Improved Therapeutic Approaches are Needed to Manage Graft-versus-Host Disease

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Abstract
Allogeneic haematopoietic stem cell transplantation (alloHSCT) offers a potentially curative therapy for patients suffering from diseases of the haematopoietic system but requires a high level of expertise and is both resource intensive and expensive. A frequent and life-threatening complication is graft-versus-host disease (GvHD). Acute GvHD (aGvHD) generally causes skin, gastrointestinal and liver symptoms, but chronic GvHD (cGvHD) has a different pathophysiology and may affect nearly every organ or tissue of the body. In Europe, GvHD prophylaxis is generally a calcineurin inhibitor in combination with methotrexate, with high-dose systemic steroids used for advanced GvHD treatment. Between 39% and 59% of alloHSCT patients will develop aGvHD and around 36–37% will develop cGvHD. Steroid response decreases with increasing disease severity, which in turn leads to an increase in non-relapse mortality. GvHD imposes a financial burden on healthcare systems, significantly increasing post-alloHSCT costs. Increased GvHD disease severity magnifies this. Balancing immunosuppression to control the GvHD whilst maintaining a degree of immunocompetence against infection is critical. European GvHD guidelines acknowledge the lack of evidence to support a standard second-line therapy, and improved long-term outcomes and quality-of-life (QoL) remain an unmet need. Evidence generation for potential treatments is challenging. Issues to overcome include choice of comparator (extensive off-label usage); blinding; selection of relevant patient-reported outcome measures (PROMs); and rarity of the condition, which may infeasibly increase timescales to achieve clinical and statistical relevance.

1 Introduction
For certain life-threatening haematological diseases and non-malignant diseases, an allogeneic haematopoietic stem cell transplantation (alloHSCT) offers patients the opportunity of a potentially curative therapy [1, 2]. Several advances in alloHSCT procedures including better tolerated and safer transplantation therapies have allowed more patients to reach complete disease response, with a lower patient burden. Subsequently, more patients have become eligible for alloHSCT, which has expanded access and also led to a reduction in transplant-related morbidity and mortality, as well as improved outcomes [3]. Increasingly, older patients with higher risk factors and those with unrelated and/or mismatched donors may now benefit from alloHSCT [4].

According to the European Society for Blood and Marrow Transplantation (EBMT) activity survey report, there were 19,798 alloHSCTs performed in Europe in 2019, with these figures coming from 700 reporting centres in 51 countries [5].

AlloHSCT procedures are extremely complex and typically can be divided into several consecutive steps:

- Selection of patients and collection of stem cells: Assessment of the eligibility for transplantation including basic investigations for fitness of both donor and recipient.
Conditioning therapy: Conditioning prepares the recipient’s marrow for transplantation, for example, myeloablation or immunosuppression [7].

Transplantation and engraftment: Donor cells are infused and the patients are then kept in hospital until they have recovered sufficient neutrophil numbers to reduce the risk of infection. Engraftment occurs when the donor’s cells are successfully integrated with the host’s [8].

Post-graft immunosuppression and post-transplant follow-up: Complications such as infection and potentially life-threatening graft-versus-host disease (GvHD) are monitored and treated [6].

Disease- and patient-related factors such as initial diagnosis, disease status (e.g. remission, refractory or relapsed disease), patient age, functional status, comorbid conditions and general condition are all key factors that influence the choice of alloHSCT approach and timing, as well as the conditioning regimen [9, 10]. Physicians need to find a delicate balance between patient characteristics, the risk of relapse/progression of the underlying malignant disease, and the late effects of the procedure.

Given the complexity of the procedure, alloHSCT requires a high level of expertise before, during and after transplantation administration, and alloHSCTs are therefore generally only administered within specialised centres operating a multidisciplinary team of physicians, laboratory scientists, pharmacists and nurses [11].

