Original Investigation

Autologous Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease
A Randomized Clinical Trial

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IMPORTANCE Case reports and series suggest hematopoietic stem cell transplantation (HSCT) may benefit some patients with Crohn disease.

OBJECTIVE To evaluate the effect of autologous HSCT on refractory Crohn disease.

DESIGN, SETTING, AND PARTICIPANTS Parallel-group randomized clinical trial conducted in 11 European transplant units from July 2007 to September 2011, with follow-up through March 2013. Patients were aged 18 to 50 years with impaired quality of life from refractory Crohn disease not amenable to surgery despite treatment with 3 or more immunosuppressive or biologic agents and corticosteroids.

INTERVENTIONS All patients underwent stem cell mobilization before 1:1 randomization to immunoablation and HSCT (n = 23) or control treatment (HSCT deferred for 1 year [n = 22]). All were given standard Crohn disease treatment as needed.

MAIN OUTCOMES AND MEASURES Sustained disease remission at 1 year, a composite primary end point comprising clinical remission (Crohn Disease Activity Index (CDAI) <150 [range, 0-600]), no use of corticosteroids or immunosuppressive or biologic drugs for at least the last 3 months, and no endoscopic or radiological evidence of active (erosive) disease anywhere in the gastrointestinal (GI) tract. Secondary outcomes were individual components of the primary composite outcome and other measures of disease activity, laboratory results, quality of life and functional status, and GI tract imaging.

RESULTS Twenty-three patients underwent HSCT and 22 received standard treatment (controls). There were no statistically significant between-group differences in proportions of patients achieving sustained disease remission, CDAI less than 150 in the last 3 months, or freedom from active disease; there was a statistically significant difference among patients able to discontinue active treatment in the last 3 months. There were 76 serious adverse events in patients undergoing HSCT vs 38 in controls; 1 patient undergoing HSCT died.

	No. (%)			
	HSCT	Control	Difference (95% CI), %	*P* Value
Sustained disease remission	2 (8.7)	1 (4.5)	4.2 (−14.2 to 22.6)	.60
Secondary outcomes				
No active treatment	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	.01
CDAI <150	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.052
Free of active disease	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.054

CONCLUSIONS AND RELEVANCE Among adult patients with refractory Crohn disease not amenable to surgery who had impaired quality of life, HSCT, compared with conventional therapy, did not result in a statistically significant improvement in sustained disease remission at 1 year and was associated with significant toxicity. These findings do not support the widespread use of HSCT for patients with refractory Crohn disease.

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Crohn disease is a chronic relapsing inflammatory condition of the gastrointestinal (GI) tract that can result in lifelong ill health, impaired quality of life, and reduced life expectancy.[1] Immunosuppressive drugs are standard of care for Crohn disease, but some patients do not respond or lose response to treatment.[1-3] Hematopoietic stem cell transplantation (HSCT) might have a role to play in some of these treatment-resistant cases.[4-10] Crohn disease has a strong polygenic immune component,[1] even though it is not a classic autoimmune condition. Allogeneic HSCT resets the immune system at a genetic level,[10,11] and autologous HSCT eliminates aberrant clones by immunoablation and replacement with uncommitted stem cells, leading to de novo generation of an altered T-cell repertoire.[12] Case reports and series describe long-term treatment-free disease regression with autologous[4-9] and allogeneic[10,11] HSCT in some[4-6,10] but not all patients[7-9] with Crohn disease and in other patients with conditions that have autoimmune pathology, such as systemic sclerosis.[13-15]

To follow up on these promising but preliminary data, we conducted the Autologous Stem Cell Transplantation International Crohn Disease (ASTIC) trial to evaluate the effect of autologous HSCT on disease activity, mucosal healing, and quality of life in patients with resistant Crohn disease.

Methods

Study Design

The ASTIC trial is a parallel-group randomized clinical trial conducted in 6 European countries at 11 centers approved for allogeneic transplantation by the Joint Accreditation Committee of the International Society for Cellular Therapy (JACIE) and the European Society for Blood and Marrow Transplantation (EBMT).[16,17] The trial was designed to evaluate the effects of autologous unselected HSCT compared with conventional therapy in patients with refractory Crohn disease, with the primary end point being assessed after 1 year. Because of the nature of the intervention, patients, clinicians, investigators, and coordinators were not blinded to treatment assignment. However, an adjudication committee that reviewed all radiology and endoscopy reports to determine the presence and activity of Crohn disease within the GI tract were blinded to time of assessment and treatment assignment. The trial protocol is available in Supplement 1.

Participants

Inclusion and exclusion criteria are reported in eAppendix 1 in Supplement 2. Briefly, we studied patients aged 18 to 50 years with an established diagnosis of Crohn disease[18] who had continuing refractory disease not amenable to surgery and who had impaired function or quality of life (defined as Inflammatory Bowel Disease Questionnaire [IBDQ] score <170,[19] European Quality of Life Visual Analogue Scale [EQ-VAS] Index[20] <85, or a Karnofsky Performance Index[21] <80) despite having tried at least 3 immunosuppressive or biological agents in addition to corticosteroids. Patients were excluded if they had organ failure or other severe comorbidities; active infection; infectious risk, including a history of tuberculosis; malnutrition; or if they were pregnant or unwilling to use contraception during the study.

Ethical Issues

All patients provided written informed consent following extensive counseling. The protocol was approved by the institutional review board at each site and complied with country-specific regulatory requirements. The study was conducted in accordance with the Declaration of Helsinki[22] and Good Clinical Practice guidelines. An independent data and safety monitoring committee reviewed safety data after every 10 patients were randomized or in the event of death or other concerns.

