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Review Article

Review Article

Autologous Haematopoietic Stem Cell Transplantation (AHSCT) in Severe Crohn's Disease: A Review on Behalf of ECCO and EBMT

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Abstract

Despite the major recent progress in the treatment of Crohn's disease [CD], there is a subset of patients in whom the disease runs an aggressive course with progressive tissue damage requiring early and repeated surgical management. Increasing evidence supports sustained and profound improvement in gastrointestinal parameters and quality of life following high-dose immunosuppressive therapy and autologous haematopoietic stem cell transplantation [AHSCT] compared to standard therapy in this context. In addition, international transplant registry data reflect the use of AHSCT in CD outside of trials in selected patients. However, AHSCT may be associated with significant treatment-related complications with risk of transplant-related mortality. In a joint initiative, the European Crohn's and Colitis Organisation [ECCO] and the European Society for Blood and Marrow Transplantation [EBMT] have produced a state-of-the-art review of the rationale, evaluation, patient selection, stem

cell mobilization and transplant procedures and long-term follow up. Given the unique spectrum of issues, we recommend that AHSCT should only be performed in experienced centres with expertise in both haematological and gastroenterological aspects of the procedure. Where possible, patients should be enrolled on clinical trials and data registered centrally. Future development should be coordinated at both national and international levels.

Key Words: Crohn's disease; inflammatory bowel disease; stem cells; transplantation; autologous haematopoietic stem cell transplantation; chemotherapy

1. Introduction

1.1. Limitations of current therapies

Crohn's disease [CD] is a life-long disease, considered to arise from disproportionate immune responses to components of the intestinal microbiota triggered by environmental factors in genetically predisposed individuals. Despite substantial progress in the development of medical and surgical therapies, there are still no curative treatment options available and a considerable proportion of patients are at high risk of side-effects of therapy, disease progression and repeated surgical procedures, all of which lead to chronic poor quality of life with recurrent hospitalization, disability or even mortality. The economic costs of severe CD to the individual and society are substantial.[1]

Currently approved medical therapies include corticosteroids, thiopurines, methotrexate and biological agents, including antibodies targeting tumour necrosis factor α [TNFα], α4β7 integrin or interleukin [IL]-12/23.[2] Conventional therapies, such as thiopurines, have only limited efficacy in maintaining remission and are associated with increased risk of side-effects including skin cancer and haematological malignancies.[3] The TNFα inhibitors infliximab, adalimumab and certolizumab pegol are among the most potent therapeutic options. Even so, around only 40% of patients achieve remission, which is subsequently maintained in only half of these patients.[2] The efficacy of these agents is further impaired by their immunogenicity, which frequently results in sub-therapeutic serum drug levels and interruption of treatment. Moreover, approximately half relapse within 2 years following discontinuation of anti-TNF therapies. In addition, sustained remission rates with the newer biologicals vedolizumab and ustekinumab do not exceed 20–25% in patients previously treated with TNF inhibitors.[4,5]

New treatment goals, such as 'mucosal healing', have been implemented in clinical trials, which correlate with improved long-term outcomes.[6] However, the long-term impact of available medical therapies is uncertain as rates of surgical resection have remained high despite introduction of new therapies.[7] These issues are of particular concern in high-risk patients, characterized by extensive involvement of the small bowel, young age and requirement for corticosteroids at primary diagnosis, a penetrating phenotype and smoking. There is a clear unmet need to establish novel medical therapies for these 'difficult to treat' patients in order to control their disease burden in the short term but more importantly to impact on the course and prognosis of their CD in the longer term.

This review covers treatment of patients with polygenic CD with autologous haematopoietic stem cell transplantation [AHSCT]. It reappraises the updated evidence base and builds upon the earlier recommendations from the European Society for Blood and Marrow Transplantation [EBMT][8,9] and other recent general reviews.[10] Allogeneic HSCT [i.e. from a related or unrelated donor] may be curative in patients with monogenic forms of inflammatory bowel disease that do not respond to conventional treatment and those with high mortality [e.g. IL-10 signalling defects, immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, Wiskott–Aldrich syndrome or increasingly X-linked inhibitor of apoptosis (XIAP) deficiency].[11] As disease onset in these patients is early in life, an in-depth review of this topic is not the purpose of this position paper. However, genetic testing should be considered in candidates for AHSCT, particularly those with disease onset in early life.

2. Clinical Evidence for AHSCT in CD

Initial reports of benefit from HSCT in CD included cases of patients in whom transplant had been undertaken for other indications, such as leukaemia and lymphoma.[12–16] Subsequent case series, cohort studies and clinical trials that assessed the impact of AHSCT as a treatment for CD are summarized in Table 1.[17–27] As of September 2017, there have been a total of 172 transplant registrations of CD within the EBMT registry, with 164 for AHSCT [unpublished data, EBMT]. CD is the third most common indication for AHSCT in autoimmune disease, after multiple sclerosis and systemic sclerosis [10].

Only one randomized controlled trial [RCT] has been completed to date – the Autologous Stem Cell International Crohn's disease [ASTIC] trial.[26] ASTIC was set up under the auspices of EBMT and the European Crohn's and Colitis Organisation [ECCO] to assess how common it was to achieve complete remission of disease and also whether it was the cyclophosphamide used in stem cell mobilization or the complete AHSCT that was responsible for any benefit seen. Eligible patients had objective evidence of active disease and impaired quality of life despite having tried at least three immunosuppressive/biological treatments. A multidisciplinary trial steering group ratified their suitability after intensive baseline clinical, endoscopic, radiological, laboratory and quality of life assessments, and guided their progress through the trial. The designated primary endpoint was the most stringent used in a clinical trial in CD: clinical remission [Crohn's Disease Activity Index, CDAI < 150] for 3 months, off all immunosuppressive medication with no evidence of active disease on radiological or endoscopic assessment [by Simple Endoscopic Score for Crohn's Disease, SES-CD].

To cover the possibility that mobilization alone might have therapeutic benefit, all patients underwent mobilization with cyclophosphamide 4 g/m^2 and granulocyte colony stimulating factor [G-CSF] before randomization to AHSCT or control treatment. Conditioning for the transplant was cyclophosphamide 200 mg/kg and rabbit anti-thymocyte globulin [rATG] and patients received unmanipulated grafts. All patients in either group could receive any additional treatment deemed necessary but investigators were required to try to withdraw existing treatment to a standard protocol if disease activity allowed.