AlloHSCT is a resource-intensive and expensive procedure [12], but there are scant data on the cost. A German retrospective claims database study found the mean direct costs of alloHSCT were €246,266 and the indirect costs were €52,939 per adult patient with acute lymphoblastic leukaemia [13]. A similar US study found that for myeloablative alloHSCT the median total healthcare cost at day 100 was $289,283 [12].

For patients, alloHSCT is an intensive potentially curative treatment that is associated with significant treatment failure, psychological morbidity and physical morbidities such as organ complications or death [14]. Failure of the alloHSCT, for whatever reason (e.g. malignant disease relapse or graft failure) leaves the patient with a poor prognosis and few options for potentially successful salvage treatment [15].

2 Graft-versus-Host Disease (GvHD) is a Life-Threatening and Expensive Complication of Allogeneic Haematopoietic Stem Cell Transplantation (alloHSCT)

GvHD is a multisystem disorder that is broadly divided into acute GvHD (aGvHD) and chronic GvHD (cGvHD) based on signs and symptoms, rather than the time of onset (i.e. less or more than 100 days after HSCT) [16]. The newer category of chronic overlap cGvHD may also be seen, along with further categories of persistent, recurrent and late-onset aGvHD [17].

Acute GvHD is driven mainly by mature donor T cells [18] and is typified by rapid onset as a result of a cytokine storm that manifests in three organs [19]:

- Skin with a maculopapular skin rash;
- Liver with bile duct damage leading to cholestasis and jaundice;
- Gastrointestinal (GI) tract with nausea, upper GI symptoms such as vomiting and anorexia and lower GI symptoms such as watery or bloody diarrhoea and abdominal pain.

Chronic GvHD is more complex and involves both T and B cells and can affect nearly every organ or tissue in the body because of its different pathophysiology from aGvHD [20].

An International task force has recommended that the MAGIC (Mount Sinai Acute GvHD International Consortium) criteria are utilised for staging aGvHD [21] and the NIH (National Institutes of Health) 2014 [22] criteria for cGvHD [16]. Regardless of the grading system used, there
has been a shift from time to onset to the severity for staging [23].

Despite the administration of GvHD prophylaxis, between 39% and 59% of alloHSCT patients will develop aGvHD [24, 25], and around 36% will develop cGvHD [25, 26]. The frequency of GvHD reported in the individual studies depends mainly on the degree of match between donor and recipient, graft type, T-cell depletion/repletion strategies, conditioning regimen, GvHD prophylaxis, and the age of the patient/donor [27].

In some studies, GvHD triples mortality rates [28, 29] and approximately 80% of patients with refractory aGvHD die [1]. Whilst GvHD may not always be fatal, the morbidity it causes places a heavy burden on the patients and the healthcare teams through their survivorship. Post-alloHSCT, GvHD is currently the most challenging issue for physicians to manage [30]. Table 1 illustrates a summary of the percentage of alloHSCT recipients developing GvHD and refractory GvHD and the associated mortality/survival. It is heartening to note that progressively over time, meaningful progress has been made in both reducing the incidence of GvHD and increasing the survival of patients following alloHSCT [31].

In HSCT survivors, GvHD is a major determinant of long-term quality-of-life (QoL) [37], but it remains to be better documented. Lee et al. [37] in 2006 reported that patients who develop aGvHD show a profound and lasting decline in their QoL compared to those who do not develop GvHD. Patients with acute or chronic GvHD may feel uncertain about the nature of GvHD and its progression, as well as struggling to deal with their symptoms and to accept new restrictions to their daily life caused by GvHD and related treatment [38].