Enrollment

Investigators identified potential patients from their own clinics or via tertiary referrals and nominated them for trial participation in a written submission to the trial steering committee (TSC). Patients provisionally approved by the TSC provided informed consent and then underwent baseline evaluations, including ileocolonoscopy, upper GI endoscopy, and small-bowel imaging. Baseline assessments were submitted to the trial coordinator, who confirmed eligibility before allowing the patient to proceed to stem cell mobilization and randomization. Patients gave blood for genotyping, were offered fertility advice, and underwent sperm, egg, embryo, or ovarian tissue storage as appropriate. The first patient was randomized on June 28, 2007, and the last on September 1, 2011; the final date of follow-up was March 2013.

Interventions and Randomization

All patients underwent stem cell mobilization using cyclophosphamide (2 g/m^2, ×2 days) and nonglycosylated granulocyte colony-stimulating factor (filgrastim; 10 μg/kg/d). To avoid undue immunosuppression during mobilization, corticosteroids and immunosuppressive drugs were reduced or stopped according to a standard protocol. Patients underwent leukapheresis when the CD34$^+$ count exceeded 20 × 10^4/mL, to a target of 3 to 8 × 10^6 CD34$^+$ cells/kg of body weight.

Patients who underwent successful mobilization were then randomized to undergo HSCT immediately or after a delay of 1 year. Randomization was centralized and used balanced nonstratified (1:1) electronically generated random number tables in permuted blocks of 4 patients prepared by the Nottingham Clinical Trials Unit. Investigators submitted information about the size of the stem cell harvest to the trial coordinator, who confirmed its adequacy before requesting the treatment assignment from the clinical trials unit; all parties, including the trial coordinator, were unaware of the randomization group until allocation.

Patients randomized to immediate HSCT transplantation received an EBMT-recommended intermediate-intensity conditioning regimen[16] consisting of intravenous cyclophosphamide (50 mg/kg/d, ×4 days) and, from day 3, rabbit antithymocyte globulin (Genzyme; 2.5 mg/kg/d) and methylprednisolone (1 mg/kg/d, ×3 days), with infusion of unselected stem cells (minimum, 3 × 10^6 CD34$^+$ cells/kg) on day 7.

All patients during mobilization and patients undergoing HSCT during conditioning received general care as deemed nec-

essary by investigators, including antibacterial, antimycotic, and antipneumocystis agents; hyperhydration; and mesna (for bladder protection) and alkalinization of urine according to local practice.

During follow-up, all patients in either trial group could receive standard care for Crohn disease, including corticosteroids, immunosuppressive agents, and biologic therapy, which was subsequently withdrawn according to local protocol if clinical improvement permitted. Enteral or parenteral nutritional support could be used according to local clinical protocol. If patients' condition deteriorated (as judged by their local investigator) despite treatment intensification, an application could be made to the TSC to approve use of surgery or accelerated HSCT according to specified criteria (eAppendix 2 in Supplement 2).

Assessments

Every 6 weeks, patients in both groups underwent history and examination and laboratory testing and were assessed for disease activity (Crohn Disease Activity Index [CDAI]/Harvey-Bradshaw Index), adverse events, use of medication and medical services, and employment history; both groups also underwent electrocardiography and antimicrobial serology testing and were assessed for quality of life at 6 and 12 months.

End Points

We established a stringent primary end point, sustained disease remission 12 months after transplantation, to reflect the benefit we judged HSCT would need to yield to justify treatment toxicity. We defined SDR as a composite variable comprising 3 components: (1) CDAI[23] less than 150 for at least the last 3 months (index based on number of liquid or soft stools, abdominal pain, general well-being, complications, use of antidiarrheal medication, abdominal mass, hematocrit <0.47 [men] or <0.42 [women], and % deviation from standard weight; lowest value, 0 for no symptoms; remission defined as <150, higher values [typically up to 600] indicate active disease); (2) no active treatment in the last 3 months; and (3) no mucosal erosion or ulceration anywhere in the GI tract as judged by a blinded adjudication committee (M.A., G.R., J.L.) using all upper and lower GI endoscopy and small-bowel imaging data (eAppendix 3 in Supplement 2). Patients who did not meet these composite criteria, and those who died or who did not complete the year without surgery or (in the control group) accelerated transplantation were categorized as having failed treatment.

Secondary end points comprised a range of exploratory outcome measures, including but not limited to the individual items of the composite sustained disease remission outcome, and measures of clinical activity (change in CDAI and in Harvey-Bradshaw Index,[24] the latter based on number of liquid or soft stools, abdominal pain, general well-being, complications, abdominal mass; remission defined as <5; higher values [typically up to 30] indicate active disease). Endoscopic disease activity was assessed by the change in Simple Endoscopic Score for Crohn Disease (SES-CD) (a sum of scores for involvement, ulceration, ulcer size, and stricturing [each on a 3-point scale] of the ileum, ascending colon, transverse colon, left colon, and rectum; theoretical maximum, 60 [higher scores are worse]).[25] Only segments examined both at baseline and 1 year were included in this analysis. Changes in functional status and generic and disease-specific quality of life were measured with the Karnovsky Index,[21] IBDQ[19] (32 questions in domains of bowel symptoms, emotional health, systemic systems, and social function [range, 32-224; higher scores indicate better quality of life and scores <170 indicate impaired quality]) and Euroqol[20] scales (a visual analogue scale [range, 0-100; higher scores indicate better quality of life and scores <85 indicate impaired quality] and self-reported description of current health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [range, 0-1; higher scores indicate better quality of life]).

Adverse events were classified as nonserious or serious (SAEs); we defined SAEs as adverse events or reactions with or without a causal relationship to treatment that resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity. We assessed adverse events every 6 weeks at each trial visit.