Of 132 patients submitted for evaluation by the trial steering committee, 48 went forward to stem cell mobilization, which was

Table 1. Summary of clinical cases of Crohn's disease undergoing autologous HSCT. Where possible, earlier reports are covered by later publications with long-term follow up, *denotes overlap between publications. Definitions of clinical remission vary between studies [Cy = cyclophosphamide, ATG = rabbit or horse anti-thymocyte globulin]

Institution	Year	No. of agents failed [median/range, including steroids]	No. of patients	Mobilization regimen [total dose of Cy]	Conditioning regimen	$CD34^+$ selection	Response	Significant toxicities	Refs.
Palermo	2004	3	1	Cy 2 g/m^2	Cy 200 mg/kg + ATG	Yes	Clinical remission, mild endoscopy lesions 5 months	Routine toxicity	17
Milan	2008, 2011	6 [5–7]	6	Cy 1.5 g/m^2	Cy 200 mg/kg + ATG	No	5/6 remained in clinical and endoscopic remission at 1 year	Routine toxicity, no TRM	19, 20
Northwestern University, Chicago	2010	8 [5–11]	24	Cy 2 g/m^2	Cy 200 mg/kg + ATG	Yes	Remission rates [supplementary drugs not initiated] 1 year 91%, 3 years 57%, 5 years 19%	Routine toxicity, no TRM	20
Leiden	2011	Up to 4	3, 2 transplanted, 1 mobilized only	Cy 2 g/m^2	Cy 200 mg/kg + ATG	Yes	2 patients in remission under treatment 5 and 6 years post-transplant. A third patient remission after mobilization lasting 2 years.	Routine toxicity, no TRM	21
Freiburg	2012	7 [4–12]	11/12 mobilized [9 received AHSCT]	Cy 4 g/m^2	Cy 200 mg/kg [no ATG]	Yes	Clinical remission in 50% after 6 months and mucosal healing in 55% after 9 months	Neutropenic fever in 7 patients, bacteraemia in 2 patients, no TRM	22
UK, various	2014	5 [4–7]	6	Cy 2–4 g/m^2	Cy 200 mg/kg + ATG	No [4] Yes [2]	Clinical and endoscopic remissions at 3 months in 5; median time to next treatment 10 months [3–16 months]. Evidence of response to previous agents.	Routine toxicity only, no TRM. Reported late complications: hypothyroidism and ovarian failure.	23
Barcelona	2016, 2017	6 [5–8]	29	Cy 4 g/m^2	Cy 200 mg/kg + ATG	No	Drug-free clinical and endoscopic remission [CDAI < 150, SES-CD < 7] in 61% at 1 year, 52% at 2 years, 47% at 3 years, 39% at 4 years, and 15% at 5 years. Evidence of response to re-introduction of biological therapy.	One fatal systemic CMV infection and one emergency colectomy for CMV and EBV colitis.	24, 25
Multi Centre ASTIC	2015	5 [IQR 4.5–5]	48 received mobilization, 45 were randomized, 23 underwent HSCT*	Cy 4 g/m^2	Cy 200 mg/kg + ATG	No	Failed primary endpoint [sustained clinical remission off medication with no evidence of active disease on endoscopy or imaging]	76 serious adverse events and one patient died of TRM [sepsis and sinusoidal obstruction syndrome]	26
Multi Centre ASTIC	2017	5 [IQR 4–5]	38*	Cy 4 g/m^2	Cy 200 mg/kg + ATG	No	1] 3 months steroid-free remission at 1 year: 38%, 95% CI 22–55 2] Complete endoscopic healing: 50%, 95% CI 34–66	76 serious adverse events occurred in 23 patients	27

TRM, transplant related mortality.

successful in 46. Following mobilization, there was a significant fall in CDAI at 6 weeks. Forty-five patients were randomized to AHSCT [n = 23] or control [n = 22] treatment. Following AHSCT, there was a further fall in CDAI at 1 year, whereas the initial improvement was not maintained in control patients, suggesting that mobilization cyclophosphamide alone is not sufficient for any benefit seen with AHSCT.

Only two patients undergoing AHSCT [vs one control] achieved the ambitious primary endpoint. Nevertheless, a number of patients improved on one or more of the component dimensions. Sixty-one per cent of AHSCT patients had been off all treatment for ≥ 3 months at 1 year follow up in comparison with 23% of controls [P < 0.01], with remission CDAI values in 35% vs 9% [P = 0.053] and no objective evidence of active disease on endoscopy and radiology in 35% vs 9% [P = 0.053]. Adverse events were significantly more common in the AHSCT group within the first 100 days and included mostly infections. One patient died 20 days after starting conditioning and had evidence of sinusoidal obstructive syndrome at post-mortem.

Patients randomized to the control group in ASTIC could undergo AHSCT after the primary endpoint and underwent the same schedule of assessments over the subsequent year. A recent report of the combined cohort includes baseline assessments in 40 and 1-year outcome in 38 patients. There were significant improvements in clinical disease activity, quality of life and endoscopic disease activity at 1 year with 43% patients being in steroid-free clinical remission, and 50% having ileocolonic ulcer healing of whom 26% had complete regression of all evidence of ileocolonic CD [SES-CD score of 0].[27]

Patients were more likely to achieve a steroid-free remission [CDAI < 150] if they had a shorter disease history and a high SES-CD endoscopic activity score at baseline. There was a poor correlation between symptom scores and endoscopy and those with high CDAI scores were less likely to respond, suggesting that some symptoms were related to previous digestive damage rather that current inflammation. The presence of perianal disease at baseline and current smoking was associated with an increased rate of serious adverse events. Informal comparisons with the results of registration trials of biological agents suggest that HSCT compares favourably with regard to clinical and endoscopic outcomes,[28] although the patient populations are different and comparisons should be treated with extreme caution.

Long-term outcome after AHSCT is reported in a single-centre cohort of 29 patients from Barcelona, which includes scheduled clinical, endoscopic and radiological assessment.[24,25] One patient died due to systemic cytomegalovirus [CMV] infection and one required an urgent colectomy for CMV and Epstein–Barr virus [EBV] colitis. Drug-free clinical and endoscopic remission [CDAI < 150, SES-CD < 7] was seen in 61% at 1 year, 52% at 2 years, 47% at 3 years, 39% at 4 years and 15% at 5 years. Although this is an impressive result in a cohort of patients who were refractory to at least two biological therapies, it is clear that AHSCT does not lead to durable disease regression in all patients as clinical or endoscopic evidence of relapse was seen in half of patients after a median of approximately 1 year. However, 80% of patients who relapsed entered clinical remission after reintroduction of anti-TNF therapy [two patients required surgery for strictures]. Thus, the proportion of patients who were in clinical remission, irrespective of requirement for medical therapy and surgery was 70% at 6 months, 73% at 1 year, 93% at 3 years, 70% at 4 years and 100% at 5 years. As in the ASTIC trial, AHSCT had no impact on perianal disease.

