Opportunities for Therapies for Graft-versus-host disease Following Hematopoietic Stem Cell Transplantation: Is Africa Prepared?

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Abstract

Hematopoietic stem cell transplantation is a therapeutic approach used to cure many malignant and non-malignant, acquired and congenital/genetic as well as benign disorders of the bone marrow. This procedure is considered to be among the major advances of modern medicine which has been marked by a growing need globally. Graft-versus-host disease (GVHD) and failure of engraftment continues to be major hurdles to the success of allogeneic hematopoietic stem cell transplantation (HSCT) as well as adoptive T cell causing high morbidity and mortality. The limited understanding of the pathogenesis of acute and chronic GvHD, coupled with the suboptimal response to front-line corticosteroid treatment and poor outcomes for patients with steroid-refractory disease, present major hurdles. Additionally, the inconsistencies in the design of prospective clinical studies evaluating new agents for GvHD have hindered progress, with few multicenter studies being conducted. While advancements have been made in grading GvHD and developing biomarkers for improved prognostic information, there is a critical need for uniform inclusion criteria and endpoints in prospective studies to facilitate multicenter research and advancements in GvHD prevention. In developing countries, HSCT is further limited by high cost, limited infrastructure, and availability of HLA-identical donors and management of complications such as GvHD. Several modalities have been employed to curb GvHD such as (drugs), additional inventions have been employed that include molecular methods that will be described in this review.

Key words: Hematopoietic stem cell transplantation, Graft-Versus-Host Disease, Therapies

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Introduction

Hematopoietic stem cell transplantation (HSCT) has shown promising results in treating sickle cell anemia in African children, with high survival rates and disease-free outcomes(Isgrò et al., 2015). The establishment of HSCT centers in low- and middle-income countries, including sub-Saharan Africa, is crucial for improving access to this potentially life-saving treatment (Faulkner, 2020), due to the increasing prevalence of blood disorders. Efforts to set up HSCT programs in Tanzania South Africa and Ethiopia are underway (Mtenga et al., 2021; Viljoen et al., 2021; Mekonnen & Farris, 2023) and is being necessitated in other Sub Sahara African countries like Kenya. Moreover, the use of umbilical cord blood as a source of stem cells for transplantation is another potential avenue for improving access to HSCT in low-income countries (Gluckman, 2015) including Kenya (Hassall et al., 2015). Graft vs host disease (GVHD) remains the most significant complication after allogeneic hematopoietic stem cell transplantation and has also limited wider application of cellular therapies particularly "off-the-shelf" cell products could be derived from healthy donors. GvHD is a complex immunological complication of allogeneic hematopoietic cell transplantation, with significant morbidity and mortality (Moalic & Ferec, 2006).

Understanding the Pathophysiology of Graft-versus-Host Disease (GvHD)

It occurs when donor T lymphocytes attacking an immune incompetent host, and can be acute or chronic (Cassano, 1991) involving host tissue damage, conditioning regimen, cytokines, and immune response effectors. Prior to HSCT, 'conditioning,' or lymphodepleting the host enhanced engraftment of the transferred T cells for reduction of tumor burden, reducing the population of inhibiting regulatory T cells (Yao et al., 2012), and inducing production of homeostatic cytokines to facilitate proliferation of the transferred T cells (Gattinoni et al., 2005). Chemotherapy and irradiation improve persistence of the transferred T cells and the clinical responses in the setting of cancer. However, conditioning damages host tissues causing release of pro-inflammatory cytokines and danger-associated molecular pattern molecules (DAMPs), activating recipient antigen-presenting cells (APCs). These host APCs then present host antigens to the donor T cells, which rapidly expand and differentiate into effector T cells that migrate to the GvHD target organs and cause organ damage. The main cellular mediators of both graft rejection and GvHD are alloreactive T-cells that recognize non-self-human leukocyte antigen (HLA) molecules on the allogeneic cells.

While acute GvHD typically manifests earlier post-HCT compared to chronic vVHD, the distinction is based on clinical symptoms (Filipovich et al., 2005). The principal organ manifestations of acute GvHD involve the skin (maculopapular rash), liver (hyperbilirubinemia and jaundice), and the gastrointestinal tract (nausea, vomiting, diarrhea). On the other hand, chronic GvHD may affect various organ systems, with the skin, eyes, and mouth being the most commonly involved. Chronic GvHD is characterized by the development of fibrotic changes, particularly sclerodermatous GvHD and bronchiolitis obliterans syndrome (Lee & Flowers, 2008). Notable clinical risk factors for acute GvHD include the extent of recipient human leukocyte antigen (HLA)

mismatching, total body irradiation usage, and intensified conditioning regimens, while risk factors more associated with chronic GvHD include older age, female donors to male recipients, previous history of acute GvHD, and the use of peripheral blood stem cells as a graft source. (Flowers et al., 2011). Disease severity grading remains clinically driven, with established consensus criteria available for practical use and in clinical trials for eligibility and response assessment (Harris et al., 2016; Jagasia et al., 2015). Biomarkers should be investigated to allow for GvHD risk stratification and give guide on therapy selection (Major-Monfried et al., 2018). Biomarkers for chronic GVHD are actively under investigation, yet none have conclusively demonstrated the ability to accurately stratify patient risk.(Wolff et al., 2018)

