trial by Dr Hawkey and colleagues[1] was interpreted as a failure of autologous hematopoietic stem cell transplantation (HSCT) compared with standard care. However, the ASTIC trial used a complex multifaceted primary end point that included all of the following: Crohn disease activity index less than 150; no active treatment; and endoscopic and radiologic remission. This end point has not been used in any prior study. The data from such a small cohort of patients would have been interpreted as encouraging if the authors had used some of their secondary outcomes as the primary end point, for example, Crohn disease activity index change from baseline (P = .04) or simple endoscopic score of Crohn disease change from baseline (P = .03).

Autologous stem cells are a supportive blood product infused to hasten hematopoietic recovery.[2] The toxicity and therapeutic effect are derived from the immune ablative drugs in the conditioning regimen.[2] In the ASTIC trial, all patients were treated with cyclophosphamide (4 g/m^2) and thereafter randomized to either continued standard of care or transplantation using cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin. The change in dosing based on surface area and body weight is confusing, but 4 g/m^2 is approximately 100 mg/kg, and this rough equivalence is important in understanding the toxicity and comparative efficacy of treatments.

The maximal allowed dose of cyclophosphamide during transplantation is 200 mg/kg.[3] At higher doses, patients develop cardiac dysfunction and hepatic sinusoid obstructive syndrome.[3] By treating the transplantation group with 100 mg/kg (4g/m^2) of cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) to mobilize stem cells, followed within 19 to 63 days with 200 mg/kg cyclophosphamide, patients in the transplantation group received a total of approximately 300 mg/kg cyclophosphamide. The transplant death from sinusoid obstructive syndrome may have been secondary to a trial design that markedly exceeded, in some cases within a short interval of time, the maximal allowed dose (200 mg/kg) of cyclophosphamide. Mobilization of stem cells in patients with autoimmune diseases is, depending on the disease, more safely performed with either 2 g/m^2 cyclophosphamide and G-CSF or with G-CSF alone.

The control group received a cyclophosphamide dose (4g/m^2, or approximately 100 mg/kg) equivalent to half a transplant dose of cyclophosphamide (200 mg/kg). In reality, the ASTIC trial did not compare transplantation with standard care but rather compared 2 experimental treatments, both based on high-dose cyclophosphamide.

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In Reply The ASTIC trial was designed to investigate the possibility, suggested by a number of case reports, that long-term, drug-free cure of Crohn disease could be achieved through autologous HSCT.[1] The lack of statistical significance of the primary end point showed that this experience is rare. However, we agree with Dr Burt and colleagues that the extent of improvement in secondary end points suggests possible therapeutic efficacy, albeit falling short of cure.

Burt and colleagues are correct that the ASTIC trial did not investigate the effectiveness of HSCT over standard care because the control group also underwent mobilization that may have had a clinically beneficial effect in its own right and that would have resulted in an underestimate of the overall effectiveness of HSCT. However, clinical and endoscopic parameters in the control group that underwent mobilization but not conditioning and transplantation were not significantly different at 1 year compared with baseline.

Burt and colleagues suggest the dose of cyclophosphamide used was too high. However, the reference they quote does not specifically address this question,[2] and there is not an established consensus about this issue. We used the

same recommended regimen[3] as the recent ASTIS trial.[4] Although it is possible that cyclophosphamide provoked sinusoid obstructive syndrome in the patient who died, this syndrome is more firmly established as a complication of busulphan-containing regimens,[2] and our case was atypical as the liver appearance and results of liver function tests were normal 4 days into the patient's final illness. However, in the ASTIC trial there were 5 cases for which a lower dose of cyclophosphamide was used for mobilization, which was successful in all of them. We believe the data suggest further study may be warranted to assess the clinical effect and safety of HSCT comparing a reduced-intensity mobilization and conditioning regimen with standard care in patients with refractory Crohn disease.

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Lung Volume Reduction Coils for Severe Emphysema

To the Editor The REVOLENS trial[1] found that bronchoscopic treatment with nitinol coils vs usual care improved exercise capacity in patients with severe emphysema and adds to the growing literature on endobronchial treatment of emphysema.[2,3]

Although bronchoscopic emphysema treatment devices have been commercially available in Europe for several years, there are currently no devices for bronchoscopic lung volume reduction approved by the US Food and Drug Administration on the market in the United States. As with other procedural or surgical techniques, lung volume reduction coil placement complications are often linked to operator experience and local expertise. Thus, the results of this study, conducted in France, might be significantly different if conducted in a country like the United States where such devices are not available apart from clinical trials. In addition, because of practitioner-level variation and the fact that 10 centers participated in the REVOLENS trial, it would be helpful to see the outcomes stratified by center to account for local variation.

Although the improvement in the 6-minute walk test was almost twice the minimum clinically important difference for 36% of patients in the study group, the majority in the coil group did not meet the prespecified criteria for effectiveness. Further research is needed to better define the population that will benefit most from the intervention. Zoumot and colleagues[4] suggested that multidisciplinary emphysema teams are the best way to ensure adequate patient selection and optimal utilization of resources for better outcomes.

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In Reply We agree with Drs Jabuonski and Lazarus that both operator expertise and a multidisciplinary approach are important for emphysema treatment.

To minimize the effect of operator experience and for safety reasons, the first 3 procedures in each center with no experience with lung volume reduction coil treatment (7 of 10 centers in the REVOLENS study) were proctored by a physician who had performed at least 10 such procedures. Jabuonski and Lazarus propose analyzing the outcomes stratified by center. However, the limited number of patients treated by lung volume reduction coils in each center (mean, 5 patients per center) does not allow any robust statistical analyses stratified by center. They also state that "the results of this study might be significantly different in a country like the United States where such devices are not available apart from clinical trials." In France, lung volume reduction coil treatments have also so far only been used in clinical trials. A large randomized multicenter study (the RENEW study) involving 26 sites with 20 sites in the United States was recently published and found a modest improve-