In summary, it is clear that AHSCT does not often 'cure' CD and is associated with a heavy burden of serious adverse events, predominantly infections related to the immunosuppression required. However, one clinical trial and several case series report significant benefit from AHSCT in patients who are refractory to currently available therapies. Importantly, patients whose disease relapses after AHSCT appear to respond to therapies to which they were previously refractory. Further well-designed controlled trials are required to define the magnitude and duration of benefit.

3. Immunobiology of CD: Potential Mechanisms of Action of AHSCT

The aetiology of CD is not fully understood. To varying degrees, environmental cues [including changes in gut microbiota] and genetic predisposition have been shown to be central to the development of CD.[29] Regardless of the causes, dysregulated innate and acquired immune responses are responsible for many of the manifestations of the disease. In particular, antigen-specific T and B cells directed towards microbial antigens may represent a mechanism for the chronic persistence of intestinal inflammation as they carry persistent effector functions. Serum antibodies against fungi and bacterial proteins are present in a higher proportion of CD patients compared to non-inflammatory bowel disease [IBD] controls.[30–33] Despite the presence of these antibodies correlating with a more severe clinical course for the disease, no pathogenic potential has been proven for antimicrobial humoral responses.

Increased CD4$^+$ T cell responses towards bacterially derived proteins have been recently described in CD patients, suggesting a potential mechanism for sustaining persistent disease.[34] Importantly, these responses were attributed a Th17/Th1 dominant response producing high amounts of IL-17, interferon γ [IFNγ] and TNFα among other cytokines previously implicated in CD pathophysiology.[35,36] In addition, Foxp3$^+$ T regulatory T_{REG} cells have been implicated in CD immunopathology. T_{REG} cells isolated from inflamed mucosa or peripheral blood of patients with IBD or animal models have been described as considerably different from those in peripheral lymphoid organs of healthy controls.[37] For example, patients with IBD exhibit reduced numbers of peripheral T_{REG} cells, whereas the mRNA expression levels of Foxp3 are elevated in the mucosa along with elevated levels of IL-17A, IL-1β and IL-6 mRNA.[38]

Mechanistic data relating to AHSCT in CD is very limited compared with other autoimmune diseases, such as multiple sclerosis [MS] and rheumatological diseases, where AHSCT has been shown to result in fundamental short- and long-term changes in the innate and adaptive immune system.[9,10] Clearly from any cytotoxic chemotherapy combined with ATG or other depleting serotherapy, there is an immediate immune-depleting effect on myeloid [granulocytic and monocytic] and lymphoid elements, including autoreactive effector T cells, B cells and plasma cells refractory to chronic immunosuppression and biological treatments.

Subsequently, a new and naive immune system is generated from haematopoietic progenitor cells which can potentially restore self-tolerance. Such immune resetting [or re-booting] is characterized by *de novo* generation of naive B cells and profound thymic reactivation with the re-emergence of thymic naive T cells with a new and diverse T cell receptor repertoire [TCR]. In addition, thymic output has been demonstrated to generate a pool of new and naive T_{REG} cells,[39–45] which may keep effector T cells under regulation that survived the conditioning regimen.[46] A small pilot study investigating the immunological effects of HSCT in CD demonstrated an abrogation of dysregulated T effector cell responses with a reduction of specifically bacterial lipopolysaccharide-recognizing TLR4-expressing as well as TNFα- and IFNγ-expressing monocytes together with an

increase in FoxP3$^+$ T_{REG} cells, which was predictive for treatment response at 3 month post-transplant.[20]

Although less well characterized, AHSCT also has profound effects on other aspects of the innate immune system. Many subsets are depleted in the acute phase of the transplant and return at varying time points following transplant. Neutrophils are among the first to recover, and subsequently natural killer [NK] cells and other innate lymphoid cells [ILCs] regenerate,[47] providing an efficient first line of defence against virus infection, e.g. NK cells in EBV and CMV infection,[48] and ILCs in opportunistic infections, preceding the generation of adaptive T cell responses. ILC3 subsets producing IL-22 seemed to play a crucial role in the protection against epithelial cell damage and in preserving intestinal stem cells and can also favour the recovery of thymic epithelial cells, thus allowing a more efficient and rapid reconstitution of the T-cell compartment.[49,50] Chronic activated dendritic cells and cytokine-secreting macrophages in secondary lymphoid organs or mucosa are also depleted. Dendritic cell subsets in peripheral blood are vastly depleted after immunoablation and only return to normal numbers beyond day +60 post-transplant.[51]

In addition to effect on the haematopoietic and immune systems, chemotherapy has profound impacts on the mucosa of the mouth and gut. The damaged gut is more permeable and a source of bacteraemia and takes time to heal with nutritional challenges and taste disturbances for several months. Following haematopoietic recovery at around 2 weeks post-transplant, mucosal healing proceeds rapidly. How this cycle of mucosal damage and healing, combined with alterations in the gut microbiome [dysbiosis] due to AHSCT and supportive treatments such as antibiotics, impacts upon the pathophysiology and relapse of CD is unknown and merits further investigation.

In summary, the potential mechanistic effects of AHSCT on CD are yet to be properly characterized. There are many aspects of the pathway to address in future studies of AHSCT in CD: the immediate effect of debulking of inflammatory cells, the disruption of the gut mucosa, and the subsequent healing alongside a regenerated but altered immune system and gut microbiota. By destroying or at least disrupting the dysfunctional immune system and other aspects of CD, AHSCT may not only provide therapeutic benefit but also provide insights as to the aetiology and pathogenesis of CD and warrants further investigation.

4. Indications and Procedural Aspects of AHSCT in CD

4.1. Severity of the disease, location and previous treatment

Consideration of AHSCT in patients with CD should be based on five pillars: a firmly established diagnosis of CD, objective evidence of inflammatory activity, severe course of the disease over time, inadequate response to available medical therapies, and consideration of surgery as an unsuitable option.