Statistical Analysis

The study was designed to provide 90% power to detect a 65% vs 20% difference in the proportion of patients achieving 1-year sustained disease remission (2-sided $\alpha = .05$) based on investigator consensus. Target trial enrollment was 48 patients, but in the context of treatment-related adverse events and after a transplant-related death, the trial was terminated after enrollment of 45 evaluable patients on recommendation of the data and safety monitoring committee.

We summarize continuous variables as medians with interquartile ranges except where otherwise stated, and report findings based on intent-to-treat analyses using outcome data at 1 year or at treatment failure, as defined in the protocol and the statistical plan. We performed between-group comparisons of primary and secondary exploratory end points using generalized linear models including 2 factors: randomization arm as a fixed covariate and study center as a random effect to account for differences between transplant centers. We estimated 95% CIs using asymptotic CIs for differences in proportions and nonparametric CIs for differences of medians (percentile bootstrap, stratified by the grouping variable).

For secondary end points where appropriate, we used data at the time of loss to follow-up, surgery, or accelerated transplantation for patients who did not complete the study or who failed treatment. The potential effect of missing patient data on secondary outcomes was assessed with worst-case sensitivity analyses and with multiple imputation for quality-of-life parameters, imputing 5 data sets using chained regression under the missing-at-random assumption.[26] After this calculation, each of the simulated complete data sets was independently analyzed using the same methods as complete case analysis to produce estimates and CIs that incorporate missing-data uncertainty, using the Rubin rules.

We used SPSS version 19 (IBM SPSS statistics) and R version 3.0.1 (R Development Core Team) for all analyses, using 2-sided testing with a significance threshold of $P \leq .05$.

Results

Patients

Of 132 patients screened for eligibility, 99 were provisionally approved by the TSC, 62 signed consent forms, and 50 proceeded to be registered for trial inclusion, having met all criteria for inclusion (**Figure**). Forty-eight underwent mobilization (1 withdrew consent, and 2 had inadequate mobilization), and 45 were randomized to undergo immediate HSCT (n = 23) vs conventional therapy (n = 22) for 1 year (followed by delayed HSCT). There were no between-group differences in baseline characteristics, although patients undergoing HSCT tended to have a longer history of disease, were more likely to be smokers, and were more likely to report a family history of inflammatory bowel disease and have arthritis as part of their disease than controls (**Table 1**). All but 1 patient (who had esophageal disease only) had colonic or ileocolonic involvement. Baseline CDAI and SES-CD scores were similar across participating transplant centers.

Mobilization, Conditioning, and Transplantation

Mobilization yielded a median of 9.0 (range, 3.8-27.0) × 10^6/kg $CD34^+$ cells in patients undergoing HSCT and 9.2 (range, 7.2-16.6) × 10^6/kg $CD34^+$ cells in control patients from 1 (n = 39) or 2 (n = 6) leukapheresis. Conditioning of the HSCT group was started a median of 30 (range, 19-63) days after successful leukapheresis, with infusion of the unselected graft 6 days later. All patients achieved engraftment, with a sustained median neutrophil count of 0.5 × 10^9/L at a median of 16 (range, 8-30) days and a sustained median platelet count of 20 × 10^9/L at 18 (range, 8-30) days after graft infusion.

Follow-up Assessments

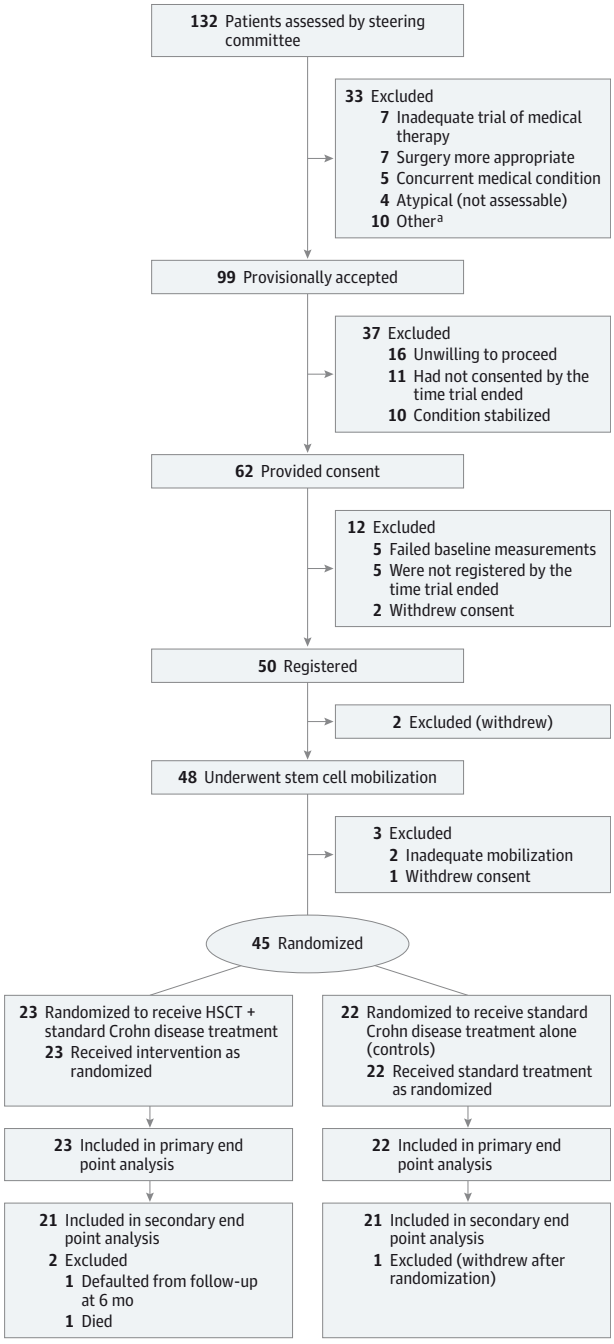
Of the 23 patients in the HSCT group, 1 died 20 days after the start of conditioning and 1 withdrew from follow-up at 26 weeks; these patients were included in analysis of primary but not secondary end points. Of the 22 control patients, one withdrew consent immediately after randomization and underwent out-of-trial HSCT; this patient was included in the analysis of primary but not secondary end points. A further 8 patients deteriorated clinically and ended as trial failures for the primary end point after a median of 183 (range, 109-259) days: 2 required urgent surgery, and 6 underwent accelerated transplantation (median CDAI score at withdrawal, 409 [range, 179-589]). Data at the time of withdrawal and treatment failure for these patients were included in analysis of both primary and secondary end points.

