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GVHD: a continuing barrier to the safety of allogeneic transplantation

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INTRODUCTION

Acute and chronic graft-versus-host disease (GVHD) remain the major clinical complication of allogeneic hematopoietic cell transplantation limiting survival and inducing major morbidity, sometimes for several years posttransplant. In this article, three authors review components of GVHD that underlie these hazards. Dr. Pavan Reddy outlines preclinical, mostly murine data detailing the current understanding of the pathophysiology of acute GVHD. Chronic GVHD, the major ongoing immunologic limitation to transplant success has complexities in its assessment and management and unfortunately, no defined best therapy. Dr. Mukta Arora outlines new strategies for its assessment and describes opportunities for better treatment of this chronic disease. Finally, it is well recognized that acute and chronic GVHD induce their morbidity not just by their end organ toxicity or the side effects of treatment, but the syndrome in itself is immunosuppressive. Chronic GVHD compromises the development of functional defenses against infection and may alter defenses against recurrence of any underlying cancer. Drs. Guimond and Mackall review the impact of GVHD on the immune development post HCT and in doing so, outline ways that therapeutical alternatives might better facilitate immunologic reconstitution.

Mouse models have been central to our identification and understanding of the pathophysiologic mechanisms of GVHD, and canine models have been critical to the development of clinically useful strategies for GVHD prophylaxis and treatment [1]. Based largely on these experimental models, the development of acute GVHD can be conceptualized in three sequential steps or phases: (1) activation of the antigen presenting cells (APCs); (2) donor T cell activation, proliferation, differentiation and migration; and (3) target tissue destruction [2].

Phase I: Activation of APCs

The first step involves the activation of APCs by the damage caused underlying disease and the HCT conditioning regimen. Damaged host tissues respond by producing “damage associated/danger” signals, including proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α), chemokines, and increased expression of adhesion molecules, MHC antigens and costimulatory molecules on host APCs [1]. Damage to the GI tract from the conditioning is particularly important because it allows for systemic translocation of additional inflammatory stimuli such as microbial products including lipopolysaccaride (LPS) or other pathogen-

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associated molecular patterns that further enhance the activation of host APCs [3]. The secondary lymphoid tissue in the GI tract is likely the initial site of interaction between activated APCs and donor T cells, but secondary lymphoid tissues are not obligatory for the induction of GVHD [4,5]. These observations have led an important clinical strategy to reduce acute GVHD by reducing the intensity of the conditioning regimen [6]. The concept that enhanced activation of host APCs increases the risk for acute GVHD unifies a number of seemingly disparate clinical associations with that risk, such as advanced stages of malignancy, more intense transplant conditioning regimens and histories of viral infections. Experimental GVHD can also be reduced by manipulating distinct subsets of APCs [7]. Both the host and donor derived hematopoietic APC subsets are relevant for the induction and severity of acute GVHD [8]. However, certain APC subsets have been shown to mitigate GVHD [9], and in addition, non-hematopoietic stem cells, such as mesenchymal stromal cells, acting as APCs can reduce allogeneic T cell responses and ameliorate GVHD, although the mechanism for such inhibition remains unclear [10]. The receptors and signaling pathways that are critical for the activation of APCs and induction of GVHD remain to be determined. Given the redundancy, the critical receptors/pathways might vary depending on the type of BMT, the preparative regimen and the other relevant host/donor conditions. Recent clinical observations suggest that certain polymorphisms that affect APC activation, such as those donor and host NOD2 and donor inflammasome protein-encoding variants in *NLRP2* and *NLRP3* might be relevant [11,12].

Phase II: Donor T Cell Activation

The core of the GVH reaction is Step 2, where donor T cells proliferate and differentiate in response to host histo-incompatible antigens presented by the APCs [8]. The damage associated signals generated in Phase I augment promote donor T cell responses to host antigens by increasing the expression of ‘secondary signals’, the costimulatory molecules and by the secretion of various ‘tertiary signals’, the proinflammatory cytokines [2,13]. Blockade of co-stimulatory pathways to prevent GVHD is successful in animal models, but this approach has not yet been tested in large clinical trials [1].