The diagnosis of CD should have been firmly established, based on clinical, endoscopic, histological and cross-sectional imaging findings.[2] Although not all these components are required in practice to establish a diagnosis of CD, patients being considered for AHSCT should undergo all these assessments to confirm the diagnosis and reassess disease extension and presence of complications such as strictures or penetrating disease with sepsis.[28]

Assessment of clinical symptoms is not sufficiently accurate to establish the severity of CD activity. Two studies demonstrated that 18% of patients with clinical symptoms [CDAI scores > 220] did not have significant lesions at endoscopy.[52,53] This discrepancy may be even higher following a therapeutic intervention; after treatment with TNF antagonists and/or immunosuppressants, 47% of patients in clinical remission [CDAI score < 150] still have severe endoscopic lesions, whereas 35% of those with persistent symptoms suggestive of active disease [CDAI score > 150] do not have ulcers.[54] Considering the discrepancy between the presence of active inflammatory lesions and symptoms in patients with CD, endoscopy, cross-sectional imaging and biomarkers are required to confirm active disease, and exclude symptoms due to structural lesions that would not respond [strictures] or worsen [internal fistula/abscess] with an intervention such as AHSCT.

Disease activity and disease severity refer to two distinct yet overlapping concepts. The chronic course of CD is typically characterized by alternating periods of active disease and remission. The pattern of relapses over time has considerable inter-individual variation; a population-based study observed that 55% of patients have a complicated course in terms of disease activity [chronic active disease or frequent relapses].[55] Whereas disease activity refers to the assessment of presence and grade of inflammation at a particular point in time, disease severity refers to the longitudinal course of the disease and integrates number, frequency and intensity [commonly referred as severity] of periods of activity, extent of disease, presence of perianal disease, past and current complications [stenosis, fistula, abscess], previous surgery requirements, presence of a stoma, length of resected bowel, and previous exposure and response to therapy.[56] It is important to consider the disease severity over time when assessing the suitability of a patient to undergo AHSCT.

Inadequate response or intolerance to all drug classes potentially available should be documented with an objective demonstration of active disease to consider a patient with CD as a candidate for AHSCT. The definition of inadequate response to each of the drug classes is essential in this evaluation. For corticosteroids, an inability to respond to therapy with methylprednisolone 1 mg/kg or equivalent after 4–6 weeks, or inability to completely withdraw the drug without a relapse, or having a relapse within 1 year of completing a course of corticosteroids, is considered as an inadequate response in current ECCO guidelines for management of CD.[2] With respect to immunosuppressants, azathioprine should be used at doses of 1.5–2.5 mg/kg/day, mercaptopurine at 0.75–1.5 mg/kg/day and intramuscular methotrexate at 25 mg/week; failure to achieve steroid-free remission after 16 weeks of therapy with these immunosuppressants should be considered as inadequate response.[2] For biological drugs, response should be evaluated at weeks 12–14 for TNF inhibitors,[2,57] week 8 for ustekinumab[58] and at week 14 for vedolizumab [after an additional administration of 300 mg of vedolizumab from week 10 in non-responders].[59] In patients not responding to induction therapy with a biological agent, and in those losing response without signs of intolerance, treatment should be intensified to the highest approved dose, possibly guided by therapeutic trough levels and potential presence of anti-drug antibodies. Confirmation of therapeutic drug levels should be considered before patients are considered resistant to anti-TNF therapy. If a response is not obtained after intensification, or the response is insufficient, switching to another biological class not previously used should be the first option.[2] If several classes of biological drugs, immunosuppressants and corticosteroids have failed, the patient could be a candidate for AHSCT.

Finally, surgery should be considered. Surgery may be unsuitable for patients with extensive disease in the small bowel, or patients who have undergone previous resections, if resection surgery in these

patients would have a risk for developing short bowel syndrome.[60] Surgery should be avoided in those patients having already developed short bowel syndrome. A further possible indication is the need to establish a permanent ostomy; some patients would never accept this type of surgery, and have continued severe active disease, which also increases the risk of mortality from CD. AHSCT may be carefully considered after balancing benefits and risks in these complex patients.

5. Selection and Assessment of Patients for AHSCT

The decision to recommend AHSCT for refractory CD requires an initial multidisciplinary consultation, taking into account patient and family considerations. Once a balanced justification for AHSCT has been reached, pre-AHSCT evaluation can be initiated. Assessment of candidates for AHSCT should include a global evaluation largely similar to patients with haematological malignancies, together with a more specific evaluation with respect to CD-related issues.

5.1. Evaluation of fitness for AHSCT

In general, patients should be in as good a general condition as possible, which should be assessed by performance status [PS] score.[61] In clinical practice, Karnofsky PS or ECOG PS are used most commonly for haematological patients. In CD patients with low PS scores, measures should be considered to improve PS before AHSCT, including parenteral nutrition and/or diversion surgery [stoma] that is reverted after completion of AHSCT. Although the age limit for AHSCT in haematological malignancies now exceeds 70 years, most CD patients will be offered AHSCT at younger age mainly due to the early age of disease presentation, with median time between CD diagnosis and AHSCT of 10–15 years in the largest trials.[17–27]

Anorexia, malnutrition and cachexia are frequent findings in patients with refractory CD and should be considered in patient selection. In the ASTIC trial body mass index ≤ 18 and serum albumin ≤20 g/L were exclusion criteria.[24] As transplant recipients are prone to conditioning-related cardiopulmonary complications, evaluation of cardiac and pulmonary function is considered mandatory in determining eligibility for transplantation. Pulmonary function tests including diffusion capacity for carbon monoxide [DLCO] may help in predicting risk for pulmonary complications post-tranplantation, with DLCO < 50% and Tiffeneau [FEV1/FVC ratio] index < 60% proposed as relative contraindications for AHSCT. In addition, attention should be given to smoking cessation pre-transplantation and offering alternatives in the peri- and post-transplant period, with similar considerations for alcohol intake. Electrocardiography should be routinely performed, along with transthoracic echocardiography [or multigated acquisition, MUGA, scan] to assess pre-transplant left ventricular ejection fraction [LVEF]. Many transplant centres will not proceed to AHSCT in patients with LVEF < 45%.[61]

Renal and liver function tests are also necessary, not only in predicting post-transplant complications, but also in determination of necessary dose reductions of conditioning regimen and supportive medication. In addition, serum ferritin levels are generally recommended because they are considered risk factors for various unfavourable transplant outcomes. However, this item may be less applicable to CD patients as red blood cell transfusion needs are generally lower compared with haematological cancers and as they may have an increased ferritin level related to chronic inflammation. Anaemia of any cause, including iron deficiency and chronic disease, needs evaluation and treatment. Full blood count and protein electrophoresis may be used to guide the decision to perform bone marrow examination prior to AHSCT, with some units routinely performing baseline marrow examination to ensure normal marrow reserve and to assess iron status. Haematinics and a coagulation screen should be checked routinely and vitamin deficiencies corrected.