The remaining patients were assessed a median of 369 (range, 346-391) days after graft infusion (n = 21 patients in the HSCT group) and 363 (range, 328-417) days after mobilization assessment plus 6 days (n = 13 in the control group). Eleven of the 13 control patients assessed at 1 year proceeded to delayed HSCT; 1 of those patients improved enough to decline HSCT, and surgery was considered more appropriate in the other.

Sustained Disease Remission and Its Components

There was no statistically significant between-group difference in the proportion of patients who met the study definition of sustained disease remission (2 [8.7%] in the HSCT group vs 1 [4.5%] in the control group; absolute difference, 4.2% [95% CI, −14.2 to 22.6%] favoring HSCT; P = .60) (**Table 2**). There were statistically significant between-group differences in 1 of the 3 exploratory individual components (Table 2); compared with

Figure. Flow of ASTIC Trial



ASTIC indicates Autologous Stem Cell Transplantation International Crohn Disease; HSCT, hematopoietic stem cell transplantation.

[a] Center not yet set up (n = 3); older than 50 years and not fit enough (n = 2); Crohn Disease Activity Index less than 250 (n = 2); infection risk (n = 1); inadequate baseline information (n = 1); patient's physician opposed (n = 1).

Table 1. Demographic Features and Baseline Characteristics

Characteristic	HSCT (n = 23)	Control (n = 22)
Age at mobilization, median (IQR), y	34.1 (26.1-41.2)	30.6 (24.0-37.6)
Women, No. (%)	13 (56.5)	11 (50.0)
Body mass index, median (IQR)[a]	23.0 (20.5-27.8)	21.1 (19.9-24.9)
Smoking, No. (%)		
Current	6 (26.1)	4 (18.2)
Former	7 (30.4)	6 (27.3)
Family history of Crohn disease, No. (%)[b]	5 (21.7)	1 (4.5)
No. of previous operations for Crohn disease, median (IQR)	2 (0.5-3.5)	2 (0.25-3)
Ileostomy, No. (%)	4 (17.4)	4 (18.2)
Age at diagnosis, median (IQR), y	19.4 (12.3-25.5)	18.2 (14.1-24.2)
Disease duration, median (IQR), y	14.9 (9.9-16.9)	11.2 (7.5-15.1)
Extraintestinal involvement, No. (%)		
Joints	14 (64)	9 (43)
Skin	4 (17)	2 (10)
Eyes	3 (13)	4 (20)
Prior drugs, No. (%)		
Azathioprine/6 mercaptopurine	22 (96)	22 (100)
Methotrexate	19 (83)	18 (82)
Anti-TNF agents[c]	23 (100)	22 (100)
Other[d]	10 (44)	9 (41)
No. of drugs used, median (IQR)	5 (4.5-5)	5 (4-5)
Months used, median (IQR)[e]	113 (63-174)	113 (50-177)
Disease activity, median (IQR)		
CDAI[f]	326 (251-414)	354 (300-444)
Harvey-Bradshaw Index[g]	13 (9-17)	14 (8.6-16.5)
Laboratory results, median (IQR)[h]		
Hemoglobin, g/dL	12.3 (11.9-14)	11.7 (10.45-12.8)
Platelets, $\times 10^9$/L	297 (249-400.5)	337 (233.8-392.3)
Albumin, g/dL	35 (30.5-39.5)	36 (31-38.75)
CRP, mg/L	11.0 (4.25-26.55)	12.3 (7.3-36)
Quality of life and functional status, median (IQR)		
EQ-VAS (0-100)[i]	60 (40-65)	43 (30-64)
EQ-5D (0-1)[j]	0.8 (0.71-0.8))	0.76 (0.70-0.80)
IBDQ (32-224)[k]	124 (102-142)	109 (83-138)
Karnofsky Performance Index (0-100)[l]	70 (70-80))	70 (63-70)
Whole GI tract evaluation, median (IQR)		
Segments examined per patient (maximum, 10)	9 (8-10)	9 (7-10)
Normal	5 (4-70)	5 (4-7)
Crohn disease involvement[m]	4 (3-5)	3 (2-4)
Ulcerated[m]	3 (1-4)	2 (1-3)
Whole GI tract free of active Crohn disease[m]	0	0
Ileocolonoscopic evaluation, median (IQR)		
Segments examined per patient (maximum, 5)[n]	4 (3-5)	4 (2-5)
SES-CD score[n]	13 (8-24)	13.5 (6.8-19.3)

Abbreviations: CDAI, Crohn Disease Activity Index; CRP, C-reactive protein; ECCO, European Crohn and Colitis Organisation; EQ-VAS: European Quality of Life Visual Analogue Scale; EQ-5D: EuroQoL 5 Dimensions Questionnaire; GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; IBDQ, Inflammatory Bowel Disease Questionnaire; IQR, interquartile range; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Family history of inflammatory bowel disease (any degree) based on patient report.

[c] Most patients had used more than 1 anti-TNF agent, including certolizumab (5 HSCT, 3 control).