Management of Graft-versus-Host

Graft-versus-Host principally relies on pharmacological immune suppression; however, such approaches are limited by drug toxicity, nonspecific immune suppression that increases the risk of infection, organ impairment, requirement for long-term therapy leading to poor quality of life and even mortality. However, with further understanding of pathophysiological mechanisms of acute and chronic GvHD through preclinical investigations, the treatment landscape has evolved towards the utilization of targeted agents, aiming to achieve improved clinical responses with minimized off-target effects. (Zeiser & Blazar, 2017; Cutler et al., 2017). The epidemiology of GvHD in Africa, particularly in the context of HIV/AIDS, is an area that requires further research. Despite significant progress in comprehending the pathophysiology, diagnosis, and predisposing factors for both acute and chronic forms of the illness, a standardized treatment approach is still absent. The management of GvHD in developing countries presents complex challenges due to limited resources and socio-economic factors. Timely diagnosis and collaborative management of GvHD necessitates a multidisciplinary approach for successful treatment. Conventional treatments, such as high-dose corticosteroids, carry significant side effects, prompting exploration of new strategies. Moreover, comprehensive supportive care including infection prevention, are crucial for optimizing patient response and survival. The limited access to medical technologies and expertise, along with the need for cost-effective diagnostics and affordable medications, highlight the necessity for comprehensive approaches encompassing infrastructure development, education, and research collaboration to bridge the gap in GvHD management between developed and developing nations, to improve patient outcomes. There is need to develop concerted efforts to explore different therapies available and assess Africa's preparedness to adopt and optimize these evolving therapeutic approaches for GvHD. This review aims to delineate existing options for the treatment and management of GVHD using conventional and molecular therapies.

Pharmacological Agents Utilized in Conventional Graft-versus-Host Disease Management

Managing GvHD poses significant challenges due to the complex pathophysiological mechanisms involved. High-dose corticosteroids serve as the primary treatment for established GvHD but their significant role in GvHD prevention remains uncertain. Corticosteroid-based immunosuppression serves as the primary treatment for both acute and chronic GvHD, leading to sustained responses in less than 50% of patients with acute GvHD and 40–50% of patients with chronic GvHD, depending on the severity of the initial disease (Bacigalupo, 2011). A range of pharmacological agents are used which include inhibitors of the interleukin-6 receptor (Tvedt et al., 2017), binding proteins such as tumor necrosis factor (TNF) (Korngold et al., 2003), and the JAK1/2 kinase inhibitor ruxolitinib (Rodríguez-Gil et al., 2021). . There are other emerging drugs under investigation for GvHD treatment and management that include monoclonal antibodies, interleukin-2, alpha-1 antitrypsin, histone deacetylase inhibitors, tyrosine kinase inhibitors, and proteasome inhibitors (Kekre & Antin, 2016). Systemic treatments for chronic GvHD include high-dose corticosteroids, calcineurin inhibitors, cytotoxic drugs, immunomodulatory substances, B-cell antibodies, and the tyrosine kinase inhibitor, imatinib (Schleuning et al., 2009). Calcineurin inhibitors like cyclosporine A (Powles et al., 1980) and tacrolimus (FK506) (Fay et al., 1996) suppress T lymphocytes (Chao & Chen, 2006) by hindering the activation and growth of donor T cells through the inhibition of nuclear factor of activated T cells (NFAT) (Powles et al., 1980). Cyclosporine A also decreases the expression of IL-2 and IL-2 receptor (IL-2R) in activated T lymphocytes. Methotrexate provides protection against GVHD by inhibiting dividing allo-reactive T-cells (Storb et al., 1986). Cyclophosphamide has been utilized post-transplant since the 1980s to prevent acute GVHD by inhibiting T cell division following myeloablative conditioning in related and unrelated allo-transplants (Kanakry et al., 2014). Mycophenolate Mofetil (MMF) demonstrates a strong cytostatic effect on T and B lymphocytes (Koreth & Antin, 2008) and has been utilized in combination with calcineurin inhibitors and/or methotrexate. Nevertheless, the incidence of grade II-IV GVHD still varied between 38% and 62% (Nash et al., 2005; Neumann et al., 2005). When combined with cyclosporine, MMF led to accelerated engraftment, but did not entirely prevent the occurrence of aGVHD and cGVHD (Koreth & Antin, 2008). Sirolimus (rapamycin) forms a complex with the mammalian target of rapamycin (mTOR), suppressing biochemical pathways and subsequently reducing DNA transcription/translation of protein synthesis and cell cycle progression, resulting in T cell immunosuppression (Koreth & Antin, 2008). When used in combination with tacrolimus, sirolimus has shown effective outcomes against acute GvHD, but no impact was observed against chronic GvHD. Generally, the efficacy of sirolimus in preventing GvHD has been moderate. These agents aim to improve the prognosis of GvHD, particularly in cases that are refractory to steroids by inhibition of allo-reactive T cells.