GvHD also has a significant impact on healthcare resource utilisation, with patients experiencing more and longer hospitalisations and incurring greater healthcare costs [39–42]. A study in the USA found significantly greater 1-year post-alloHSCT costs for patients with aGvHD compared to those without aGvHD ($466,720 vs. $263,568; P < 0.001), with inpatient care being the primary cost driver [43]. A Swedish real-world study found that the cumulative direct medical costs over 3 years post-alloHSCT for patients

| Type of GvHD | Percent of alloHSCT recipients developing GvHD | Percent developing GvHD by grade | Survival with GvHD by grade | Mortality with GvHD | Percentage of GvHD patients developing refractory GvHD |
|--------------|---------------------------------------------|---------------------------------|---------------------------|-------------------|-----------------------------------------------|
| aGvHD        | 39% with sibling donors [24]                 | 12% grade II [25]               | 91% 100-day overall survival (OS) grade II [32] | 16.2% aGvHD (5.3% without GvHD) [28] | 36% grade II–IV steroid-refractory aGvHD [25] |
|              | 59% with unrelated donors [24]              | 11–16% grade III–IV [25, 31]    | 65% 100-day OS grade III–IV [32] | 8–16% [35] |                                                |
|              | 49% [25]                                    |                                 | 86% 1-year OS grade III–IV [33] | 49% grade IV aGvHD 1-year treatment-related mortality (TRM)* [34] |                                                |
|              |                                            |                                 |                            | 79% 2-year OS grade III–IV [33] |                                                |
|              |                                            |                                 |                            | 29% 3-year OS grade III–IV [31] |                                                |
|              |                                            |                                 |                            | 38% 1-year OS grade IV [34] |                                                |
| cGvHD        | 36% [26]                                    | 19% grade 2 [25]                | 82%, 73% and 71% OS with moderate to severe cGvHD at 1, 2 and 3 years, respectively [33] | 35% TRM (11% without cGvHD) [29] | 31% all grades steroid-refractory [25] |
|              | 37% [25]                                    | 8% grade 3 [25]                 | 53% 3 years OS [26] | 8–11% 3-year mortality [35] |                                                |
|              |                                            |                                 |                            | 45% 5 years OS [26] |                                                |

Note: AlloHSCT outcomes are dependent on multiple factors, making it difficult to provide generally applicable ranges, especially when considering recent trends of improved alloHSCT procedures and regimens [31, 36]. Relevant factors include recipient age, patient fitness/co-morbidities, underlying malignant/non-malignant disease, graft source, donor type/age, conditioning regimen, pre alloHSCT treatment, GvHD prophylaxis and post-alloHSCT treatment

*Transplant-related mortality defined as death unrelated to relapse or disease progression
with moderate-to-severe cGvHD were approximately fourfold higher than for patients without cGvHD [41].

As GvHD severity increases, post-alloHSCT costs are significantly increased, for example, grade III versus grade IV aGvHD,  𝑃 = 0.03 [41, 44]. This may be because increasing severity indicates steroid-resistant GvHD. Such steroid-resistant GvHD had been shown to double the costs of patients compared to those without GvHD [45]. The mean total initial hospitalisation costs of patients with aGvHD who were either steroid-resistant or high risk were $205,880 compared to $97,417 (𝑃 < 0.001) for those with no aGvHD as reported in a US retrospective claims database analysis [46]. For patients with steroid-resistant cGvHD, mean total costs were $532,673 versus no cGvHD costs of $252,909 (𝑃 < 0.001) in the 2 years following alloHSCT in another US retrospective claims database analysis [45].

### 3 Current and Potential Treatments

Currently in Europe, the immunosuppressive prophylaxis regimen for GvHD is provided after myeloablative conditioning and relies on a calcineurin inhibitor (CNI) in combination with methotrexate [30]. Typically, patients undergoing reduced-intensity conditioning will be given cyclosporine A alone or in combination with mycophenolate mofetil (MMF) as prophylaxis, although these have not been tested with a large, randomized, prospective clinical trial [30]. In recent times, antithymocyte globulin (ATG) or post-transplant cyclophosphamide is more frequently used to decrease the occurrence of acute and chronic GVHD [30, 47, 48].

