New approaches for preventing and treating chronic graft-versus-host disease

Stephanie J. Lee

Despite improvements in the practice of allogeneic hematopoietic stem cell transplantation (HCT) over the last 25 years, chronic graft-versus-host disease (GVHD) remains a substantial problem with little change in the incidence, morbidity, and mortality of this complication. In fact, with increased use of peripheral blood, transplantation of older patients, and less immediate transplantation-related mortality, the prevalence of chronic GVHD may increase. One of the difficulties in combating chronic GVHD is a lack of understanding about the pathophysiology of the syndrome. Inherent difficulties in conducting human clinical trials also contribute to the lack of meaningful progress. This review covers potential new approaches to the prevention and treatment of chronic GVHD. (Blood. 2005;105:4200-4206)

Introduction

Chronic graft-versus-host disease (GVHD) is the most serious and common long-term complication of allogeneic hematopoietic stem cell transplantation (HCT), occurring in 20% to 70% of people surviving more than 100 days. Approximately half of affected people have 3 or more involved organs, and treatment typically requires immunosuppressive medications for a median of 1 to 3 years. Because of higher treatment-related (nonrelapse) mortality, chronic GVHD remains the major cause of late death despite its association with a lower relapse rate. In addition, secondary malignancies are more common in people with chronic GVHD, particularly of commonly involved tissues such as mouth and skin, suggesting that chronic inflammation, prolonged exposure to immunosuppressive medications, or immune dysregulation facilitates the development of new cancers. Finally, the functional consequences of chronic GVHD organ involvement are major determinants of the health and quality of life of survivors. Despite the well-recognized adverse effects of chronic GVHD on the long-term success of allogeneic transplantation, its pathophysiology is poorly understood, and management strategies beyond systemic corticosteroids have not been established.

While there are some lessons that can be translated from basic and clinical studies of acute GVHD, several lines of evidence suggest that chronic GVHD is not simply a continuation of acute GVHD, and that separate approaches will be required for its prevention and management. First, except for T-cell depletion and use of umbilical cord blood, the major innovations that have improved acute GVHD rates do not seem to have affected chronic GVHD incidence. Second, while there is significant overlap between the organs involved in acute and chronic GVHD, the distribution of affected organs in chronic GVHD is much broader. Fully evolved chronic GVHD is largely an inflammatory and fibrotic process, while acute GVHD is more likely to reflect apoptosis and necrosis. Although traditionally the boundary between acute and chronic GVHD has been set at 100 days after transplantation, more recent definitions hinge on different clinical manifestations rather than time of onset. Third, while acute GVHD is highly associated with subsequent chronic GVHD, approximately 25% to 35% of chronic GVHD is de novo without any preceding acute manifestations, while 20% to 30% of people who had acute GVHD do not go on to develop chronic GVHD later.

This paper will review current beliefs about the pathophysiology of chronic GVHD and discuss the evidence for emerging approaches to prevent or treat this complication. Readers interested in reviews focusing on clinical management are referred to other sources.

Rodent models

Both human and murine studies will be reviewed throughout this article, although it is important to recognize the similarities and differences between the 2 species. In mice, chronic GVHD manifestations are highly dependent on the age of the mice, the strain combinations selected, the number and type of donor cells injected, and the preparative regimen. In contrast to humans, mice are not given pharmacologic prophylaxis against GVHD or treatment for GVHD.

Murine chronic GVHD can be induced by transplantation across class I, class II, or minor histocompatibility antigen barriers using irradiation-based regimens. Clinically, these models produce late weight loss, lymphoid atrophy, and lymphocyte infiltration of affected organs. Fibrosis of the skin, liver, lung, and exocrine glands is seen. Autoreactive T helper (Th) clones can be isolated. One minor mismatch model mimics human scleroderma with skin and lung fibrosis, a process that can be blocked by anti–transforming growth factor β (TGF-β) antibody treatment. Another murine model mimics systemic lupus erythematosus with splenomegaly, B-cell expansion, autoantibodies, and glomerulonephritis. This syndrome is induced by transplantation of parental (P1) cells into F1 (P1 crossed with P2) nonirradiated recipients in strain combinations with inherent or induced deficiencies in donor CD8+ T cells. Th2 cells secreting interleukin-4 (IL-4), IL-6, and...
include older age, certain diagnoses (eg, chronic myeloid leukemia, associated with increased chronic GVHD are not modifiable, and syndrome following HCT is questionable. resemblance to chronic GVHD, their relevance to the human affected children appear similar. Many recipient risk factors risk factors for, organ manifestations in, and clinical impact on Choice of donor, graft source, and GVHD prophylaxis Approaches to chronic GVHD prevention