All patients planned for AHSCT need to be screened for serious and/or chronic infections, including hepatitis B and C virus, HIV, human T-lymphotropic virus [HTLV] and *Treponema pallidum*. This is mandatory because of safety issues during stem cell collection and cryopreservation and, at least for some viruses, because of association with several post-transplant complications.[8] An infection-orientated medical history and determination of CMV, EBV, herpes simplex virus [HSV] and varicella zoster virus [VZV] serology is recommended particularly as the use of greater immunosuppression with ATG results in risks of viral reactivation more akin to allogeneic transplantation. Many centres also include a pre-transplant dental evaluation although the benefit is controversial.[62] Finally, fertility issues need to be discussed with patients in the reproductive period of life with consideration of semen cryopreservation in males and reproductive medicine consultation in females.[8,63] The prospect of a premature menopause also requires counselling and plans for hormone replacement therapy, where appropriate.

Whether co-morbidity scoring systems, as widely used in other diseases, have value in predicting different post-transplant outcome parameters in CD is not clear. Prospective scores are needed to assess whether the HCT-CI [co-morbidity index], which has been validated in patients undergoing transplantation for haematological malignancies, can also be useful for CD patients selected for AHSCT.[64]

5.2. Evaluation of CD status

Pre-transplant assessment of disease status should be performed with the aim of selecting only those patients with severe CD who have failed or are intolerant to all approved medical therapies and in whom intestinal damage is not irreversible [i.e. fibrotic stenosis]. The baseline assessment is also essential to gauge the benefit of AHSCT during follow-up. The severity of the clinical manifestations of CD should be evaluated with an established index of activity such as CDAI[65] or Harvey Bradshaw index. Ileocolonoscopy is the first-line procedure to establish the extent and severity of lesions, which should be quantified by an endoscopic activity index. The Crohn's Disease Endoscopic Index of Severity [CDEIS][66] and SES-CD[67] are validated endoscopic scores and those most used in both studies and clinical practice.

An upper endoscopy should be performed if there is previous history or suspicion of oesophageal–gastro-duodenal involvement. Given that transmural inflammation in CD can extend beyond the reach of endoscopy, imaging has an important role both in assessing disease activity and in excluding complications of CD, including structuring disease, fistulae and abscesses.[68] Cross-sectional imaging includes ultrasonography [US], computerized tomography [CT] and magnetic resonance [MR]. The diagnostic accuracy of US, CT and MR is high and not statistically different among the three modalities.[69] MR, which avoids the radiation of CT[70] and is less operator-dependent than US, is commonly used, and also provides the ability to quantify disease severity using validated radiological indices of activity. The magnetic resonance index of activity [MaRIA] seems to have the best operational characteristics for detecting not only disease activity but also for grading CD severity.[71,72]

It is important to exclude occult intra-abdominal or pelvic abscesses and other sources of sepsis as these patients may have had

multiple prior surgical procedures, developed fistulae and strictures as well as mesh repairs. Pre-transplant work-up should include a detailed assessment of the abdomen and pelvis to identify any potential sources of infection. Data from the ASTIC trial suggest that the presence of perianal disease is a risk factor associated with the development of serious adverse events.

Surgical intervention should be considered for specific complications such as stenosis or fistulae before starting the process of transplant to improve outcomes and to prevent infectious complications. Pelvic MR is mandatory in those patients with fistulizing perianal CD. Extensive drainage of abscesses and/or seton placement should be performed to prevent worsening of the disease or septic complications during the transplant period. In patients with perianal disease, surgical drainage of abscesses should be performed before the beginning of the procedure.[24]

6. AHSCT Procedure

6.1. Patient consent

AHSCT is a complex multistage procedure requiring informed written consent in accordance with the current standards of the Joint Accreditation Committee of ISCT [International Society of Cellular Therapy] and EBMT [JACIE, http://www.jacie.org]. Consent should be obtained following several consultations and associated assessments with the treating gastroenterologists and haematologists and their teams involved in the procedure. In practice, informed consent is routinely required for multiple stages, including mobilization chemotherapy, leukapheresis and the AHSCT procedure, along with some supportive care procedures [such as central venous catheter insertion]. Information, including written literature, should be provided in language patients can easily understand, along with the opportunity to ask questions and receive satisfactory responses. Specific information related to the potential risks and anticipated outcomes based on the appraisal of the current evidence base and assessments [of CD and fitness] should be provided on an individual basis, according to best estimates of the treating clinicians. In addition, all patients should provide separate consent for submission of their anonymised treatment and outcome data to the EBMT [or equivalent] registry in accordance with relevant data protection and other regulations, so as to permit inclusion in retrospective studies, prospective non-interventional studies and activity surveys. Patients on clinical trials should be treated in accordance with ICH Good Clinical Practice [GCP] [as per JACIE standards], including specific informed written consent for the trial.

6.2. Peripheral blood stem cell [PBSC] mobilization in CD

AHSCT is commonly performed with PBSCs [as opposed to bone marrow] based on a more straightforward procedure and better engraftment characteristics. The administration of G-CSF alone may induce flare in some autoimmune diseases and combining G-CSF with 'priming' chemotherapy, usually intermediate doses of cyclophosphamide, helps prevent flare, reduces T cell numbers in the graft and improves PBSC yields.[73–75] In addition, there may be a beneficial effect of cyclophosphamide on disease activity,[24] which although temporary, may control the disease prior to transplant and add to the overall therapeutic benefit.

The benefits and risks of cyclophosphamide priming depend on the dose used. No systematic studies have analysed the different types of mobilization chemotherapy, but the majority of patients received priming doses of cyclophosphamide of 2–4 g/m^2 with uromixetan [Mesna] and cautious hyperhydration followed by G-CSF 5–10 µg/kg.[17–26] Cyclophosphamide doses of 2 g/m^2 are usually sufficient and potentially safer than higher doses and a current trial is exploring a lower dosing of 1 g/m^2. When scheduling mobilization, immunosuppressive or immunomodulatory drugs should be discontinued as early as possible, which should help to minimize risks and prevent any inhibitory effects on successful mobilization.