Currently, second-line treatments for steroid-refractory acute and chronic GvHD consists of extracorporeal photopheresis or immune modulators such as methotrexate, rituximab and mycophenolate mofetil (Garnett et al., 2013), anti-thymocyte globulin (ATG), ruxolitinib, a Janus kinase (JAK) 1/2 inhibitor; daclizumab, inolimomab, and basiliximab which are interleukin 2 receptor (IL-2R) antibodies; sirolimus and everolimus which are inhibitors of mammalian target of rapamycin (mTOR); infliximab and etanercept, which are tumor necrosis factor-alpha (TNF-α) inhibitors; anti-CD52 antibody alemtuzumab, anti-α4β7 integrin antibody vedolizumab, and mesenchymal stroma cells (Martin et al., 2012; Penack et al., 2020; Kasikis et al., 2021). The combination of basiliximab and etanercept achieved a clinically meaningful response in over 90% of patients with steroid-refractory acute GvHD and also demonstrated a 5-year overall survival (Tan et al., 2017). Similarly, (Wolff et al., 2011) reported some efficacy of rituximab, alemtuzumab, and etanercept in selected patients with chronic GvHD. Moreover, serotherapy comprising of antibodies that target T cells and other immune cells that would theoretically modulate GvHD intensity. Agents such as antithymocyte globulin and alemtuzumab, a monoclonal antibody to CD52, (Schroeder et al., 2010), adoptive transfer of ex vivo expanded CD4+CD25+CD127- T regulatory cells (Trzonkowski et al., 2009) and low-dose subcutaneous interleukin-2 (IL-2)(Asano et al., 2016) a combination of a calcineurin inhibitor and corticosteroids (Arora, 2008), B-cell antibodies, and the tyrosine kinase inhibitor imatinib have been explored. Notably, the US Food and Drug Administration (FDA) has approved treatment agents for GvHD: ruxolitinib for both acute and chronic GvHD, ibrutinib and belumosudil for chronic GvHD (Martini et al., 2022; Kovalenko et al., 2023).

Adverse Effects of Pharmacological Agents Employed in Graft-versus-Host Disease Management

Therapeutic approaches for GvHD have historically involved broad systemic immunosuppression, which, despite being associated with suboptimal response rates and an elevated risk of opportunistic infections,(Norkin et al., 2019) has been the standard of care. Between 30% and 70% of patients who receive allogeneic hematopoietic stem cell transplants develop some degree of GVHD, with steroids typically being the first line of treatment. Steroids are associated with numerous well-established side effects, such as immunosuppression, hyperglycemia, and osteopenia, necessitating a careful consideration of the balance between the benefits and risks of prolonged courses. Even so, 35% to 50% of GVHD cases do not respond to steroid treatment and prolonged use of corticosteroids can lead to severe adverse events (Asano et al., 2016). There is still no consensus on the optimal approach for tapering steroids in responsive patients.

A range of pharmacological agents are used in the management of GvHD, each with its own set of side effects. The adverse effects of topical treatments like budesonide, dexamethasone, and clobetasol, including burning sensations, fungal infections, and gastrointestinal disorders(Haas & Cruz-Pamplona, 2023). Additionally,other long-term side effects of glucocorticoid therapy, include cardiovascular issues, musculoskeletal problems, gastrointestinal disorders, dermatological issues, neuropsychiatric complications, endocrine disturbances, ocular complications, weight gain, high blood pressure, adrenal insufficiency, osteoporosis, and a high risk of infections (Oray et al., 2016),drowsiness and reversible behavior disorders (Reynolds, 1992). Other significant side effects of systemic glucocorticoids, include Cushing's syndrome, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, osteoporosis, psychiatric disturbances, and immunosuppression, particularly at high doses and prolonged usage (Alan & Alan, 2018)

Despite ongoing research, there is a scarcity of randomized controlled trials focusing on the management of steroid-refractory GVHD. The evaluation of treatment options is complicated by the diverse nature of the patient group involving varying organ complications, age, conditioning regimens, GVHD prophylaxis, and type of HSCT, the absence of a clear definition of corticosteroid-refractory disease, and inconsistent treatment endpoints. Consequently, there is no definitive consensus on the best second- and third-line options in GVHD management, and local treatment approaches often rely on financial considerations, therapy availability, and the preferences as well as the experience of treating physicians.