[d] Ten HSCT patients received 12 other immunosuppressive/anti-inflammatory drugs (cyclosporine [3]; micophenolate [3]; tacrolimus [2] thalidomide [2]; vedolizumab [1]; natalizumamb [1]). Seven control patients had received 9 other immunosuppressive/anti-inflammatory drugs (tacrolimus [3]; cyclosporine [2]; micophenolate [2]; thalidomide [2]).

[e] Summation of durations of use for each drug (some of which may have been concurrent). When data were imprecise (eg, year of starting or finishing only) we averaged the maximum and minimum possible duration (57 of 117 drugs in the HSCT group and 56 of 106 drugs in the control group).

[f] Eight-component index based on number of liquid or soft stools, abdominal pain, general well-being, complications, use of anti-diarrheal medication, abdominal mass, hematocrit less than 0.47 (men) or less than 0.42 (women), and % deviation from standard weight. Scores up to 150 indicate remission; higher values (typically up to 600) indicate active disease.

[g] Five-component index based on clinical criteria: number of liquid or soft stools, abdominal pain, general well-being, complications, abdominal mass. Scores less than 5 indicate remission; higher values (typically up to 30) indicate active disease.

[h] Normal ranges vary slightly between centers. Nottingham normal values are: hemoglobin, 13.0-18.0 g/dL (men) and 11.5-16.5 g/dL (women); platelets, 150-450 $\times 10^9$/L; albumin, 30.0-45.0 g/dL; C-reactive protein, 0-5 mg/L.

[i] Self-rated health status using a visual analogue scale, which records the person's perceptions of their own current overall health and can be used to monitor changes with time. Higher scores indicate better quality of life (scores <85 indicate impaired quality).

[j] Self-reported description of the person's current health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Higher scores indicate better quality of life.

[k] Tool to measure health-related quality of life in adult patients with inflammatory bowel disease, with 32 questions scored in 4 domains: bowel symptoms, emotional health, systemic systems, social function. Higher scores indicate better quality of life (scores <170 indicate impaired quality).

[l] Performance scale measuring functional impairment, ranging from 0 (dead) to normal function (<80 indicates impaired performance).

[m] Based on ECCO consensus guidelines. Ulceration regarded as evidence of active Crohn disease.[18]

[n] Simple Endoscopic Score for Crohn Disease summation of scores for involvement, ulceration, ulcer size, and stricturing each on a 3-point scale in each of ileum, ascending colon, transverse colon, left colon, and rectum. Theoretical maximum score, 60 (higher scores are worse).[24]

control patients, 38.1% (95% CI, 9.3% to 59.3%) (P = .01) more patients in the HSCT group were able to stop immunosuppressive drugs. Although 25.7% (95% CI, 1.08% to 47.1%) (P = .054) more patients in the HSCT group were free of active disease on imaging and 25.7% (95% CI, 1.08% to 47.1%) (P = .052) more

Table 2. Final Assessments

	No. (%)					
	HSCT (n = 23)		Control (n = 22)		Difference Median, % (95% CI)[a]	*P* Value (Adjusted for Center)
Primary Outcome[b]						
Sustained disease remission[c]	2 (8.7)		1 (4.5)		4.2 (−14.2 to 22.6)	.60
Components of primary outcome						
No active treatment last 3 mo	14 (60.9)		5 (22.7)		38.1 (9.3 to 59.3)	.01
CDAI <150 last 3 mo	8 (34.8)		2 (9.1)		25.7 (1.08 to 47.1)[a]	.052
Free of active disease on imaging	8 (34.8)		2 (9.1)		25.7 (1.08 to 47.1)[a]	.054
Secondary Outcomes[d]	**Median (IQR)**	**No.**	**Median (IQR)**	**No.**	**Difference (95 CI)**	
Disease activity						
CDAI change from baseline	−150.7 (−62.0 to −196.3)	21	−63.0 (34.0 to −120.8)	21	−87.7 (−13.5 to −155.0)	.04
Harvey-Bradshaw Index change from baseline	−6 (−4 to −9)	21	−2 (3 to −4)	21	−4 (−1 to −9)	.002
Endoscopic activity						
SES-CD change from baseline[e]	−7 (−4 to −13)	21	0 (5 to −8.5)	19	−7 (−13 to −1)	.03
Quality of Life[f]						
Change from baseline						
EQ-VAS	20 (−2.5 to 30)	19	5.5 (−11.5 to 19.5)	14	14.5 (−7.5 to 33)	.50
EQ-5D	0.025 (−0.022 to 0.163)	17	0 (−0.013 to 0.093)	13	0.025 (−0.072 to 0.163)	.41
IBDQ	35.5 (−6.3 to 53.8)	18	1 (−11.3 to 23.3)	16	34.5 (−8 to 54.5)	.54
Karnofsky Performance Index	10 (0 to 20)	15	0 (0 to 10)	14	10 (−7.5 to 20)	.85

Abbreviations: CDAI, Crohn Disease Activity Index; EQ-VAS: European Quality of Life Visual Analogue Scale; EQ-5D: EuroQoL 5 Dimensions Questionnaire; HSCT, hematopoietic stem cell transplantation; IBDQ, Inflammatory Bowel Disease Questionnaire; IQR, interquartile range.

[a] Asymptotic CI for difference between proportions and nonparametric CI for difference between medians, based on the medians (percentile bootstrap, stratified by grouping variable). Discrepancies between *P* value and 95% CI are attributable to inclusion of a center effect in calculating *P* values but not 95% CIs.

[b] Assessed 12 months after transplantation or at time of study withdrawal or treatment failure.

[c] No active treatment and CDAI less than 150 for at least the last 3 months and free of active disease on imaging at 1 year.