Several T cell subsets have been shown to be important in causing, amplifying, perpetuating or regulating acute GVHD. In mouse models, where genetic differences between donor and recipient strains can be tightly controlled, $CD4^+$ cells induce acute GVHD to MHC class II differences, and $CD8^+$ cells induce acute GVHD to MHC class I differences [14]. In the majority of HLA-identical HCTs, both $CD4^+$ and $CD8^+$ subsets respond to minor histocompatibility antigens and can cause GVHD in HLA-identical HCT. Naïve donor T cells cause GVHD. By contrast memory subsets from the donors are less efficient in inducing GVHD [8]. However, alloreactive memory subsets that develop in the host have been shown to perpetuate GVHD [15]. Regulatory T cells (Tregs) can suppress the proliferation of conventional T cells and prevent GVHD in animal models when added to donor grafts containing conventional T cells [16]; while host type regulatory T cells have also been shown to mitigate GVHD in certain models [8]. Natural Killer T cell (NKT) 1.1^+ subsets of both the host and donors that have also been shown to modulate acute GVHD [17]. A recent clinical trial of total lymphoid irradiation used as conditioning significantly reduced GVHD and enhanced host NKT cell function [18]. Th1 cells (IFN-γ, IL-2 and TNF-α) aggravate or regulate acute GVHD depending on the model system. Nonetheless, IL-2 production by donor T cells remains the principal target of many current clinical therapeutic and prophylactic approaches to GVHD, such as calcineurin inhibitors (CNIs) cyclosporine, tacrolimus and monoclonal antibodies (mAbs) directed against IL-2 and its receptor [19]. In this context it is important to note that CNIs also have other effects on T cell activation.. But emerging data indicate an important role for IL-2 in the generation and maintenance of $CD4^+CD25^+$ Tregs, suggesting that prolonged interference with IL-2 may have an unintended consequence of preventing the development of long term tolerance after allogeneic HCT [20]. Likewise the role of Th2

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polarization also is likely to be dependent on the type of model. Emerging data suggest that Th17 (IL-17A) polarization does not appear to be specifically pathogenic for GVHD. However, whether T cell polarization causes distinct target tissue damage with a varied pathogenic response remains incompletely understood and explored.

Phase III: Cellular and Inflammatory Effector Phase

The effector phase of this process is a complex cascade of both cellular mediators such as cytotoxic T lymphocytes (CTLs) and NK cells and soluble inflammatory mediators such as TNF-α, IFN-γ, IL-1 and nitric oxide [1,21]. These soluble and cellular mediators synergize to amplify local tissue injury and further promote inflammation and target tissue destruction.

The cellular effectors of acute GVHD are primarily CTLs and NK cells [3]. CTLs that preferentially use the Fas/FasL pathway of target lysis and appear to predominate in GVHD liver damage (hepatocytes express large amounts of Fas) whereas GVHD CTLs that use the perforin/granzyme pathways are more important in the GI tract and skin [1,22]. It is relevant to note that while hepatocytes are the dominant targets of injury in murine models, the bile duct epithelial cells are the primary targets of human GVHD. Chemokines direct the migration of donor T cells from lymphoid tissues to the target organs where they cause damage. Chemokines are over-expressed as a result of inflammation and enhance the homing of cellular effectors to target organs during experimental GVHD [1,23,24]. Expression of integrins, such as α4β7 and its ligand MadCAM-1, are also important for homing of donor T cells to Peyer's patches during intestinal GVHD [1]. Microbial products such as LPS and others that leak through a damaged intestinal mucosa or skin may stimulate secretion of soluble mediators such as inflammatory cytokines [3,25]. The GI tract is particularly susceptible to damage from TNF-α, and plays a major role in the amplification and propagation of the "cytokine storm" characteristic of acute GVHD [3]. Nonetheless the reasons for the unique specificity of acute GVHD target organs remain unclear.