Molecular Approaches to Alleviating Graft-versus-Host Disease (GVHD)

***In Vitro* T Cell Manipulation Strategies for Depleting Alloreactive T Cells**

Various T cell manipulation strategies that have been implemented to minimize the risk of GvHD which by immunological or physical depletion methods have been discussed in several reviews (Vadakekolathu & Rutella, 2017). T cell manipulation strategies, particularly αβ T cell depletion, have shown promise in preventing GvHD in allogeneic hematopoietic stem cell transplantation (Abdelhakim et al., 2017). However, this approach has been associated with an increased risk of graft failure, particularly in HLA nonidentical donors (Friedrich et al., 1985) . Ex vivo depletion of donor T cells has been found to effectively prevent acute and chronic GvHD without the need for additional post-transplant immunological prophylaxis (Busca, 2011). Despite the reduction in GvHD, T cell depletion has been linked to an increased rate of graft rejection and impaired immune reconstitution(Drobyski, 2000). The use of the monoclonal antibody Campath 1G for T lymphocyte depletion has also been explored (Jacobs et al., 1994). Fas-mediated selective depletion of host-sensitized donor lymphocytes ex vivo has been found to prevent GvHD without impairing T cell support of engraftment or graft-versus-tumor activity (Askenasy et al., 2013).

HLA mismatch antigens are primary targets for alloreactive T cells in HLA-incompatible cellular T-cell products, potentially leading to severe GvHD and reduced recipient survival. The frequency of these alloreactive T cells within the naïve T-cell

repertoire is estimated to range from 0.1 to 10%. (Ashwell et al., 1986), (Heeger, 2003), (Suchin et al., 2001). Complete depletion of T cells from the donor grafts can be highly effective, but it can also increase susceptibility to infections and the recurrence of malignancy due to prolonged immune system reconstitution period (Bacigalupo, 2011). To address this, a range of in vitro strategies have been developed to deplete alloreactive T cells, with the aim of reducing the risk of graft-versus-host disease (GVHD) while preserving beneficial immune responses. These strategies include selective T-cell depletion techniques have been developed to remove naive T-cells implicated in causing GvHD using CD45RA and CD62L microbeads (Verfuerth et al., 2015;; Teschner et al., 2014); (Triplett et al., 2018);(Bleakley et al., 2014) selection of memory T cells has been observed to have reduced alloreactivity as compared to the naïve T cell subset (Mangare et al., 2022). The T cell differentiation stage is crucial in determining the capacity of T cells to induce GVHD. Memory T cells have been shown to have a lower potential to generate GVHD, partly due to non-alloreactive TCR enrichment, with evidence that memory cells are less likely to traffic to GVHD target tissues (Chan et al., 2015). Other T cell depletion techniques include CD3/CD19 depletion and TCR-αβ/CD19 depletion (Bleakley et al., 2015). Other depletion techniques includes the soybean lectin, E-rosette depletion technique, *In vivo* administration of anti-T cell globulin (Mohty, 2007); (Finke et al., 2009) or anti-CD52 mAb, CAMPATH-1 (Kottaridis et al., 2000; Schnitzler et al., 2009; O'Reilly et al., 2015), reduce the donor T cell burden, while resulting in a state of T cell deficiency. Trimetrexate and interleukin-2 immunotoxin have been utilized to induce apoptosis in alloreactive T cells (Szabolcs et al., 2004), CD95-mediated activation-induced cell death to selectively deplete alloreactive T cells (Hartwig et al., 2008), and immunomagnetic cell selection to deplete cells expressing CD25 or CD69 (Fehse et al., 2000). Whitehill and colleagues treated alloactivated T cells with purine nucleotide adenosine that preserves quiescent lymphocytes, regulatory T cells (Treg), and T cells that have antiviral and antileukemic specificities (Whitehill et al., 2015). Other methods utilized CFSE dye dilution, activation antigen selection, and dendritic cell stimulation to deplete alloreactive T cells (Godfrey et al., 2004).