When cyclophosphamide-primed mobilization fails, a second attempt at PBSC mobilization can be performed and despite the lack of evidence in patients with autoimmune diseases, the use of plerixafor and G-CSF may be reasonable in this situation, although the drug is currently unlicensed in this indication. In this setting a bone marrow harvest can be an option in selected cases.

Patients with CD undergoing mobilization are at increased risk of severe infection during the neutropenic period. Therefore, antibiotic prophylaxis and increased monitoring is recommended.[23] For this reason, consideration should be given to admitting the patient to the in-patient facility for the entire mobilization procedure, or at least during the neutropenic period. For patients undergoing mobilization as outpatients, a rapid pathway for hospital readmission and treatment of neutropenic sepsis with intravenous antibiotics within 1 h is strongly recommended.

In line with EBMT recommendations, the minimum dose of CD34$^+$ cells is 2 × 10^6/kg. In some units, a minimum of 3–4 × 10^6/kg CD34$^+$ cells may be collected, enabling clinicians to administer a higher dose to promote engraftment or store cells for back-up.

6.3. Conditioning regimens in CD

In CD, the most commonly used conditioning regimen has been cyclophosphamide 200 mg/kg with anti-T-cell serotherapy, in accordance with EBMT guidelines.[8] The choice of anti-T-cell serotherapy will depend on availability, but has been most commonly polyclonal rATG [from various pharmaceutical suppliers], although horse-derived ATG [hATG, again from various pharmaceutical suppliers] and other serotherapy, including monoclonal antibodies such as alemtuzumab, have been used in other autoimmune diseases in accordance with the EBMT guidelines. Caution should be exercised with ATG. Febrile reactions are commonly seen as a first dose effect with cytokine release. Such reactions are usually easily controlled with steroids and anti-histamines, but rarely anaphylaxis can occur. Staff involved in ATG administration should be aware of this risk, with appropriate treatment available.

EBMT guidelines have previously specified a conditioning regimen with fludarabine [150 mg/m^2], cyclophosphamide [120 mg/kg] and anti-T-cell serotherapy [such as rATG] for paediatric patients. Although not previously used in CD, this regimen has been incorporated into the current UK 'ASTIC-lite' trial protocol [available via clinicaltrials.gov] for adults to assess its safety and efficacy. However, outside of this trial, cyclophosphamide 200 mg/kg + rATG regimen [dose range 5–7.5 mg/kg] continues to be regarded as the standard of care in line with EBMT guidelines.[8]

6.4. The question of graft manipulation in autologous HSCT

There is no support for the routine use of graft manipulation in most autoimmune diseases,[8] despite early guidelines recommending the use of positive and negative lymphocyte depletion technology, most commonly as positive CD34$^+$ cell selection +/– negative lymphocyte subset depletion. Apart from some weak evidence in systemic lupus

erythematosus [SLE], none of the EBMT registry outcome analyses supports graft manipulation, whilst other data suggest that CD34+ selection may be associated with excess infective complications. In addition, the selection procedure adds significantly to the costs of AHSCT and potentially requires additional numbers of CD34+ cells to be harvested. One conflicting issue is that if ATG or other serotherapy is included in the conditioning regimen, detectable levels and biological depleting activity of therapeutic antibodies persist for several weeks beyond re-infusion of the autologous graft, and potentially into the weeks of engraftment and immune recovery. Although more studies are required, it may be that any potential benefits [or negative effects] of graft selection are overcome by the '*in-vivo*' T-cell depletion of ATG or other serotherapy.

In relation to CD, there have been only a small number of cases where CD34+ selection has been used, and these are insufficient for meaningful analysis in the EBMT dataset.[76] In the absence of evidence of benefit, the recommendation is that CD34+ selection or other graft manipulation is not used outside a clinical trial setting.

7. Early and Late Post-Transplant Follow Up

7.1. Early post-transplant complications in patients with CD

As CD patients typically have a long history of immunosuppression and added infective risks due to their disease, which will be compounded during the several phases of AHSCT [stem cell mobilization, conditioning and transplantation], additional measures over standard supportive care for autologous transplantation are required during these three periods.[17–27] Engraftment, defined by neutrophil count ≥ 0.5×10^9/L and unsupported platelet count ≥ 20×10^9/L, for three consecutive days is typically rapid in patients with CD. Some units avoid G-CSF based on potential disease flare, although this has not been reported following engraftment in CD patients.

The management of patients in the early post-transplant phase is focused on supportive care measures during conditioning and the subsequent cytopenic phase whilst awaiting engraftment. Although ambulatory [or 'outpatient'] transplants can be performed in other diseases, we do not recommend that this approach is used for patients with CD, who should be admitted and monitored as in-patients given their higher risk. This may reasonably extend to the PBSC mobilization phase, which is associated with several days of neutropenia.

The main risks in the early phase include drug-related toxicity, febrile neutropenia, and fluid and electrolyte imbalances, bleeding, gut toxicity, anaemia and complications of in-dwelling venous catheters [especially infections and thromobotic events]. ATG is a particular source of side-effects. These include infusion-related reactions which should be adequately managed according to transplant centre protocols with steroids and anti-histamines. Although ATG is usually given with high doses of methylprednisolone, there remains a potential for febrile and other reactions following cessation of the corticosteroids, potential serum sickness, which may require additional doses. Slow tapering of steroids over the first 7–10 days after ATG is recommended, whilst appropriate vigilance and cover for infection is maintained. The hyperhydration required for cyclophosphamide administration combined with the fluid retention associated with high-dose steroids and ATG may lead to fluid overload from an early stage and particular attention is required for fluid and electrolyte imbalance from the start of the conditioning.

As per local procedures, patients should be closely monitored with regular routine observations, along with once or twice daily weight measurements, fluid balance and stool chart recordings. Replacement fluids and electrolytes, blood product support [including irradiated products] and anti-microbial agents are given as per transplant centre protocols. Local barrier nursing policy should be enforced, including strict hand washing, en-suite rooms with clean air [high-efficiency particulate air filter and laminar air flow] and limited visitor access. Patients should be placed on a neutropenic diet as per centre protocols. The benefits of parenteral nutrition with nil-by-mouth regimens, used in some units treating CD with AHSCT, particularly those with fistulizing perianal disease, are unclear and decisions regarding nutritional support should be left to individual clinicians.