Future Studies—Experimental studies from the past few years have allowed for a more refined understanding of the cellular interactions and networks, and for the identification of a number of new cell types that impact upon GVHD. The next few years will undoubtedly bring these heterogenous and perhaps additional cell types into greater focus so that we can identify and isolate them with greater precision, understand factors that stimulate or repress. Advances in understating the basic biology of the chronicity of inflammatory processes, the cellular interactions and molecular pathways of tolerance, the mechanisms for target organ and leukemia sensitivity/specificity, the genomic and proteomic profiling analyses will add texture and refinement to our understanding of GVHD.

Novel Therapies for Chronic Graft-versus-Host Disease

Chronic graft versus host disease (CGVHD) is the major cause of late morbidity and mortality post hematopoietic cell transplant. Traditionally, corticosteroids along with calcineurin inhibitors have been the mainstay of therapy for CGVHD. However, recently there has been renewed interest in treatment of this disease and several new agents have been the focus for both primary treatment and treatment of steroid refractory or dependent disease.

Pathophysiology of CGVHD—The pathophysiology of CGVHD is less well understood than the pathophysiology of acute GVHD. Alloreactive T cells are believed to be responsible for manifestations of CGVHD. Both CD4+ and CD8+ T cells have been implicated as primary mediators of CGVHD, and data support the role of dendritic cells as well(1). This is based upon the hypothesis that donor immune system recognizes antigens other than human leukocyte antigen (HLA) as targets of attack. Differences in these antigens (mHAs) between donor and host form the basis of the immune attack. Previously characterized mHAs in humans include

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both autosomal and Y-chromosome coded (H–Y) antigens. Other factors implicated in the pathogenesis are B cells and certain cytokines [tumor necrosis factor (TNF) and interferon gamma (IFN-γ)] and T regulatory cells.

Initial Systemic Therapy—Several studies document response rates of about 50–55%(2) with 25–50%(2,3) requiring prolonged immunosuppression beyond four years. Complications arise as a result of both active disease and prolonged systemic immunosuppression contributing to the high morbidity and mortality. Several studies are evaluating new agents either as initial therapy or in patients with steroid refractory or dependent disease to improve response and survival in these patients.

A combination of prednisone with calcineurin inhibitor has been the standard initial therapy for CGVHD based upon earlier reports documenting improved survival using combination therapy versus prednisone alone.(4) However, in a more recent randomized comparison of cyclosporine and prednisone versus prednisone in patients with platelet count > 100,000/μl, (3) similar rates of discontinuation of immunosuppression, requirements of secondary immunosuppressive therapy and mortality were seen.(3) Two randomized, double-blind multicenter trials tested newer agents (hydroxycholoroquine (P.I.: A.L. Gilman, University of North Carolina, Chapel Hill) or mycophenolate mofetil (P.I.: Paul Martin, Fred Hutchinson Cancer Research Center, Seattle)) added to standard treatment to improve outcomes in CGVHD and we await presentation of their results.

Salvage Therapy—There is no standard second line therapy for patients with CGVHD. Several agents have been tested in case series and small phase II trials. The studies are heterogeneous in patient population selection and definition of response criteria. The NIH Consensus working group has proposed incorporation of newer, more objective measures of patient selection for trials as well as cleaner definition of response. This should improve the quality and comparability of data for studies testing salvage therapy for CGVHD.

Mycophenolate Mofetil: Several studies have documented response rates of 46–75% in steroid refractory disease. Baudard et al.(5) reported similar high response rate of 69%, but observed higher rates of opportunistic infections. Higher serum trough levels of mycophenolic acid were associated with improved response rate.

Rituximab: B cells may be implicated in the pathogenesis of CGVHD as is evidenced by antibody production against sex-mismatched, Y chromosome encoded minor HLA antigens in association with CGVHD. Cutler et al.(6) tested rituximab in a phase I/II study in refractory chronic GVHD. The drug was well tolerated and toxicity was limited to infectious events. The clinical response rate was 70%. The results of these preliminary studies highlight potential activity of Rituximab with particularly high efficacy for skin and musculoskeletal involvement including scleroderma.