The Role of Regulatory Cells (Tregs and Bregs) in Alleviating Graft-versus-Host Disease

Regulatory cells, including Bregs and Tregs, have shown promise in preventing graft-versus-host disease (GvHD) while maintaining graft-versus-leukemia (GVL) effects. Regulatory cells such as $CD4^{+}CD25^{+}$ $FOXP3^{+}$ Tregs (Edinger et al., 2003) together with conventional T cells (Tcons) (Martelli et al., 2014) could suppress the early expansion of alloreactive donor T cells. *In vitro* induced Tregs (iTregs), myeloid-derived suppressor cells can induce immunosuppressive cells such as Tregs and skew macrophages toward a proinflammatory type 2 phenotype via IL-10 production (Highfill et al., 2010) and mesenchymal stem cells inhibit the activation, proliferation, and function of T cells via arginase-1, NO, reactive oxygen species, chemokines, TGF-β, and IL-10 (Galleu et al., 2017; Mohty & Gaugler, 2015) demonstrated the potential of ex vivo expanded human Tregs in preventing lethal GvHD. Hefazi et al., discusses the therapeutic potential of Tregs in preventing and treating GVHD, emphasizing their role in maintaining immune homeostasis, inducing tolerance post-HSCT, and possessing tissue reparative functions. He explored the safety profile of polyclonal Tregs and prospects for enhancing their functionality through genetic engineering, offering insights into different Treg subtypes and approaches for optimizing their application in allo-HSCT (Hefazi et al., 2021). Kellner showed the safety of infusing ex vivo expanded cord blood Tregs and low risk of acute GvHD with umbilical cord blood-derived Tregs (Kellner et al., 2017). Engelhardt indicating that Treg tissue-homing subsets may help regulate organ-specific risk and severity of acute GvHD(Engelhardt et al., 2011). Furthermore, it has been reported that administration of the serine protease inhibitor α-1 antitrysin could dampen the severity of GvHD (Tawara et al., 2012). In this study by Tawara and collegues, they reported that administration of α-1 antitrysin decreased the proliferation of alloreactive T effector cells while promoting the restoration of Tregs, resulting in a shift in the ratio of donor T effector to Tregs, favoring the reduction of the GvHD pathological process (Tawara et al., 2012).Another study found that B regulatory cells (Bregs) can prevent acute GvHD without compromising GVL activity (Hu et al., 2017). Bregs prevented onset by inhibiting Th1 and Th17 differentiation and expanding regulatory T cells (Hu et al., 2017). Cell-based therapies, such as regulatory T cells being explored as a potential solution (Leventhal et al., 2012) and tolerogenic cells (Mathew et al., 2018). Other approaches include altering the immune system to achieve tolerance to organ transplants and prevent GvHD (Strober, 2014). Overall, these cells reduce detrimental T cell responses to foreign antigens.

Photodynamic Therapy for Depleting Alloreactive T Cells to Prevent Graft-versus-Host Disease

Photodynamic depletion of alloreactive T cells has shown promise in targeting GvHD mediators while enabling rapid immune reconstitution in HSCT (Perruccio et al., 2008;Boumedine et al., 2004). This method, which involves the use of a photosensitizer and light to selectively eliminate activated T cells, has been found to be effective in reducing the frequency of alloantigen-specific T cells while preserving pathogen-specific responses(Perruccio et al., 2008). Photodynamic therapy with TH9402 (4,5-dibromorhodamine methyl ester), a photosensitizer, has arisen as a potentially intriguing alternative treatment for GVHD patients. Upon activation with visible light, it demonstrates targeted toxicity against activated T lymphocytes while safeguarding resting T cells (Bastien et al., 2007). Eliminating host-reactive donor T cells by targeting activation-based changes in p-glycoprotein results in an altered efflux of the photosensitizer TH9402 has been demonstrated. In this procedure, expanded lymphocytes are cocultured with responder cells from HLA-matched or -

mismatched donors and incubated with TH9402. This is followed by exposure to light energy, reducing alloreactive T-cell precursors (Mielke et al., 2008). This process consists of different phases; coloration, extrusion, and light exposure, which targets activation-based changes in P-glycoprotein, that result in an altered efflux of the photosensitizer TH9402. This method has the advantage that specific anti-viral and anti-bacterial immunity is preserved in the generated products.