For patients who develop Grade I aGvHD (involving skin only), first-line treatment is with topical steroids alone, but for Grades II–IV, first-line treatment is with high-dose systemic steroids (e.g. methyl-prednisolone) [1]. However, the likelihood of steroid response decreases with increasing aGvHD severity [1], with around a third to half of patients becoming steroid-resistant and having a poor prognosis [30]. Lack of response, or steroid resistance, is typically seen within a few weeks of treatment initiation and will increase the patients’ risk of non-relapse mortality compared to those responding to treatment [49].

Following alloHSCT, cGvHD first-line treatment includes steroids either alone or in combination with a CNI [4]. For mild cGvHD (with one to two involved organs), topical steroids, topical CNI or phototherapy may be considered, however, for moderate or severe cGvHD (≥ three involved organs), systemic steroid (prednisone) treatment should be considered [4].

For physicians treating GvHD, the key aim is to balance the need for immunosuppression in order to control the GvHD, whilst maintaining a degree of immunocompetence against infection [1, 4]. This means that viral and fungal infections are frequent complications of prolonged steroid therapy, and anti-infective prophylaxis including revaccinations should be considered for these patients [1].

With second-line and subsequent lines of therapies for GvHD, a wide range of pharmaceutical agents are currently recommended [50]. However, there is no accepted standard-of-care treatment for patients with steroid-refractory aGvHD, with treatment choice generally down to physician experience [51] (Figs. 1 and 2). Currently (in the USA only) ruxolitinib is indicated for steroid-refractory aGvHD and ruxolitinib may therefore be used second line, although efficacy evidence in this population is currently limited to an open-label phase III clinical trial [52]. However, with new and ongoing trials [53, 54], the treatment landscape in Europe is expected to change, with new options becoming available and current second-line therapies becoming third and subsequent lines of therapies.

For steroid-refractory patients, physicians may add in another therapy in combination with steroids, but the goal would be to taper the dose of steroids down as soon as possible, to avoid the detrimental side effects on patients associated with prolonged use of corticosteroids. Subsequent lines of therapy might be combined, for example etanercept plus basiliximab [51]. The short-term duration of the effect with these subsequent lines of therapy can be extremely disappointing, with around an 80% mortality rate seen, especially if the lower gastrointestinal tract is involved in patients with aGvHD [1].

Other non-pharmacological therapies such as extracorporeal photopheresis (ECP) are recommended as second-line treatment in some guidelines, for example the British Committee for Standards in Haematology guidelines for both aGvHD [55] and cGvHD [56].

The most recent update of the EBMT recommendations on GvHD prophylaxis and management were published in 2020 [57]. These guidelines acknowledged recent research and recommend initiation of systemic treatment only for grade II or higher aGvHD and lower steroid doses for grade II aGvHD with isolated skin or upper gastrointestinal tract manifestations [57].

However, the long-standing debate over a suitable choice of second-line therapy for GvHD was not resolved in the current guidelines due to a lack of evidence [57]. Therefore, the consensus group were unable to recommend a standard second-line treatment for aGvHD despite the wide range of second-line treatment options including alemtuzumab, α1-antitripsin, basiliximab, cellular therapies such as mesenchymal stromal cells and regulatory T cells, daclizumab, ECP, faecal microbiota transplantation, JAK inhibitors, mycophenolate mofetil, methotrexate, pentostatin, rabbit anti-thymocyte globulin, sirolimus and vedolizumab [57]. The best recommendation the group could offer for
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Second-line treatment of GvHD was that physicians should follow their institutional guidelines and patients should be treated within clinical trials when possible [57]. In this field, a few drugs show promise and have been approved in the USA by the Food and Drug Administration (FDA):

- In 2017, ibrutinib was approved for steroid-resistant cGvHD based on a phase II/II trial (NCT02195869) [62], and a phase III trial (NCT02959944; iNTEGRATE) was completed in 2020 [63, 64].
- In 2019, ruxolitinib was approved for steroid-refractory aGvHD based on phase II trials only (although a phase III trial (NCT02913261; REACH2) has subsequently been completed) [52, 54].
- In 2021, belumosudil, a kinase inhibitor, was approved for the treatment of adult and paediatric patients with cGvHD after failure of at least two prior lines of systemic treatment based on a phase II trial (NCT03640481; ROCKstar) [61].