Human pathophysiology

In humans, chronic GVHD is exceedingly rare after autologous or syngeneic transplantation despite similar preparatory regimens. In the allogeneic setting, the onset of chronic GVHD is usually delayed until 4 to 6 months after transplantation, rarely appearing before day +80 and with less than 5% of cases developing after 1 year. These observations suggest that alloreactivity is a key requirement, and that the processes leading to chronic GVHD either have a long latency or they exert their effects slowly on target tissues.

The current understanding of human chronic GVHD etiology starts with pathogenic donor T cells that expand in response to alloantigens or autoantigens unchecked by normal thymic or peripheral mechanisms of deletion. Critical donor or recipient tolerance-promoting cells may be absent. These pathologic T cells then attack target tissue directly through cytolytic attack, secretion of inflammatory and fibrosing cytokines, or promotion of B-cell activation and autoantibody production. Tissue damage leads to fibrosis and dysfunction. Chronic GVHD or its treatment leads to death from organ failure or infection. Thus, prevention and treatment of chronic GVHD has focused on interrupting this process through elimination or inhibition of pathogenic T cells, induction of tolerance, cytokine therapy, elimination of B cells, or modulating effects on local tissues.

Approaches to chronic GVHD prevention

Choice of donor, graft source, and GVHD prophylaxis

Clinical studies have identified many recipient, donor, and transplant factors associated with higher rates of chronic GVHD. Children experience lower rates of chronic GVHD, but the major risk factors for, organ manifestations in, and clinical impact on affected children appear similar. Many recipient risk factors associated with increased chronic GVHD are not modifiable, and include older age, certain diagnoses (eg, chronic myeloid leukemia, aplastic anemia), and lack of an HLA-matched donor. Other modifiable factors are associated with lower rates of chronic GVHD, and although causality is not proved, avoidance of high-risk factors may decrease the risk of clinically significant chronic GVHD. Assuming multiple HLA-matched donors are available, then selection of a younger related donor, use of bone marrow rather than peripheral blood, and limitation of CD34+ and T-cell dose infused may minimize the risk of chronic GVHD. Two reports suggest that chronic GVHD is also more likely to be extensive and difficult to treat in recipients of related and unrelated peripheral blood compared with bone marrow. Comment on the incidence and clinical manifestations of chronic GVHD after nonmyeloablative or reduced-intensity conditioning regimens awaits more definitive reports. If the recipient is male, then avoidance of a female donor, especially someone multiparous, may decrease the risk of chronic GVHD. Donor ABO compatibility and cytomegalovirus (CMV) seronegativity have also been associated with lower risks of chronic GVHD. While umbilical cord blood is currently a graft source of last resort in adults, it appears to be associated with lower rates of chronic GVHD.

As most HCT procedures use HLA-matched donors, so-called “minor” histocompatibility antigens (mHAs) must contribute to the pathophysiology of acute and chronic GVHD. Minor antigens are polymorphic proteins encoded in the genome that are degraded and presented to T cells in the context of HLA, thus inducing MHC-restricted immune responses. Conceivably, identification and avoidance of important minor mismatches could prevent both acute and chronic GVHD. In human transplantation, studies of predictors of acute GVHD have primarily focused on mHA-1 and mHA-2, expressed solely on hematopoietically derived cells (including dendritic and Langerhans cells) and presented in the context of HLA-A*0201. Other antigens are broadly expressed on tissues: mHA-3 is presented by HLA-A*0101, while mHA-8 is presented by HLA-A*0201 and HLA-A*0202. However, none of these mHAs has been associated with chronic GVHD.

An increased risk of chronic GVHD has long been recognized when a male recipient receives a graft from a female donor, particularly one who may have been alloimmunized by pregnancy or transfusion. The best explanation for this clinical observation is that mHAs encoded on the Y chromosome can elicit responses from female donors in male recipients. In a murine skin explant model, female cytotoxic T lymphocytes (CTLs) specific for the H-Y antigens found in males caused severe changes consistent with acute GVHD when exposed to male but not female skin.