Knocking out HLA molecules

This methods has been used to eliminate HLA class I expression, by knocking out individual HLA molecules or beta-2 microglobulin (B2M), which is a universal component of all HLA class I molecules (Torikai et al., 2013). In 1980, Miller introduced the concept of a "veto cell" that can specifically eliminate analloreactive T-cell (Miller, 1980). Recently, a study by Quach et al demonstrated how primary human T-cells could be engineered to enhance their veto activity(Quach et al., 2019). B2M/CD3-zeta protein termed as Chimeric HLA Accessory Receptor (CHAR) was engineered using virus specific T cells which could limit the activation and expansion and elimination of alloreactive T-cells. This strategy could prevent rejection of allogeneic cell therapy products hence increasing the persistence of off-the-shelf cell therapies (Quach et al., 2019). Some investigators have knocked out the endogenous TCR in T cells to develop donor derived T cells without the effects of TCR activation. Moreover, Chimeric antigen receptor (CAR)- T cells have been generated by selectively deleting the endogenous T cell receptor (TCR). With current gene editing technologies, the endogenous TCR could be removed using gene editing strategies (Osborn et al., 2016), concurrently, the absence of an endogenous TCR eliminates the possibility of GvHD. Using the same techniques, major histocompatibility (MHC) class I could be deleted on donor-derived, off-the-shelf T cells to avoid rejection of transferred cells and potential development of GvHD (Torikai et al., 2013). A number of studies have explored other approaches to prevent GvHD by targeting HLA molecules such asselective depletion of donor alloreactive T cells and/or host antigen presenting cells particularly dendritic cells, can effectively control GvHD(Chen et al., 2013). Bu et al., proposed that high levels of HLA-G5, a nonclassical HLA class I molecule, could inhibit the incidence of GvHD (Bu et al., 2021).

Targeting epigenetic modifiers

Recent studies have explored the potential of targeting epigenetic modifiers in preventing graft versus host disease (GvHD) after hematopoietic cell transplantation. These include: acetyl and methyl-transferases, inhibiting Notch signalling, micro-RNAs, mitochondrial ATP-ase, JAK/STAT signalling and inhibiting protein kinase-C, have all emerged as potential therapeutic targets for GvHD control (Vadakekolathu & Rutella, 2017). The inhibition of histone methylation using DZNep (3-deazaneplanocin A) was shown to result in apoptosis of activated alloreactive T cells and diminished tissue damage resulting to reduced tissue injury in the host (S. He et al., 2012). Notch signalling is one of the key regulators of T-cell and dendritic cell development. The inhibition of Notch signalling in T cells resulted in reduced pro-inflammatory cytokine production without compromising immune cell proliferation(Sandy et al., 2013). Gatza et al. also showed that targeting mitochondrial ATPase could reduce the frequency of alloreactive T cells in GvHD without affecting T-cell responses (Gatza et al., 2011). PKC-α is a key regulator of T-cell signalling through its interaction with several transcription factors, including JAK-STAT inhibitors (Choi et al., 2014), NF-AT (Haarberg et al., 2013), selective TNFR2 activation(Chopra et al., 2016) could reduce GvHD occurence. Other studies that utilised histone deacetylase inhibitors such as vorinostat showed the efficacy to mitigate the effect of GVHD by impairing the function of host APCs (Reddy et al., 2004). Chen et al highlighted the potential of targeting BCL6, a transcriptional repressor , the germinal centers, and specific epigenetic regulators, in preventing GvHD (Chen et al., 2023). These studies collectively suggest that targeting various epigenetic modifiers and signaling pathways could be a promising approach in preventing GvHD.

TCR sequencing technologies

Recent advancements in TCR sequencing technologies have significantly improved our understanding of graft vs host disease (GVHD) and its management. It has been reported that CDR3-size spectratyping of the TCRVβ-chain can characterize and differentiate alloreactive from GvT-specific T-cell repertoire responses, highlighting the potential for tailoring the donor product to target recipient's malignant cells while minimising GvHD (Patterson & Korngold, 2001). Studies have highlighted the potential of TCR sequencing in characterizing T cell populations and reconstitution in GVHD patients(Zheng et al., 2020). However, the use of TCR gene therapy in inducing immune reactivity, as discussed by (Bendle et al., 2010), also poses a risk of autoimmune pathology. (Arruda et al., 2019) further emphasizes the role of TCR repertoire in clinical outcomes post-transplantation, while (Pai & Satpathy, 2021) underscore the utility of high-throughput and single-cell TCR sequencing technologies in tracking T cell clones and understanding transplant biology. Some studies have shown that TCR sequencing in GvHD-affected tissues can reveal unique T cell clones that are not abundant in circulation or shared across multiple patients. This suggests that the TCR repertoire in GVHD-affected tissues is distinct and reflects the differential expression of alloantigens at different anatomical sites. Understanding the TCR repertoire in GVHD is important because it can provide insights into the specific T cell populations driving the immune response in different tissues (DeWolf et al., 2020). Moreover, the T-cell receptor alpha repertoire of CD8+ T cells plays a critical role in regulating immune responses, maintaining tolerance, and preventing GvHD following allogeneic stem cell transplantation. Thus, understanding the dynamics of the T-cell receptor alpha repertoire could play a role in tailoring therapeutic interventions to minimize the risk of GvHD while preserving effective immune surveillance

(Link-Rachner et al., 2019). This underscores the potential of TCR sequencing in personalized GVHD management and provides insights into development of targeted therapies to modulate the alloimmune response and improve outcomes for patients undergoing transplantation.