However, it is important to note that FDA approval, especially when based on phase I or II data, demonstrates the unmet clinical need but not necessarily the actual clinical benefit when utilised outside of a carefully controlled clinical trial. For example, one can consider the recent furore over aducanumab for Alzheimer’s disease, which was granted accelerated FDA approval based on a surrogate endpoint with some disputing if it will actually lead to clinical benefit [65].

Ideally, GvHD should be prevented but there are still no European Medicines Agency (EMA)-approved agents for the prevention or treatment of aGvHD. According to the EBMT Handbook, what may be required is earlier risk-adapted or pre-emptive treatment strategies [1], as treatment of aGvHD may currently be initiated too late, when tissue destruction by the allogenic immune response is already advanced [19]. Therefore, biomarkers might be useful in identifying high-risk patients at an earlier stage [19] so that current treatments can be better utilised [66]. The so-called MAGIC biomarkers (ST2 and REG3α) [67] are the most advanced and best

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**Fig. 1** Overview of treatment options for acute graft-versus-host disease (aGvHD). Source: Modified from Dignan, Clark, et al. [55] and Penack et al. [57]. "Ruxolitinib has US FDA approval for patients with aGvHD based on phase II trials only (although a phase III trial (NCT02913261; REACH2) has subsequently been completed) [52, 54]. CSA cyclosporine, ECP extracorporeal photopheresis, FDA Food and Drug Administration, GI gastrointestinal, IL-2 interleukin-2, IV intravenous, mTOR mechanistic target of rapamycin, MMF mycophenolate mofetil, TNF tumour necrosis factor

| Grade I                                      | Grade II                                      | Grade III-IV                              |
|----------------------------------------------|-----------------------------------------------|-------------------------------------------|
| CSA and topical agents                       | Start oral/IV corticosteroids                 | Start IV methylprednisolone              |
| Enrolment in clinical trials                 | Optimization CSA level                        | Skin: topical agents                      |
| Methotrexate                                 | If no improvement after 5 days or progression within 72 hours, add second-line agent | GI: nonabsorbable steroids                |
| Pentostatin                                  | First-line options                            | Ruxolitiniba                              |
| Methotrexate                                 | Methotrexate                                  | Methylprednisolone                        |
| Enrolment in clinical trials                 | Pentostatin                                   | MMF                                       |
| Methotrexate                                 | Methotrexate                                  | Rabbit anti-thymocyte globulin            |
| Methotrexate                                 | Methotrexate                                  | ECP                                       |
| Cell therapy i.e. mesenchymal stem cells and regulatory T cells | Cell therapy i.e. mesenchymal stem cells and regulatory T cells | Cell therapy i.e. mesenchymal stem cells and regulatory T cells |
| Cell therapy i.e. mesenchymal stem cells and regulatory T cells | Cell therapy i.e. mesenchymal stem cells and regulatory T cells | Cell therapy i.e. mesenchymal stem cells and regulatory T cells |
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Researchers are utilizing advances in the understanding of the pathological mechanisms of aGvHD to investigate new treatment strategies for aGvHD. For instance, lymphocyte trafficking to affected organs plays an important role leading to aGvHD, and vedolizumab inhibits the migration of both naïve and activated lymphocytes and is therefore being investigated further [68, 69]. Table 2 provides a summary of the products currently being investigated for both aGvHD and cGvHD.