Sirolimus: Sirolimus is a macrocyclic triene antibiotic with immunosuppressive, antitumor and antifungal properties. Sirolimus prevents T and B cell activation by cytokines which in turn prevents cell cycle progression and proliferation. Efficacy of sirolimus in refractory CGVHD was tested in a phase II trial by Couriel et al.(7) The overall response rate was 63%. Major adverse events were hyperlipidemia, renal dysfunction, cytopenias and infectious complications. Thrombotic microangiopathy developed in four cases. This is likely related to higher sirolimus levels that exaggerate vascular toxicity of calcineurin inhibitors. When used together, serum levels of both agents must be monitored carefully and maintained in a lower therapeutic range.

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Extracorporeal Photopheresis (ECP): ECP is a technique where lymphocytes collected by apheresis are exposed to PUVA. Several mechanisms have been proposed to explain the efficacy of ECP, including induction of lymphocyte apoptosis, changes in dendritic cell differentiation and function, induction of regulatory T cell subsets, synthesizing IL-10, and in the long term, restoration of the DCI/DC2 and T helper 1 (Th1)/Th2 balance in favor of DC2/Th2.(8) In a prospective randomized trial of ECP + standard therapy versus standard therapy alone in patients with steroid non responsive skin GVHD, no benefit favoring ECP was seen in total skin scores at the end of 12 weeks, however, the proportion of patients who had at least 25% decrease from baseline in total skin score and at least 50% reduction in steroid dose was significantly higher in the ECP arm.(9) In a report by Couriel et al.(8) 71 patients with steroid resistant CGVHD were treated with ECP. The overall response rate was 61%. These results support responsiveness of both skin and visceral disease in ECP.

High dose steroids: In a study by Akpek et al.(10), 61 patients with severe refractory CGVHD were treated with methylprednisone at 10mg/kg/day for 4 consecutive days. Major and minor response was seen in 48% and 27% of patients. The treatment was well tolerated with no serious adverse events.

Pentostatin: In a report by Jacobsohn et al.(11), 58 patients with steroid refractory CGVHD were given pentostatin 4 mg/m^2 IV every 2 weeks for 12 doses. Of 58 patients, 32 (55%) had an objective response. Infection was the most significant toxicity.

Hydroxychloroquine: Hydroxychloroquine is a 4-aminoquinoline antimalarial drug used for the treatment of autoimmune diseases. Forty patients with steroid-resistant or steroid-dependent chronic GVHD were treated with hydroxychloroquine.(12) A response rate of 53% was seen. No major toxicity (including retinal) was reported with hydroxychloroquine.

Oral Beclomethasone: An enteric coated oral formulation of corticosteroid beclomethasone may have some topical activity in gastrointestinal GVHD. A recent randomized trial tested the drug in acute gastrointestinal GVHD.(13) Patients were randomized to receive oral beclomethasone versus placebo. There was a reduction in risk of treatment failure (though not statistically significant) at day 50.

Thalidomide: Thalidomide has known immunomodulatory properties and has been used in treatment of refractory CGVHD. In a trial of 80 patients with refractory GVHD,(14) treated with thalidomide, 20% of patients responded. Thirty six percent discontinued the medication because of side effects which included sedation, constipation, neuritis, skin rash, and neutropenia.

Other strategies that have been reported include pulse cyclophosphamide, clofazimine, etretinate, daclizumab, etanercept, alemtuzumab, low dose methotrexate, total lymphoid irradiation, and mesenchymal stem cell infusion.

Supportive Care—A multidisciplinary approach to management of patients with CGVHD is needed. Potential side effects of treatment include infections, osteoporosis, hypertension, hyperglycemia, renal insufficiency and hyperlipidemia. In addition the disease is associated with reduced quality of life and psychosocial disturbances. Appropriate care of these patients requires antimicrobial prophylaxis against encapsulated bacteria, pneumocystis pneumonia, cytomegalovirus, varicella zoster and herpes simplex viruses (in patients at risk) and antifungal prophylaxis. Nutritional support and physical therapy are important components of their treatment. Considerable attention and sub-specialty opinion may be required for management of these patients.