Suicide Gene-Transduced T Cells for control of GvHD

A promising approach to manage GvHD is suicide gene therapy, where donor T cells are genetically modified ex vivo with a suicide gene. This modification enables the selective removal of the cells *in vivo* if GvHD develops. Research on suicide gene-transduced T cells for the control of GvHD has shown promising results. (Rettig et al., 2003), and (Cohen et al., 1999) both demonstrated the successful transduction and selection of human T cells with CD34/thymidine kinase chimeric suicide genes, leading to efficient control of GvHD. (Kornblau et al., 2007) further improved the safety and function of these cells, showing that retrovirally transduced suicidal lymphocytes can generate a potent graft-versus-leukemia effect while controlling GVHD. (Ciceri et al., 2005); (Georgoudaki et al., 2010); (Tiberghien, 2001) expanded on these findings, highlighting the potential of suicide gene-modified T cells in mismatched transplantation and the prevention of GVHD. (Mailly et al., 2010) and (Sato et al., 2005)addressed the limitations of this approach, proposing improvements such as CD3/CD28 co-stimulation. Helene et al., provided further evidence of the feasibility of controlling GVHD using a T cell-controlled suicide gene (Helene et al., 1997). Herpes simplex virus type 1 thymidine kinase (HSV1-tk) gene, combined with the antiviral prodrug ganciclovir (GCV), is used to control GvHD after introduction of this suicide gene into donor T lymphocytes (Ciceri et al., 2005). However, the efficiency of HSV1-tk is suboptimal and the issue of host immunogenicity against this heterologous effector gene product can hamper outcomes. A different gene construct was used for the transduction of donor T cells by Di Stasi and co-workers (Di Stasi et al., 2011). Human caspase-9 (C9) was fused to a modified human FK506-binding protein whose dimerization, in the presence of a synthetic bio inert drug, was shown to trigger the activation of C9 and death of the cells expressing the construct (Vadakekolathu & Rutella, 2017). Inducible T-cell safety switch characterized by fusion of caspase 9 to a modified human FK-binding protein, that allows conditional dimerization, if exposed to a synthetic dimerizing drug. The inducible caspase 9 (iCasp9) becomes activated and leads to the rapid death of cells expressing this construct. Patients who received AP1903, an otherwise bioinert small-molecule dimerizing drug, if GvHD developed (Di Stasi et al., 2011). A single dose of the dimerizing drug AP1903, which has a half-life of 5 hours in vivo, results in the elimination of 90% of the transgenic cells within 30 minutes post-infusion, with further substantial depletion within the next 24 hours (Di Stasi et al., 2011).

Gene editing techniques

Gene editing techniques have shown promise in managing graft vs host disease (GVHD). Suicide gene therapy, which involves modifying donor T cells with a suicide gene to selectively eliminate them in case of GVHD, has been explored (Georgoudaki et al., 2010). Similarly, the use of herpes simplex virus thymidine kinase-transduced T lymphocytes has been proposed to manage GVHD (Burt et al., 2003). Allogeneic CAR T cells are developed and used to generate universal CAR T cells (UCART) (Depil et al., 2020). CRISPR Therapeutics' CTX-110 employs clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 multiplexed gene editing technique is used to eliminate T cell receptor (TCR) and major histocompatibility complex class I (MHC-I) expression, thereby minimizing the risk of GvHD and recognition and rejection by a patient's own T cells. In Servier/Allogene Therapeutics' UCART19, *TRAC* and *CD52* genes are disrupted, thereby allowing administration in non-HLA (human leukocyte antigen)-matched patients (Dupouy et al., 2022). However, it is important to note that some gene therapy approaches, such as T-cell receptor gene transfer, can induce severe GVHD(Ferrara et al., 2010). Hence further research is needed to optimize the safety and efficacy of these gene editing techniques in managing GVHD.