[d] Based on 22 patients undergoing HSCT and 21 control patients unless otherwise noted. Excludes 2 patients (1 in each group) for which there are no data.

[e] There was no endoscopy at the 1-year time point in 5 patients who were excluded completely from the analysis (2 HSCT [1 not performed, 1 died] and 3 control patients [1 withdrew, 2 did not have colonoscopy, 1 of whom had no colonic disease at baseline]). Within this analysis, there were no 1-year data for 6 segments in 5 patients for whom baseline data were available, and there were no baseline data for 10 segments in 7 patients for whom 1-year data were available. In total, there were data missing for at least 1 segment from 10 patients.

[f] Positive values indicate better scores for HSCT patients than for controls.

had a CDAI less than 150 for the final 3 months, the differences did not reach the trial's predefined threshold of statistical significance. There were no statistically or clinically significant differences between transplant centers in the composite or individual outcomes.

Exploratory Secondary End Points

The effects of HSCT on secondary end points are summarized in Table 2 and eTable 1 in Supplement 2. Differences in change in measures of disease activity (CDAI illustrated in the eFigure in Supplement 2) were statistically significant and favored HSCT (decrease in CDAI from baseline of 87.7 [95% CI, 13.5 to 155.0]) more in patients in the HSCT group compared with those in the control group (*P* = .04); decrease in Harvey-Bradshaw Index of 4 (95% CI, 1 to 9) more in patients undergoing HSCT than in control patients (*P* = .002) (Table 2), although in a sensitivity analysis imputing worst-case values for missing data, the differences in change lost statistical significance (decrease in CDAI, 81.8 [95% CI, −168.3 to 58.4]) more in patients undergoing HSCT than in control patients (*P* = .22), decrease in Harvey-Bradshaw Index of 5 (95% CI, 1 to 9.5) more in patients undergoing HSCT than in control patients (*P* = .06) (eTable 2 in Supplement 2). Among 21 patients in the HSCT group and 19 in the control group in whom colonoscopy data were obtained at baseline and final assessments, SES-CD scores between paired segments decreased by 7 (95% CI, 1 to 13) (*P* = .03) points more in patients undergoing HSCT than in control patients. Further sensitivity analyses that imputed best- and worst-case values for missing data did not qualitatively change other conclusions (eTable 2 and 3 in Supplement 2).

There were no statistically significant differences in change from baseline of any of the quality-of-life scores (European Quality of Life Visual Analogue Scale, EuroQoL 5 Dimensions Questionnaire, Inflammatory Bowel Disease Questionnaire, Karnofsky Index) using available data (Table 2) and in analyses accounting for missing data (eTable 3 in Supplement 2).

Platelets declined more in the HSCT group than in the control group, but there were otherwise no between-group differences in change in laboratory values (eTable 1 in Supplement 2).

Use of medical therapy was lower in the HSCT group compared with the control group; 8 patients undergoing HSCT were given corticosteroids (median, 16.3 weeks) vs 10 control patients (median, 31.4 weeks); 3 patients undergoing HSCT were given immunosuppressive drugs (median, 25.3 weeks) vs 6 con-

trol patients (median, 21 weeks); and 3 patients undergoing HSCT required biologic agents (median, 30.3 weeks) vs 7 control patients (median, 17.3 weeks).

Adverse Events

Serious adverse events were frequent (76 in 19 patients undergoing HSCT vs 38 in 15 control patients; median difference in number of events, 0 [95% CI, −1 to 4; *P* = .07]; percentage of patients, 14.4% [95% CI, −10.6% to 37.7%; *P* = .28]) (**Table 3**) and were more common among patients undergoing HSCT in the 100 days following conditioning and transplantation (34 SAEs in 13 patients undergoing HSCT vs 5 SAEs in 4 control patients [Table 3]; median difference, 1 [0 to 2] more SAE; *P* = .02; and 38.34% [95% CI, 10.02% to 59.24%] more patients [*P* = .01] with HSCT). There were no statistically significant between-group differences in number of SAEs during mobilization or in the 9-month postconditioning period.

Nearly all patients experienced nonserious adverse events (265 in 22 patients undergoing HSCT vs 134 in 20 control patients [eTable 4 in Supplement 2]; median difference, 4 [95% CI, −1 to 10] more adverse events with HSCT; *P* = .04), which were more common in the 100 days following conditioning and transplantation (117 adverse events in 19 patients receiving HSCT vs 27 adverse events in 11 control patients; median difference, 3.5 [95% CI, 0.5 to 8] more nonserious adverse events with HSCT) (eTable 4 in Supplement 2).

Infections were common in patients in the HSCT group and more common in the 100 days following conditioning and transplantation (13 SAEs attributable to infection in 8 patients in the HSCT group vs 0 in the control group; median difference, 0 [95% CI, 0 to 1] more infectious SAEs [*P* = .01] and 34.8% [95% CI, 13.0% to 55.1%] more patients [*P* = .002] with HSCT [Table 3]; 25 nonserious adverse events in 13 patients receiving HSCT vs 3 in 3 control patients) (eTable 4 in Supplement 2). Of the infections classified as an SAE, 9 were viral infections in 5 patients undergoing HSCT (vs 0 in control patients) comprising Epstein-Barr virus reactivation (n = 3), cytomegalovirus reactivation (n = 2), herpes zoster (n = 1), BK virus (n = 1), intestinal adenovirus (n = 1), and varicella zoster virus (n = 1); 8 were presumed neutropenic sepsis with an organism isolated on 1 occasion; 2 were pneumonia (*Klebsiella* [n = 1], pneumocystis [n = 1]), and 3 were anal or perianal abscesses (the latter 3 in a single patient). Gastrointestinal symptoms were common, including nausea and vomiting (n = 6), diarrhea (n = 1), and abdominal pain (n = 2). Worsening of Crohn disease was recorded as an adverse event or SAE in 6 patients undergoing HSCT and 8 control patients.