Platelet and red cell transfusions should be administered according to centre policy. Patients should receive irradiated blood products [to protect against transfusion-related graft versus host disease] from 7 days prior to mobilization and continued according to unit policy. CMV-negative blood products may be considered according to local policy, although universal leucodepletion by many blood services may mean this is deemed unnecessary.

Antimicrobial prophylaxis with broad-spectrum antibacterials [such as an oral quinolone] with extension to intravenous prophylactic broad-spectrum antibiotics [such as tazobactam-piperacillin or carbopenems] can be considered in conjunction with local microbiological advice. Active treatment of infection should follow institutional protocols and local microbiological advice. Prophylactic antifungal agents [e.g. azoles] should be given from the start of the conditioning regimen or from day 0 until 3 months post-transplant, with careful monitoring of liver function tests. Anti-herpes virus treatment [aciclovir or valaciclovir] should be given from the start of conditioning for 12 months post-transplant. Pneumocystis jiroveci prophylaxis [oral co-trimoxazole or atovaquone or nebulized pentamidine according to local policies and tolerance] should be given following stable engraftment for at least 6 months and/or until adequate recovery of peripheral blood CD4+ counts as per local protocols. All patients positive for anti-toxoplasma antibodies should receive oral co-trimoxazole daily until day –1 then after reconstitution of blood counts for 6 months, as tolerated [since nebulized pentamidine does not provide prophylaxis for toxoplasma]. In addition, consideration should be given to risk of reactivation of tuberculosis and hepatitis viruses, with prophylaxis through the period of immune suppression where appropriate. Pet exposure should be avoided until adequate immune recovery as per unit protocols.

Given the prolonged history of corticosteroid treatment in many patients, a high suspicion of adrenal insufficiency, especially during the management of febrile episodes, is recommended at all stages of the transplant.

7.2. Post-discharge monitoring and complications

All patients should remain under the direct routine care of the Transplant Programme specialist for at least 100 days post-transplant, or longer, if considered necessary. Central venous catheters should be removed at the earliest opportunity and ideally prior to discharge from the in-patient unit to reduce the risk of infection.

Viral reactivation should be managed with screening and pre-emptive treatment according to the centre policy. Prospective screening of quantitative CMV and EBV PCR for 3 months or until CD4 recovery is recommended. A high suspicion of CMV, EBV and other viral reactivations is also recommended in cases of fever of unknown origin or other infective complications. Local protocols for pre-emptive treatment of CMV reactivation should be followed. At present, the majority of EBV reactivations following AHSCT for autoimmune diseases are self-resolving, although data are limited in CD.

EBV reactivation rarely results in post-transplant lymphoproliferative disease [PTLD] and patients should only be given pre-emptive rituximab if there is evidence of raised lactate dehydrogenase or a positive PET-CT scan or other imaging, and ideally following rapidly obtained confirmatory biopsy, if feasible.

Weekly investigations post-AHSCT include full blood count, C-reactive protein [CRP], liver, renal and coagulation function, CMV, EBV and potentially other viruses by peripheral blood PCR from discharge to day +60. Virology monitoring can be reduced to fortnightly until day +100 if PCRs are consistently negative.

From day +100, full blood count, CRP, liver, renal and coagulation function, CMV, EBV and other viruses by peripheral blood PCR, immunoglobulin profile, and lymphocyte subsets should be repeated on a 3-month basis through the first year. Thereafter the follow up and investigations should depend on the discretion of the transplant and gastroenterology teams, but indefinite follow up on a minimum 6- to 12-month basis is recommended both for monitoring of the CD and also for screening for AHSCT-related late effects.

7.3. Gastroenterological follow-up and management of CD activity post-transplant

The first year after treatment includes an early safety visit at month 1. Further visits are scheduled for months 3, 6 and 12 with formal assessment of intestinal symptoms, perianal manifestations and lesions, description of extra-intestinal manifestations and quality of life assessments. In addition to the routine blood tests outlined above, endoscopic assessments and surveillance are also recommended at 6 months post-HSCT and again at 12 months and then annually for the first 5 years.

Considering the severe course of the disease in these patients before AHSCT, the persistence or recurrence of endoscopic lesions should lead to the re-introduction of specific therapies. If relapse or progression is suspected by the gastroenterologist, formal assessments to confirm disease activity and presence of complications must be undertaken. Confounding factors such as *Clostridium difficile* and viral infections must be excluded.

Although the persistence of endoscopic lesions [excluding those related to infections] may be considered as a treatment failure, recent experiences suggest that the re-introduction of drugs which were previously considered as failures may be worthwhile. This is an area that requires formal evaluation. In the meantime, we recommend treatment with highly effective therapy for CD, such as the combination of immunosuppressants and a TNF inhibitor in patients with endoscopically or radiologically active disease according to the current ECCO guidelines.

7.4. Late effects and long-term complications following AHSCT in CD

Long-term complications following AHSCT are a product not only of the conditioning, but also of the many years of prior treatment, current maintenance treatment and treatment for relapsed disease alongside the underlying disease process. Late effects include endocrinopathy and reproductive failure, infection, cardiovascular risk, secondary auto-immune diseases [especially thyroid or immune thrombocytopenia], secondary malignancies [in particular skin cancers and myelodysplastic syndrome], along with fatigue and psychological problems.[8,77,79,80] Annual assessment in a dedicated post-transplant late effects clinic in accordance with current guidelines is recommended.[8,77] Post-transplant revaccinations should be given according to international guidelines.[8,9,77,78]

A summary of the procedural recommendations is available as the Supplementary material (available at *ECCO-JCC* online) to this review.

8. Future Development of AHSCT in CD

Ideally future development of AHSCT in CD should take place within well-structured clinical trials. However, inclusion in a clinical trial is by no means possible in every patient and patients will continue to be treated on an individual compassionate basis according to clinical need. It is standard practice to register all patients undergoing HSCT with the EBMT registry database, which facilitates retrospective studies. Alternatively, EBMT-approved prospective non-interventional studies are a form of audit which enable data collection in a standardized format and thereby have advantages over retrospective studies. Collaboration between the EBMT and ECCO aims to maximize registration in the database and long-term disease-specific follow-up for meaningful analysis. Alongside it is hoped that these recommendations will promote safe high-quality delivery of AHSCT, whether patients are treated on or off trials.