Immunomodulation for controlling GvHD

Immunomodulation plays a crucial role in controlling GvHD following bone marrow transplantation either by reducing graft immunogenicity and vulnerability to attack by immune competent cells and inflammatory mediators. Various strategies have been explored to achieve this, including the use of CpG to trigger the innate immune system (Morecki et al., 2009), glucocerebroside to alleviate chronic GvHD (Nagler & Nagler, 2004), and the modulation of immunoglobulin dysregulation in GvHD by the murine IL-4 receptor (Schorlemmer et al., 1995). High concentrations of immunoglobulin have also been found to inhibit lymphocyte activation, potentially preventing GvHD (Maeba et al., 2012). Furthermore, granulocyte colony stimulating factor-treated granulocytes have been shown to inhibit acute GvHD (Vasconcelos et al., 2006), and cytokine dysregulation has been proposed as a key factor in acute GvHD (Antin & Ferrara, 1992). Lastly, glucocerebroside has been associated with the alleviation of both acute and chronic GvHD in a murine model (Ilan et al., 2007). The immunomodulatory properties of mesenchymal stem cells (MSCs) in GvHD involve their ability to suppress the immune response, reduce inflammation, and promote tissue repair. Mesenchymal stem cells exert these effects through the secretion of anti-inflammatory and immunomodulatory molecules, the induction of regulatory T cells, and the inhibition of pro-inflammatory immune cells making these cells a promising therapeutic option for GVHD treatment (Godoy et al., 2019). Furthermore, ex vivo induction of alloantigen-specific anergy in donor T cells by allo-stimulation in the presence of costimulatory blockade by blocking B7/CD28 by adding CTLA-4-Ig or anti-B7-1 and B7-2 antibodies during co-culture (Davies et al., 2008). Immunomodulation using antisera and monoclonal antibodies has shown promise in

controlling GvHD. (Watkins et al., 2014) demonstrated the efficacy of a novel anti-CD28 antibody in preventing primate GvHD, while(Herve et al., 1985) and (Thierfelder et al., 1986) reported successful prevention of acute GvHD using pan-T monoclonal antibodies. Some clinical trials using murine monoclonal anti-T cell antibodies and a combination of monoclonal antibodies and complement, have been used preventing and treating GvHD, particularly those targeting specific cell types and effector mechanisms (Kathleen et al., 1984; Racadot et al., 1985 Bruner & Farag, 2003).More recent studies have focused on manipulating the immune response to prevent and treat GVHD, including strategies targeting T-cell–dendritic cell interactions and proinflammatory cytokines (Filippini & Rutella, 2014).

Immunotherapies involving checkpoint inhibitors in GvHD

While these inhibitors have shown promise in cancer treatment (Regalla et al., 2018), they can also lead to severe GVHD(Ferrara et al., 2010). The modulation of donor T cells through PD-1 and CTLA-4 signaling pathways within the recipient's body may contribute in controlling GvHD in patients undergoing allogeneic HSCT. It has been reported that blocking PD-1 or PD-L1 with monoclonal antibodies increases GvHD toxicity, while PD-L1 expression in host tissues is necessary to reduce GvHD (Blazar et al., 2003; Saha et al., 2013), Furthermore, inhibitory signaling through CTLA-4 binding to CD80/CD86 also restricts GvHD by blocking the CD28-B7 co-stimulatory pathway and inhibiting donor T cell allo-reactivity in allo-HSCT recipients (Alegre et al., 2001). Notably, deficiency of CTLA-4 in Tregs leads to severe autoimmune diseases in mice19. Moreover, inducible donor Tregs expressing foxp3 and the addition of in vitro expanded donor Tregs to the graft have shown promising therapeutic potential in preventing GvHD (Duramad et al., 2000; Cao et al., 2001). The challenge lies in identifying pathways that minimize adverse immune suppression (X.-S. He et al., 2017). Studies on the use of immune checkpoint inhibitors in managing GvHD is still in its early stages, with potential benefits and risks. It has been reported that that targeting the CTLA-4 pathway can prevent GvHD, while anti-CTLA-4 antibody treatment can exacerbate it (Gao et al., 2021). Yoo and colleagues demonstrated that transgenic expression of CTLA-4 can reduce T cell proliferation in a GvHD model (Yoo et al., 2012), suggest that CTLA-4 plays a crucial role in GvHD and its modulation could be a potential therapeutic strategy.

Summary

Graft-versus-host disease (GVHD) presents a significant challenge in allogeneic hematopoietic stem cell transplantation. Although there is good evidence for the first-line management of both acute GVHD and chronic GVHD with steroids, the most appropriate second-line treatment in both conditions remains unclear. The side effects associated with pharmaceutical drugs have necessitated the intervention of molecular methods to alleviate GvHD some of which have shown great success. Hence, as the treatment and management of GvHD is continuously evolving, it necessitates large systematic randomized studies to assess the efficacy and side effects of therapies. Standardizing assessment tools and detailed laboratory analysis may help identify potential biomarkers and therapeutic targets for both acute and chronic GVHD as well as predicting risk, severity, and treatment responses.

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