One patient randomized to HSCT died 20 days after the start of conditioning, with postmortem evidence of sinusoidal obstructive syndrome.[27,28] He was taking no drugs at trial entry and had no antecedent risk factors for sinusoidal obstructive syndrome.[27,28] He had been thought to have intraperitoneal sepsis and underwent (negative) laparotomy 2 days before death, when his liver appeared normal and results of liver function blood tests were normal. His condition then deteriorated, with clinical and biochemical evidence of acute liver failure. Tests for alternative causes of liver pathology were negative.

Delayed Transplantation

Of the 11 control patients who underwent delayed transplantation after 1 year, 12-month outcome data were available for 10 and 6-month data for 1. One of the patients experienced sustained disease remission; 3 experienced clinical remission (CDAI <150) (1 patient was missing CDAI data at 1 year [n = 10]); 2 experienced clinical remission and were not receiving medication; and 4 were free from ulceration on imaging.

Discussion

In this randomized trial of HSCT for patients with refractory Crohn disease not amenable to surgery with impaired function or quality of life, HSCT was not superior to standard therapy at inducing sustained disease remission, defined as clinical remission while not receiving medical therapy for 3 months, with no evidence of active disease on endoscopy and GI imaging at 1 year. Exploratory analyses suggest that more patients in the HSCT group were able to discontinue all immunosuppressive therapy and that clinically but not statistically significantly more patients in the HSCT group may have been in clinical remission and free of active disease on imaging in the months prior to assessment. Exploratory analyses also suggested that HSCT improved measures of clinical and endoscopic disease activity. Nevertheless, because very few patients achieved sustained disease remission, we conclude that HSCT is unlikely to alter the natural history of Crohn disease, and our findings argue against extension of HSCT to a wider group of patients outside of future additional trials.

The ASTIC study was prompted by a literature search (PubMed English language search of [*Stem cell transplant* and *Haematopoietic*] and [*Colitis* or *Crohn** or *IBD*]) between 1985 and 2005 that identified reports of clinical and endoscopic improvement with HSCT in patients with Crohn disease,[2-11] some[4-6] but not all[7-9] of which described apparent disease regression over many years after autologous HSCT. We sought to evaluate the benefits and toxicities of HSCT using a randomized design, blinded adjudication of detailed clinical, endoscopic, and quality-of-life assessments, and a composite primary end point more stringent than those previously used to determine how many patients experienced true sustained disease regression after HSCT. We updated our literature search to July 2015 after completion of the trial to identify additional reports in the literature. A further 29 cases of HSCT for refractory Crohn disease have been reported in case reports and case series,[8,29,30] although several patients had been included in prior reports. Thus, to our knowledge, the ASTIC trial includes the largest cohort of patients undergoing HSCT for refractory Crohn disease and is the only report of a randomized clinical trial of this procedure.

Although we were unable to demonstrate superiority of HSCT over standard therapy for achieving sustained disease remission, the negative finding is based on a very small number of outcomes, and the confidence bounds surrounding the between-group difference in those outcomes are consistent with both large harm and large benefit of HSCT. That imprecision in our estimate of effect of HSCT is attributable to the

Table 3. Serious Adverse Events[a]

	Mobilization[b]				Conditioning[b]				Follow-up[b]				Total			
	HSCT		Control		HSCT		Control		HSCT		Control		HSCT		Control	
	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients
Duration (range), d	45 (33-78)		41 (39-43)		100		100		276 (96-298)		256 (17-325)		418 (252-455)		397 (158-465)	
Total SAEs, No.	17	11	11	8	34	13	5	4	25	9	22	10	76	19	38	15
Median (95% CI) difference between HSCT and controls[c]																
No. of SAEs	0 (−1 to 1)		*P* = .38		1 (0 to 2)		*P* = .02		0 (−1 to 1)		*P* = .85		0 (−1 to 4)		*P* = .07	
% Patients	11.5 (−16.4 to 36.9)		*P* = .46		38.3 (10.0 to 59.2)		*P* = .01		−6.3 (−32.5 to 21.0)		*P* = .65		14.4 (−10.6 to 37.7)		*P* = .28	
Infectious SAEs, No.	5	5	5	5	13	8	0	0	8	4	7	2	26	11	12	7
Median (95% CI) difference between HSCT and controls[c]																
No. of SAEs	0 (0 to 0)		*P* = .93		0 (0 to 1)		*P* = .01		0 (0 to 0)		*P* = .95		0 (−1 to 2)		*P* = .99	
% Patients	−0.99 (−25.0 to 22.8)		*P* = .93		34.8 (13.0 to 55.1)		*P* = .002		8.3 (−13.1 to 29.1)		*P* = .42		16.0 (−11.9 to 40.7)		*P* = .27	
Break down for infectious SAEs, No.																
Viral	0	0	0	0	8	5			1	1	0	0	9	5	0	0
Sepsis	5	5	4	4	3	2			1	1	0	0	9	8	4	4
Localized	0	0	1	1	2	1			6	4	7	2	8	5	8	3
GI SAEs	6	4	1	1	4	3	2	2	8	3	9	8	18	7	12	8
Median (95% CI) difference between HSCT and controls[c]																
No. of SAEs	0 (0 to 0)		*P* = .14		0 (0 to 0)		*P* = .53		0 (0 to 1)		*P* = .82		0 (−1 to 1)		*P* = .53	
% Patients	12.9 (−7.3 to 32.9)		*P* = .20		4.0 (−16.6 to 24.1)		*P* = .70		−23.3 (−45.7 to 2.0)		*P* = .08		−5.9 (−31.4 to 20.4)		*P* = .66	
Break down for GI SAEs, No.																
Disease flare	1	1	0	0	1	1	2	2	5	3	8	7	7	5	10	7
Nonflare symptoms	5	3	1	1	3	2	0	0	3	1	1	1	11	4	2	1