Whilst many agents have been evaluated either alone or in combination with steroids for first- or second-line use in GvHD, there is a scarcity of randomized, double-blind, controlled trials and for most of the agents, long-term efficacy still evades researchers [1]. This means that numerous products are being used off-label [75] and it is hoped that some of the new treatment strategies currently being evaluated might be able to definitively prove their efficacy and be recommended by the EBMT rather than just offered as options.

**Fig. 2** Overview of treatment options for chronic graft-versus-host disease (cGvHD). Source: Modified from Dignan, Amrolia, et al. [56] and Saidu et al. [58]. A phase III trial for ruxolitinib in patients with cGvHD (NCT03112603; REACH3) is expected to complete in 2022 [59], although results have been published [60]. bIrbrutinib is US FDA approved for patients with cGVHD after failure of at least two prior systemic therapies [61]. ECP extracorporeal photopheresis, mTOR mechanistic target of rapamycin, MMF mycophenolate mofetil

4 Conclusion

Despite significant progress in the understanding and management of alloHSCT complications, the high incidence rate of GvHD and its severe consequences remain a major setback in the face of both the patient’s personal and the healthcare system’s investment in the transplant. To ensure optimal clinical benefit from alloHSCT, the long-term goal is to treat according to individual disease biology, and it is imperative to prevent or control GvHD whilst preserving the beneficial effects of the graft (i.e., the graft-versus-cancer effects against residual disease) particularly for high-risk transplant populations [76].

Newer treatment strategies to improve long-term post-transplant outcomes and the QoL of the HSCT recipients remain an unmet need in this therapeutic field [18]. It would be appropriate to develop targeted treatment of the root cause of GvHD, rather than focussing on the consequence, such as systemic inflammation (e.g. cytokine storm) and the resulting immunosuppression. This strategy would allow selective inhibition of alloreactive T cells whilst preserving the anti-tumour adaptive immune responses, that is, maintaining the
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...impact on cancer while limiting the damage to tissues. In the meantime, patients and clinicians would settle for better and more evidence-based therapeutic options that improve clinical outcomes and QoL for patients who develop GvHD.

Guidance on cGVHD trials was issued by the National Institutes of Health (NIH) Consensus Conference that was convened in 2020 [77]. However, generating a suitable evidence base will be challenging, and trade off may be required to achieve the most appropriate trial design. For example, an adaptive trial design may be considered to increase the number of participants allocated to the most effective treatment arm, although such trial designs may be more appropriate for early drug development [77]. Randomised, double-blind, controlled trials are the gold standard, but have proven to be challenging in rare conditions [78]. Choice of comparator is difficult when there is no EMA-approved product for steroid-refractory GvHD and products are used off-label, with different policies in different institutions and European countries. Comparison to the physician’s best available therapy (BAT) may be a solution [77], but this may compromise the feasibility of the blinding or require a burdensome complex trial protocol, which may not be possible. Finally, when non-pharmacological comparators such as ECP are considered, blinding becomes unrealistic.

Patient-relevant endpoints fit for purpose should also be identified to assess the impact of such therapies. Very little is known so far on the adequacy of patient-relevant endpoints for GvHD trials, and many health technology assessment (HTA) agencies do not accept PROMs when trials are not blinded. In addition, sensitivity to disease states may be an issue with many multi-domain instruments [78], which need to be assessed over a sufficient timescale.

We are therefore left mostly with objective clinical endpoints rather than those subject to a clinician’s judgement,