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Selected studies of Novel agents as secondary therapy in CGVHD

Study	Novel Therapy	Sample size	Response	Survival(follow up)
Lopez et al.(15)	MMF	24	75%	85% (2 years)
Baudard et al.(5)	MMF	15	69%	80% (19.5 months)
Mookerjee et al.(16)	MMF	26	46%	-
Ratanatharathorn et al.(17)	Rituximab	8	50%	100% (27–99 months)
Cutler et al.(6)	Rituximab	21	70%	-
Couriel et al.(7)	Sirolimus	35	63%	41% (2 years)
Jurado et al.(18)	Sirolimus	47	81%	57% (3 years)
Flowers et al (randomized trial of ECP vs. no ECP)(9)	ECP	95	Improvement in skin score 14.5% in ECP arm vs 10.4% in non ECP arm (NS)	98% in ECP arm, 94% in non ECP arm (12 weeks)
Couriel et al.(8)	ECP	71	61%	53% (1 year)
Gilman et al.(12)	Hydroxychloroquine	40	53%	75% in responders, 40% in nonresponders(30 months)
Akpek et al.(10)	Pulsed steroids	61	75%	81% (2 years)
Jacobsohn et al.(11)	Pentostatin	58	55%	70% (2 years)
Browne et al.(19)	Thalidomide	37	38%	41% (2years)
Parker et al.(14)	Thalidomide	80	20%	53% (2.7 years)

Agenda for future Studies—Data regarding chronic graft versus host disease are difficult to interpret because of heterogenous patient population, small sample size, retrospective study design and inconsistent definitions for diagnosis and response. The NIH Consensus working group has proposed incorporation of newer, more objective measures of patient selection for trials as well as cleaner definition of response. Future studies should incorporate and test these new criteria. Definitive evaluation of salvage therapy for CGVHD requires prospective controlled studies. A prospective multi-center phase II/III randomized trial in patients non-responsive to initial therapy is planned through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Impact of GVHD on Immune Reconstitution following Allogeneic HCT

Allogeneic hematopoietic cell transplant (HCT) recipients often experience profound, long lasting lymphopenia, rendering them vulnerable to infections and potentially to disease recurrence. Graft-versus-host disease (GVHD) remains a serious and common complication of allogeneic HCT and the adverse effects of GVHD on immune reconstitution greatly exaggerate the immunodeficiency associated with HCT. In addition to the immunosuppressive treatments rendered to treat GVHD, current models hold that the adverse impact of GVHD on immune reconstitution relates to three primary factors:

1. GVHD mediated damage to the microenvironment of the thymus and marrow, which are critical for T and B cell immune reconstitution respectively
2. Clonal exhaustion, senescence and bystander apoptosis of mature T cells during acute GVHD
3. Disruption of the peripheral niche responsible for homeostatic expansion and survival of naïve peripheral CD4+ and CD8+ T cells

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GVHD Mediated Damage to Lymphopoietic Microenvironments—Regeneration of lymphocytes occurs via thymopoiesis, which recapitulates thymic ontogeny and regenerates TCR diversity and/or via thymic-independent "homeostatic peripheral expansion" wherein mature T lymphocytes extensively proliferate and partially replenish their number, albeit with diminished repertoire diversity. Thymopoiesis occurs within a specialized microenvironment comprised of 1) thymic epithelium that serves as a source of growth factors and MHC presentation for thymic selection, 2) marrow derived, early T cell progenitors and 3) other thymic stromal elements (e.g. adipose tissue, neural cells and hormonally responsive elements). MHC expression on thymic epithelium renders it a prime target for T cell mediated alloreactivity and as a result, the thymus is a primary target organ of acute GVHD. GVHD associated thymic toxicity is further compounded by preparative regimen- and age-associated thymic toxicity, resulting in absent thymic function in most patients with GVHD. Similarly, B cell development within the bursal equivalent of the bone marrow requires a specialized microenvironment, which is significantly damaged in the long term by even a limited course of acute GVHD. Thus, GVHD induced damage to lymphopoietic microenvironments within the thymus and bursal equivalent in the marrow greatly diminishes T and B cell immune reconstitution following HCT. Although KGF has shown promising effects in preventing GVHD mediated thymic damage, it remains unclear whether KGF or other therapies can reverse GVHD induced damage.