(continued)

Table 3. Serious Adverse Events[a] (continued)

	Mobilization[b]				Conditioning[b]				Follow-up[b]				Total			
	HSCT		Control		HSCT		Control		HSCT		Control		HSCT		Control	
	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients	SAEs	Patients
Hematologic SAEs, No.	2	2	0	0	3	2	0	0	3	1	0	0	8	3	0	0
Median (95% CI) difference between HSCT and controls[c]																
No. of SAEs	0 (0 to 0)		$P = .17$		0 (0 to 0)		$P = .19$		0 (0 to 0)		$P = .34$		0 (0 to 0)		$P = .27$	
% Patients	8.7 (−7.4 to 26.8)		$P > .99$		8.7 (−7.4 to 26.8)		$P > .99$		4.4 (−10.9 to 21.0)		$P > .99$		13.0 (−4.1 to 32.1)		$P > .99$	
Break down for hematologic SAEs, No.																
Anemia	0	0			2	1			3	1			5	1		
Neutropenia	2	2			0	0			0	0			2	2		
Pancytopenia	0	0			1	1			0	0			1	1		
Fever SAEs, No.	1	1	1	1	3	3	0	0	0	0	0	0	4	4	1	1
Renal SAEs, No.	1	1	2	2	1	1	0	0	0	0	0	0	2	2	2	2
Respiratory SAEs, No.	1	1	0	0	2	2	0	0	1	1	0	0	4	4	0	0
Other	1	1	2	2	8	4	3	2	5	4	6	5	14	8	11	8

Abbreviations: GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; SAE, serious adverse event.

[a] Serious adverse events defined as an adverse event, adverse reaction, or unexpected adverse reaction, respectively, that does not necessarily have a causal relationship to the treatment, and that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or consists of a congenital anomaly/birth defect or is otherwise medically significant. Patients could have more than 1 SAE, so numbers comprising breakdowns might sum to more than the reported totals.

[b] Conditioning phase covers 100 days from start of conditioning (or reference day for control patients). Mobilization phase covers period from start of mobilization to start of conditioning. Follow-up phase covers period from end of conditioning phase to 1-year assessment.

[c] Median (95% CI) difference in the number of SAEs experienced per patient and the median (95% CI) difference in the percentage of patients experiencing an SAE between patients undergoing HSCT and control treatment. Asymptotic CI for the difference of proportions or nonparametric CI for difference of medians (percentile bootstrap, stratified by the grouping variable). Any discrepancies between *P* value and 95% CI are attributable to inclusion of a center effect in calculating *P* values but not 95% CIs.

premise underlying both our stringent primary end point definition and our sample size calculations, namely, that many more patients undergoing HSCT than standard treatment would have to realize a clearly defined benefit to justify the exposure of participants to the toxicity of HSCT. We found favorable effects of HSCT on end points used in other studies of Crohn disease, like clinical disease activity (CDAI) or endoscopic mucosal healing (SES-CD); and while those were exploratory end points in this trial, improvements falling short of sustained disease remission may still be clinically meaningful in this group of patients, who have no other therapeutic options and a markedly impaired quality of life. This is not the case for treatment-naive patients, for whom it is appropriate to prescribe therapies with reduced toxicity, even if they are less effective.[2,3,31,32]

HSCT was associated with more adverse events than conventional therapy, most importantly proven or presumed infections associated with the pancytopenia induced by the conditioning regimen, and 1 patient died. The number of adverse effects likely contributes to our failure to show an unequivocal improvement in quality of life in the first year after HSCT. Whether the sinusoidal obstructive syndrome seen in the patient who died was a result of endothelial injury induced by chemotherapy or an agonal event in a septic patient is uncertain but raises the prospect that prophylaxis with defibrotide or possibly ursodeoxycholic acid[33,34] might be considered in any future studies of HSCT for Crohn disease.

The study has limitations. The trial's primary end point (sustained disease remission) has not been used before but is based on individual validated measures of disease.[23-25] Our primary end point relied in part on CDAI, a symptom-based assessment of disease activity that might have captured noninflammatory symptoms relating to prior structural intestinal damage. More patients withdrew from the control group than the HSCT group before 1 year to receive salvage therapy, and the change in measures of disease activity lost statistical significance when data for these early withdrawals were imputed using worst-case sensitivity analyses. Also, we used different methods for small-bowel radiology in the course of the study, leading to possible inconsistency in assessment of disease activity on imaging, although only 1 patient with ulcerative ileal disease on barium follow-through at both baseline and follow-up was categorized exclusively on the basis of radiology.

Based on these trial findings, further study of HSCT in patients with refractory Crohn disease may be warranted. It is possible that optimal sustained remission after HSCT may require maintenance immunosuppressive therapy. It is also possible that patients will regain responsiveness to treatments to which they were previously refractory. Therefore, future trials should assess the benefit of maintenance therapy. Toxicity will remain the most significant barrier to HSCT in patients with Crohn disease. Therefore, identification of factors that predict either the risk of adverse effects or response to treatment will enhance the utility of this treatment in clinical practice.

Conclusions

Among adult patients with refractory Crohn disease not amenable to surgery who had impaired quality of life, HSCT, compared with conventional therapy, did not result in a statistically significant improvement in sustained disease remission at 1 year and was associated with significant toxicity. These findings do not support the widespread use of HSCT for patients with refractory Crohn disease.

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