Prevention of acute GVHD

Acute GVHD is a major predictor of chronic GVHD, and 70% to 80% of people with grades II to IV acute GVHD develop chronic GVHD. The nature of the observed association is highly controversial, and at least 4 explanations have been offered. Chronic GVHD has been suggested to be a later manifestation of allogeneic acute GVHD, a result of tissue damage (particularly thymus) caused by acute GVHD, a result of treatment (particularly steroids) for acute GVHD, or an epiphenomenon that is associated with but not etiologically linked to acute GVHD. These distinctions are important because interfering with the development of acute GVHD may prevent chronic GVHD if any of the first 3 mechanisms is operative, but would not affect chronic GVHD incidence if the last were true. In fact, some successful attempts to decrease acute GVHD may have actually increased chronic GVHD rates. Two reports have suggested that exposure to steroids as
prophylaxis for acute GVHD tends to increase the rate of subse-
quent chronic GVHD.32,33

Some attention has recently focused on the role of recipient
and donor APCs in prevention of acute GVHD while preserving
graft-versus-tumor effects. Slomchik et al34 reported murine
studies in which recipient antigen-presenting cells are critical
for initiation of acute GVHD by donor CD8 cells. Human
reports also suggest that APCs may be important. In patients
with myeloid malignancies undergoing haplotype-mismatched
and killer immunoglobulin-like receptor (KIR) mismatched
transplantations, decreased rates of acute GVHD, decreased
relapse rates, and higher overall survival in patients were reported.
Chronic GVHD rates were not reported. The proposed mechanism
of action is elimination of host APCs (decreasing acute GVHD) and
host tumor cells (decreasing relapse rate) by uninhibited donor
natural killer (NK) cells.35 This interpretation was supported by a
similar study in unrelated donor transplantation that included
anti–thymocyte globulin (ATG) for GVHD prophylaxis. KIR
mismatching was associated with better survival and marginally
lower rates of acute GVHD, although rates of chronic GVHD were
comparable.36 Studies in other populations have disputed these
findings or identified other important NK factors; however, chronic
GVHD rates were not mentioned.37,38 A second approach to depletion
of host APCs uses extracorporeal photopheresis (ECP) prior to
infusion of donor stem cells. In a small series, Chan et al39 reported
lower rates of extensive chronic GVHD, especially when donor
dendritic cell (DC) chimerism is achieved by day 100.

Two other studies looked at donor APCs, specifically plasmacy-
toid DC2 cells. Clark et al40 reported that people with chronic
GVHD had normal numbers of donor-derived plasmacytoid DC2s
in their blood compared with reduced numbers in posttransplant-
tion controls without chronic GVHD. In contrast, Waller et al41
reported that patients receiving bone marrow grafts with higher
numbers of CD3+CD4+bright, presumably DC2 cells, had a lower
incidence of chronic GVHD. A better understanding of the role of
APCs in chronic GVHD awaits additional studies.

Chronic GVHD prophylaxis

Attempts to prevent chronic GVHD through prolonged use of
immunosuppressive medications or addition of other agents have
been unsuccessful. Based on observational reports that extended
calcineurin inhibitor treatment may have decreased the incidence
of chronic GVHD,52 a randomized trial by the Seattle group
compared 6 months versus 24 months of cyclosporine in patients
with prior acute GVHD or evidence of subclinical chronic GVHD
on skin biopsy. No statistically significant difference was seen in
rates of clinical extensive chronic GVHD.45 Chao et al44 studied
thalidomide beginning 80 days after transplantation in a random-
ized, double-blinded, placebo-controlled study and found a higher
rate of chronic GVHD and mortality in patients receiving active
drug. Ringden et al45 treated a small number of patients with grade I
or higher acute GVHD with steroids until 6 months after transplanta-
tion in an attempt to prevent chronic GVHD. They abandoned
this approach when a higher than expected incidence of severe
chronic GVHD was noted.