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**Table 2** Summary of selected key investigational products for graft-versus-host disease (GvHD) (not exhaustive) Source: Frisone [70]; Hill et al. [18]; Watkins et al. [71]; Socié et al. [72]

| Category                              | Products investigated for:                                                                 |
|---------------------------------------|------------------------------------------------------------------------------------------|
|                                       | **aGvHD**                                                                                 |
| Immunomodulatory drugs                | Methotrexate                                                               | Mycophenolate mofetil          |
|                                       | Mycophenolate mofetil                                                              | Pentostatin                  |
|                                       | Pentostatin                                                                       | Sirolimus                   |
| Immune checkpoint blockade            | Abatacept                                                                   | Abatacept                   |
| Protease inhibitor (PI)               | Bortezomib                                                                    | Bortezomib                  |
| Cytokine modulation                  | Alpha-1 antitrypsin                                                             | Interleukin-2                |
| Kinase inhibitors                     | Itacitinib*a                                                                 | Baricitinib                 |
|                                       | Ruxolitinib*b                                                                 | Entospletinib               |
| Monoclonal antibodies                 | Alemtuzumab                                                                  | Obinutuzumab                |
|                                       | Basiliximab                                                                   | Ofatumumab                  |
|                                       | Begelomab                                                                    | Rituximab                   |
|                                       | Brentuximab vedotin                                                             |                             |
|                                       | Inolimomab                                                                   |                             |
|                                       | Natalizumab                                                                  |                             |
|                                       | Vedolizumab                                                                  |                             |
| Adoptive cell therapy                | Mesenchymal stromal cells (MSCs)                                               | MSCs                        |
|                                      | regulatory T cells                                                             |                             |
| Cellular photoimmunotherapy          | Extracorporeal photopheresis                                                   | Extracorporeal photopheresis|
| Microbiome restoration               | Faecal microbiota transplantation                                              | None noted                  |

*aGvHD* acute graft-versus-host disease, *cGvHD* chronic graft-versus-host disease, *MSCs* mesenchymal stromal cells

*a* Itacitinib is currently in a phase III trial (NCT03584516; GRAVITAS-309) [73]

*b* Ruxolitinib has been investigated in phase III trials for aGVHD (NCT02913261; REACH2) [54] and cGVHD (NCT03112603; REACH3) [74]
which significantly limits the endpoint possibilities. Survival remains an important criterion, but it may require long-term follow-up, which is not easily managed because of the rarity of the condition. Extending the trial duration to achieve a sufficient sample size to generate clinically and statistically relevant data may not be feasible. Composite endpoints of morbidity and mortality such as GvHD-free/relapse-free survival (GRFS) may be used as a surrogate marker but the subjective nature of the diagnosis of GvHD makes these a poor surrogate, especially in open-label studies.

From a HTA standpoint, longer-term overall survival (12 months or 24 months) is seen as the gold standard for demonstrating efficacy, and if it is not possible to use overall survival as a primary endpoint, it should be considered as a secondary endpoint. HTA agencies are also keen to examine cost-effectiveness, often in terms of quality-adjusted life years (QALYs) or life years gained. However without the appropriate studies, such calculations might be meaningless.

Until high-quality evidence for a standard, second-line GvHD treatment is available, the choice of therapeutic options is based on individual physician experience. Improving and expanding the evidence base should be a priority for those investigating new therapeutic agents to challenge the current standards of care.

Declarations

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Conflict of interest Kristin Grabe-Heyne and Christof Henne are both employees of Medac GmbH, a company working in the field of allogeneic HSCT. Deborah Hooker and Jim Furniss are independent market access consultants who were supported by Medac GmbH for the preparation of this article and other work. They provide consulting to many different pharmaceutical companies. Peter Bader was not funded by Medac for this article. He declares grants received from Medac, Novii and Riemser and consulting fees or honorarium from Amgen, Jazz, Medac, Novartis, and Riemser, and payment for lectures including service on speakers bureaus from Novartis. PB is a patent holder of chemical grade mesenchymal stem cells and receives royalties from Medac. Mondher Toumi was not funded by Medac for this article. He has no conflicts of interest to declare.

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Code availability Not applicable.

Authors' contributions DH performed the literature search, wrote the draft manuscript, edited the draft manuscript and approved the final version. KG-H, CH, PB, MT and JF critically examined the published data, edited the draft manuscript and approved the final version.

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Consent for publication Not applicable.

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