8.1. Accreditation, quality, economics and delivery of AHSCT in CD

HSCT is a complex multidisciplinary medical specialty, needing both the involvement of a multidisciplinary staff and an advanced level of diagnostic expertise. Such complexity and the high frequency of potentially severe adverse events, particularly in the allogeneic setting, have led to an increasing need for standardization of the process. Almost 20 years ago, the EBMT established JACIE, which is the acronym of Joint Accreditation Committee of ISCT [International Society of Cellular Therapy] and EBMT. The goal was an internationally harmonized accreditation system based on agreed quality standards and implemented by teams of voluntary inspectors. The JACIE system has quickly developed as a popular tool to promote a homogeneous standard of care across Europe, supporting the concept that a quality system created within standards established by experienced professionals could become a part of the everyday work, providing better control of this complex process and including clinical care of patients, collection of stem cells and donor care and processing/characterization of the graft. Since inception, JACIE has performed over 530 accreditation inspections [62% first-time; 38% reaccreditation] in 25 countries, representing approximately 40% of transplant centres in Europe. JACIE accreditation can be obtained for autologous and allogeneic HSCT. Recently published data showed a positive impact of JACIE accreditation in the clinical outcome of patients.[81]

Safety of the AHSCT procedure is a major concern in the setting of chronic, non-neoplastic diseases, such as CD, in which there may be existing damage to vital organs, and it requires a strong interaction between the IBD specialists and the transplant team, together with specific training of the nursing staff. CD patients may have existing damage to the gut and potentially other organs with the possibility of multi-resistant microbiological colonization. The inclusion of ATG and/or therapeutic monoclonal antibodies in conditioning regimens resulting in a higher degree of immunosuppression necessitates more cautious post-transplant monitoring compared with other patients undergoing autologous HSCT for standard indications, akin to that following allogeneic HSCT. Special protocols for prevention and intensive treatment of infective complications must be in place. In addition, networks of specialists with an interest in AHSCT for CD would also be valuable for non-specialist gastroenterologists to seek

advice regarding the suitability of AHSCT in given patients. This is especially important as identification of poor-prognosis patients at an early and potentially reversible stage of CD is key to improved outcomes through arresting progression and limiting toxicity. JACIE accreditation for centres performing transplants for CD is highly recommended, ideally to the level of accreditation for allogeneic HSCT, requiring broader experience with severely immunosuppressed patients and other higher risks typical of this transplant type.

As well as long-term efficacy and safety, there are also major health economic questions between AHSCT and standard alternatives in CD. The costs of the AHSCT procedure are limited to a one-off treatment where effects may be sustained potentially for several years, which contrasts with the ongoing costs of modern biological therapies for CD, potentially administered indefinitely to complex patients, as explored in relation to AHSCT in other autoimmune diseases.[82,83] Formal health economic modelling is warranted in CD to fully evaluate the cost-effectiveness of HSCT vs the standard of care in other diseases. This is most appropriately performed in conjunction with prospective clinical trials where appropriate health-related quality of life measures are collected prospectively.[84]

8.2. Clinical trials and other research questions

ASTIC remains the only controlled trial of AHSCT in patients with treatment-refractory CD.[26,27] As discussed above it was reported as a negative trial as few patients after AHSCT met the stringent primary composite endpoint of clinical remission for 3 months off all therapy with no evidence of active disease on endoscopy and radiology of the entire intestine. In addition, there was a high burden of side-effects in patients undergoing AHSCT and one patient died. However, it should not be assumed that this single trial provides the definitive answer regarding the benefit of AHSCT in CD. In addition to the stringent primary endpoint, there are several further drawbacks to the ASTIC trial design. Firstly, the doses of cyclophosphamide used are higher than current guidelines recommend, which may have added to the burden of toxicity reported.[85,86] In addition, all patients received 4 g/m^2 cyclophosphamide at mobilization prior to randomization; so even patients in the control group had significant cyclophosphamide exposure. Finally, patients were not treated with maintenance therapy after AHSCT.

Importantly, those restarted on anti-TNF therapy due to disease recurrence appeared to respond even though they had been refractory to this drug class prior to HSCT.[23,25] Therefore, further clinical research is required to address the following unanswered questions:

1] What is the absolute benefit risk ratio of AHSCT compared to best conventional care using a straight randomization between each care pathway?
2] What is the benefit of AHSCT compared to conventional care using clinical endpoints such as mucosal healing?
3] Can you maintain efficacy but reduce morbidity with a low-intensity mobilization/conditioning regimen?
4] What is the duration of benefit of AHSCT?
5] Will patients respond to therapies to which they were previously refractory?
6] Would introduction of such maintenance therapy improve outcome and the duration of benefit?
7] What is the nature of the immune reconditioning that occurs in CD following AHSCT?
8] How does HSCT impact on the dysbiosis of intestinal microbiota, which is probably related to the pathogenesis of CD?

Several of these questions will be answered by projects that are currently ongoing, including analysis of the long-term follow up of patients undergoing AHSCT as part of the ASTIC trial as well as an analysis of all patients who have undergone AHSCT for CD registered on the EBMT database.[76] Analysis of the mucosal T cell repertoire and disease activity before and after AHSCT will investigate the mechanisms of disease remission and relapse.[87] However, further clinical trials are required to give clear answers as to the benefit and risks of AHSCT using a low-intensity mobilization and conditioning regimen [as in the new ASTIC-lite trial]. These should use currently required endpoints such as mucosal healing and patient-reported outcome. Planned re-introduction of maintenance anti-TNF therapy in patients with evidence of mucosal disease recurrence will allow the impact and efficacy of early salvage/maintenance therapy to be assessed. Long-term follow up will be required to assess the duration of benefit and the health economic impact of AHSCT. We should not underestimate the morbidity and cost related to allowing patients with refractory active CD to continue on partially effective therapies.

9. Conclusions

AHSCT for CD has evolved gradually on the back of circumstantial data, sporadic treatments, small-scale clinical trials, large database studies and one RCT. Close co-operation between haematology [EBMT] and gastroenterology [ECCO] is continuing at a European level, but is also needed at national levels. Accredited centres of specialization and experience will be required to bring AHSCT appropriately into clinical practice alongside modern biological treatments in tandem with further basic scientific studies, clinical trials and health economic evaluations.

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Author Contributions

All authors made substantial contributions to all of the following: [1] the conception and design of the review, [2] drafting the article and revising it critically for important intellectual content, [3] final approval of the version to be submitted, with declarations of interest declared to the JCC Office as per

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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