Preemptive treatment of minimal chronic GVHD

A provocative study that attempted to avert clinical chronic GVHD
by preemptive treatment of subclinical chronic GVHD noted that
most (70%) went on to develop chronic GVHD, and that the relapse
rate was higher in patients who underwent transplantation in
relapse who did not develop chronic GVHD.46

Eosinophilia is associated with Th2 allergic disorders and may
precede the diagnosis of clinical chronic GVHD, leading at least
one pediatric center to start treatment when eosinophilia alone is
noted after transplantation. No long-term results of this strategy
were reported.47

New approaches to treatment

More than 20 years ago, corticosteroid therapy was shown to
improve survival in patients with chronic GVHD compared with no
therapy.48 However, extended corticosteroid therapy has well-
known, long-term adverse effects, and alternative treatments are
generally unsatisfactory.49 Other reviews concisely summarize data
on primary and salvage therapies currently available to treat
chronic GVHD, so this information will not be reviewed here.
Instead, potential new approaches to control of chronic GVHD are
emphasized. Two ongoing randomized, double-blinded multicenter
studies of hydroxychloroquine or mycophenolate mofetil added to
standard corticosteroid initial treatment seek to improve initial
therapy (A. L. Gilman, University of North Carolina at Chapel Hill,
and P. J. Martin, Fred Hutchinson Cancer Research Center, oral
communication, July 2004).

Elimination or inhibition of pathogenic T cells
through pharmacologic therapy

Pharmacologic inhibition of T cells forms the backbone of modern
chronic GVHD therapy. In human cutaneous chronic GVHD, most
infiltrating lymphocytes are CD8+;50,51 although one recent report
suggests that alloreactive CD4+ infiltrating cells are also important
and pre-exist in the donor.52 Newer agents under study include
mycophenolate mofetil,53 sirolimus,54 daclizumab,55 pentostatin,56
and alemtuzumab. When pharmacologic therapy is stopped, be-
tween 10% to 25% of patients flare and require reinstatement of
systemic treatment.57 Optimally, novel methods of T-cell inhibition
would target specifically the T cells responsible for chronic GVHD
while sparing other cells that could provide protective immunity.
For example, given the relative lymphopenia with fewer recent
thymic emigrants (as measured by T-cell receptor excision circle
levels) and a relative deficit of central memory populations
(CD45−CCR7+), precursor effector cells) noted in chronic GVHD,
preservation of any nonpathologic T cells might help decrease
serious infections.51,58,59

In humans, OX-40 (CD134, a member of TNF receptor
superfamily responsible for costimulation) expressing CD4+ cells
are reportedly associated with onset of chronic GVHD and
decreased response to initial therapy.50 If OX-40 is a marker of cells
involved in chronic GVHD, then targeting these cells or their
interactions at the onset of chronic GVHD may be therapeutic. In
mice, antibody to the OX-40 ligand (OX-40L) decreases acute
GVHD, but to this point, human trials have not been conducted.

Inhibition of pathogenic T cells through cellular therapy

Cellular approaches to inhibiting T cells have recently focused on
so called T regulatory cells (Tregs), a small subset of T cells that can
suppress proliferation and function of T effector cells, particularly
of the Th1 class. Tregs are activated in an antigen-specific manner, perhaps with involvement of IL-10, TGF-β, and immature dendritic cells, causing them to express high levels of CD25+ (IL-2 receptor alpha chain) constitutively. They are unresponsive to mitogens, express CTLA-4, and are able to block production of IL-2 and interferon-γ (IFN-γ) by effector T cells in a manner that relies on cell-to-cell contact. Most reports suggest that Tregs function in an antigen-nonspecific manner as tested in vitro, although at least one report suggested that they may be antigen specific in vivo. Tregs may also have inhibitory effects on APCs, and their high expression of CCR4 and CCR8 suggests aberrant trafficking. Recently, a distinction has been made between “natural” Tregs, important in preventing autoimmunity responses to continually expressed antigens in the noninflammatory setting, and “adaptive” Tregs, which are important in developing tolerance to foreign antigens and quelling inflammatory processes.