Clonal Exhaustion, Senescence and Bystander Apoptosis of Mature T Cells During Acute GVHD—The pathophysiologic processes that initiate acute GVHD have been extensively studied. Fundamental elements include preparative regimen related tissue damage, LPS leakage across the gut mucosa, pro-inflammatory cytokine release and T cell mediated alloreactivity. Early after HCT, homeostatic T cell expansion in response to a broad array of self-antigens can provide substantial immune competence. During acute GVHD however, alloreactive T cells dominate this process, undergoing dramatic expansion and inducing severe skewing of the T cell repertoire. This phase of profound activation and expansion is followed by widespread apoptosis. Pre-clinical models have demonstrated that both alloreactive and non-alloreactive (e.g. bystander) populations undergo apoptosis during acute GVHD, resulting in diminished peripheral T cell numbers and widespread immune dysfunction [1].

Recent studies have demonstrated that IL-7 is required for homeostatic T cell expansion and that IL-7 therapy can enhance immune reconstitution following HCT. On the other hand, murine models have shown that IL-7 is required for GVHD induction, that pharmacologic levels of IL-7 lower the T cell number required to induce GVHD and that IL-7 neutralization can diminish and/or prevent GVHD. Moreover, a recent clinical study demonstrated that high levels of IL-7 on Day 14 following non-myeloablative stem cell transplant is a potent predictive factor of GVHD [2]. Thus, IL-7 appears to be play important roles both in facilitating immune reconstitution via homeostatic expansion as well as a potential cofactor in the development of GVHD.

Disruption of the Peripheral Niche Responsible for Homeostatic Expansion and Survival of Naïve Peripheral CD4+ and CD8+ T Cells—Survival of mature T cells requires continuous access to self-MHC molecules (Class II for CD4+ and Class I for CD8+ cells) and homeostatic cytokines (IL-7 for naïve cells and IL-15 and/or IL-7 for memory cells) within the context of a peripheral niche. The diminished efficiency of CD4+ vs. CD8+ homeostatic peripheral expansion raises the prospect that the more limited distribution of MHC Class II, which is essential for the CD4+ niche may limit CD4+ homeostatic peripheral expansion whereas the broadly available MHC Class I, which is essential for the CD8+ niche, may permit more efficient CD8+ expansionin this setting. Animal studies have recently provided functional data to suggest that GVHD induced impairment of the peripheral niche may be a more important factor in limiting immune reconstitution than clonal exhaustion and

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immune senescence of the T cells themselves [3,4], since T cells obtained from GVHD hosts expand considerably in non-GVHD recipients but not in recipients with GVHD. The specific cells necessary for the peripheral CD4+ niche have not been defined, but following HCT, myeloid DCs recover early while the recovery of plasmacytoid DCs (pDCs) requires months or years [5]. Furthermore, patients with Grade III–IV GVHD show reduced pDCs, which correlate with low CD4 counts [6–10]. Similar findings were made in the setting of HIV infection where an inability to regenerate their CD4 T cells may correlate with diminished pDCs. Thus, emerging science raises the prospect the some component of GVHD induced impairment of immune reconstitution may relate to damage to the peripheral T cell niche in general and the CD4+ T cell niche in particular. Future studies that more accurately define the critical elements within the CD4+ niche required for survival of mature CD4+ T cells could open the way to more effective therapies to augment immune reconstitution following HCT.

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Pathophysiology of GVHD

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Chronic GVHD Therapy

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