In murine models, infusion of CD4+CD25+ T cells is able to prevent acute GVHD while graft-versus-tumor is maintained. Removal of CD4+CD25+ T cells from the graft or blockade by CD25+ antibodies worsened acute GVHD. Another model suggested that chronic GVHD incidence and severity is higher in the absence of recipient CD4+CD25+ cells, and that repletion with recipient or host Tregs is protective. These murine observations led to the hypothesis that human chronic GVHD results from a low Treg population, and that expansion ex vivo and replacement could help control chronic GVHD. However, a small study of 17 patients with chronic GVHD showed higher numbers of CD4+CD25+ cells in people with chronic GVHD but lower CD62 ligand (CD62L) expression compared with people without chronic GVHD, although absolute numbers and functionality were similar to controls. A more recent study of people considered to have allogeneic transplantation disease showed higher numbers of CD4+CD25+ cells in people with chronic GVHD but lower CD62 ligand (CD62L) expression compared with people without chronic GVHD, although absolute numbers and functionality were similar to controls.

Cytokine therapy

Cytokines secreted by T cells, APCs, and damaged target tissues may contribute to chronic GVHD. T-cell cytokines are generally classified as Th1-type (IL-2, IFN-γ) and Th2-type (IL-4, IL-5, IL-9, IL-10). APCs and damaged target tissue can secrete TNF-α and IL-1. While animal studies have demonstrated the importance of cytokine availability to chronic GVHD development, documentation in human systems has been less convincing. Human studies in chronic GVHD have focused on circulating cytokine levels (IL-10, TGF-β1), tissue cytokine expression (IL-2, IFN-γ, IL-4, IL-5, IL-10, IL-1α, TNF-α, platelet-derived growth factor [PDGF], TGF-β), and donor or recipient cytokine polymorphisms (IFN-γ, IL-6, IL-10, IL-1α, IL-1β, IL-1Ra, TNF-α, TGF-β). To date, only cytokine blockade (TNF-α) has advanced to human trials for treatment of chronic GVHD.

Studies with limited numbers of patients suggest that circulating IL-10 levels are lower in people with chronic GVHD, while IL-1β, IL-6, TNF-α, and TGF-β1 levels are higher. A small study suggested that in vitro mononuclear cell IL-10 secretion after stimulation was lower in patients with chronic GVHD, while use of IL-10 blocking antibodies increased IFN-γ secretion. This contrasts with the murine parent into F1 studies in which high IL-10 is associated with chronic GVHD and IL-10 antibodies can block chronic GVHD manifestations. Of note, any human trials of exogenous IL-10 supplementation will have to be undertaken carefully as observational studies in human transplant and nontransplant settings document an association between higher serum IL-10 levels, greater severity of septic shock, and fatal outcome.

Ochs et al. used reverse-transcription–polymerase chain reaction (RT-PCR) to study transcription of cytokines in a limited number of skin biopsies from people with active chronic GVHD, people without active chronic GVHD, and healthy controls. Although IFN-γ transcript levels were elevated in people with active chronic GVHD, the other cytokine levels studied were not different. Certain donor and recipient cytokine polymorphisms have been associated with chronic GVHD, but results are conflicting. In contrast with the findings of studies measuring circulating IL-10
levels, polymorphisms of IL-10 associated with higher donor or recipient IL-10 production were associated with chronic GVHD. Two recipient IL-1α polymorphisms were associated with chronic GVHD, although one polymorphism is associated with increased IL-1α while the other, with decreased IL-1α production. In another study, neither recipient IL-10 nor IL-1 polymorphisms were associated with chronic GVHD. Recipient IL-1Ra polymorphisms associated with lower production of IL-1Ra, and thus perhaps more biologic activity of IL-1 were also associated with chronic GVHD.

Recipient IL-6 polymorphisms have been associated with chronic GVHD in 2 reports, though these studies failed to find an association with other donor or recipient polymorphisms (TNF-α, TNF-β, IL-1, IL-10, IFN-γ). A study by Stark et al identified an association between chronic GVHD and donor homozygosity for the 196R allele of the TNF type II receptor (TNFRII), associated with decreased TNFRII levels and thus increased functional levels of TNF. Eternacept, a recombinant soluble TNF inhibitor, has reported activity in 10 steroid-refractory patients with chronic GVHD. Another TNF inhibitor, infliximab, has been associated with invasive fungal infections when used to treat steroid-refractory acute GVHD, and there are no reports of its use in chronic GVHD.

**Eliminate B cells**

Circulating autoantibodies and polyclonal hypergammaglobulinemia were noted in the earliest reports of human chronic GVHD, but more recent studies show hypogammaglobulinemia and fewer precursor and mature B cells. Nevertheless, the similarity between many autoimmune diseases associated with autoantibodies and the clinical manifestations of chronic GVHD has always been intriguing. Patients with CMV infection may have anti-CD13 antibodies, which recognize normal structures in skin. Patients with sclerodermatous chronic GVHD are more likely to have immunoglobulin G (IgG) antibodies to nuclear proteins (95%), but these antibodies are also common in patients with chronic GVHD. Miklos et al have found antibody responses to H-Y antigens in male recipients with female donors, and these antibodies were associated with development of chronic GVHD.

Rituximab is a chimeric murine-human CD20+ antibody that has reported activity in treating chronic GVHD and other autoimmune diseases. Two case series suggest that transient B-cell depletion can improve clinical manifestations of chronic GVHD with durable responses.

**Minimize effects on target tissues**

Even if the systemic causes of chronic GVHD cannot be controlled, treatments aimed at target tissues may still minimize morbidity and improve functionality. One of the major debilitating tissue responses is fibrosis. Halofuginone has been given topically or systemically to inhibit TGF-β-induced collagen α1 gene overexpression. Halofuginone inhibits smad3 phosphorylation, particularly in fibroblasts induced to oversecrete collagen by activation with TGF-β or activating mutations, via a mechanism that relies on protein synthesis. If applied topically, halofuginone is not absorbed and effects are reversible after 3 months. In a rat model of liver fibrosis, halofuginone was able to reverse fibrosis. In human and murine studies, normal collagen production was unaffected. Despite great interest in studying halofuginone for sclerodermatous chronic GVHD, this drug is not yet available for studies of chronic GVHD in the United States.

Excess collagen deposition may also be combated through physical rehabilitation, similar to the treatment of burn victims and people with scleroderma, many of whom also suffer from excess collagen deposition. Aggressive heat therapy, massage, and passive range-of-motion exercises can help maintain function until the sclerotic process can be controlled. To date, there are no studies specifically evaluating rehabilitative methods in people with chronic GVHD.

Ursodeoxycholic acid has reportedly improved the biochemical profile of patients with hepatic chronic GVHD. As a less hydrophobic acid, ursodeoxycholic acid replaces the human bile acids and may result in less cholestatic damage. It may also cause decreased expression of HLA class I molecules on hepatocytes. However, this medication is very expensive and in one study of patients with chronic GVHD, biochemical improvements were lost upon discon- tinuation of the drug. In primary biliary sclerosis, ursodeoxycholic acid has improved liver function tests but not changed the natural history of the disease. No long-term studies of this drug in chronic GVHD have been reported.

Biedermann et al studied skin biopsies in a small number of people with acute, chronic, or no GVHD after allogeneic transplantation, and found fewer microvessels and higher levels of von Willebrand factor in people with chronic GVHD. They hypothesize that endothelial damage happens first, followed by fibrosis akin to what happens in solid organ rejection. Thus, methods to prevent endothelial damage may have efficacy in chronic GVHD prevention or treatment.

Topical immunosuppressives such as corticosteroids and calcineurin inhibitors can improve local symptoms in the eyes, mouth, skin, and vaginal area. Small series report efficacy for autologous serum eyedrops in Sjögren syndrome and UVB laser for lichen planus. As new approaches to local therapy are developed for autoimmune diseases, rapid translation and testing in the chronic GVHD population seems warranted.

**Summary**

A better understanding of chronic GVHD and discovery of ways to prevent or control this complication without compromising disease-free survival stand as major barriers to the success of allogeneic transplantation. Far too many people suffer and die from chronic GVHD long after the acute risks of transplantation have passed. A National Institutes of Health (NIH) consensus conference has convened to try to formulate better research methods and foster collaboration so that research into the pathophysiology and treatment of chronic GVHD can be furthered. There are many promising treatment approaches on the horizon based on a better understanding of immune regulation. It is realistic to hope that less morbid treatments targeted specifically to the cause of chronic GVHD can be identified, and that a review of chronic GVHD therapy a decade from now will see some of these concepts successfully translated into practice.

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