



Mini-review

Chronic graft-versus-host disease: clinical manifestation and therapy

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Summary:

Chronic graft-versus-host disease (GVHD) is a major cause of morbidity and mortality in long-term survivors of allogeneic stem cell transplantation. The immunopathogenesis of chronic GVHD is, in part, TH-2 mediated, resulting in a syndrome of immunodeficiency and an autoimmune disorder. The most important risk factor for chronic GVHD is prior history of acute GVHD and strategies that prevent acute GVHD also decrease the risk of chronic GVHD. Other important risk factors are the use of a non-T cell-depleted graft, and older age of donor and recipient. Whether recipients of peripheral blood stem cells are at increased risk of chronic GVHD remains unsettled. There are no known pharmacologic agents which can specifically prevent development of chronic GVHD. Agents which have efficacy in the treatment of autoimmune disorders have been utilized as therapy for established chronic GVHD and are associated with response rates of 20% to 80%. Most responses are confined to skin, soft tissue, oral mucosa and occasionally liver. Bronchiolitis obliterans responds infrequently to therapy and is associated with a dismal prognosis. Newer, promising therapeutic strategies under investigation include thalidomide, photopheresis therapy, anti-tumor necrosis factor and B cell depletion with anti-CD20 monoclonal antibody. *Bone Marrow Transplantation* (2001) 28, 121–129.

Keywords: chronic graft-versus-host disease; immunosuppressive therapy; cyclosporine; tacrolimus; extracorporeal photochemotherapy; allogeneic stem cell transplantation

Chronic graft-versus-host disease (GVHD) occurs in approximately 60–80% of long-term survivors of allogeneic hematopoietic cell transplant (HCT).^{1,2} This immunologic complication is a major cause of morbidity and mortality,³ accounting for about one-quarter of deaths in long-term survivors of transplants performed for leukemia and two-thirds of deaths in long-term survivors of allografts undertaken for severe aplastic anemia.⁴ The incidence of chronic GVHD is

likely to rise due to the increasing availability and use of unrelated donors^{5,6} as well as the inclusion of older recipients of non-myeloablative ('reduced conditioning') regimens. Chronic GVHD, as initially defined, resembled an autoimmune disorder occurring 100 days after allogeneic transplantation. The arbitrary day of onset, however, may not be as crucial in separating acute from chronic GVHD; rather, these two syndromes appear to result from different mechanisms.^{7,8} The classification for severity of chronic GVHD is depicted in Table 1.

Immunology and pathology of chronic GVHD

Donor T cells play a central role in the immunologic attack on host tissues in both acute and chronic GVHD. While the cytokine production pattern of acute GVHD is mostly TH1 type, TH2 cytokines predominate in chronic GVHD.⁹ Furthermore, the elevation of TH2 cytokines is consistent with the clinical manifestations of chronic GVHD in both man and animal models (eg associations of elevated IL-

Table 1 Classification of chronic GVHD⁷

Subclinical GVHD
Histologically positive but no clinical symptoms
Clinical limited chronic GVHD
Either or both
Localized skin involvement
Hepatic dysfunction (due to chronic GVHD)
Clinical extensive chronic GVHD
Either
Generalized skin involvement
Or
Localized skin involvement or hepatic dysfunction due to chronic GVHD or both
Plus
Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis
Or
Involvement of the eyes (Schirmer's test less than 5 mm wetting) or
Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy
Or
Involvement of other target organ (lung, kidney)

Chronic GVHD also classified according to the pattern of onset of clinical disease: *de novo*, quiescent and progressive disease¹⁰⁴ (see text).

5 with eosinophilia, IL-4 with gammopathy and possibly scleroderma).^{10,11} Thus, chronic GVHD appears to be a syndrome of immune dysregulation resulting in immunodeficiency and autoimmunity – a TH2 disease.^{12,13}

Most patients with chronic GVHD have evidence of B cell dysregulation with a high prevalence of autoantibodies to several cell surface and intracellular antigens, although the role of these autoantibodies in the pathogenesis of chronic GVHD is unclear.^{14–18}

The pathogenetic role of autoantibodies in the autoimmune disease has been elusive for the past several decades, because of the difficulty in identifying the autoantibody-associated effector mechanisms. Plausible effector pathways have been proposed for the role of autoantibodies in various autoimmune diseases, such as rheumatoid arthritis (RA)¹⁹ and other autoimmune diseases.²⁰ In RA, IgG rheumatoid factor (RF) complexes may account for the articular and extra-articular features of RA,²⁰ ultimately through ligation of FcγRIIIa by IgG RF with the subsequent generation of TNFα, an inflammatory cytokine highly expressed on macrophages in synovium intima and other target tissues.^{21,22} Similar mechanisms have been postulated for other autoimmune disorders, such as systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, and progressive systemic sclerosis,²⁰ which share similar clinical manifestations as chronic GVHD. Immune thrombocytopenia can also be associated with a number of autoimmune disorders.²³ In patients with extensive chronic GVHD, anti-platelet antibodies are frequently detected in chronic GVHD-associated thrombocytopenia.²⁴

Risk factors associated with chronic GVHD

The risk of acquiring chronic GVHD is increased with increasing HLA disparity between recipient and donor. Recipients of unrelated donor marrow have a higher incidence of chronic GVHD.^{1,2} The most important risk factors for developing extensive chronic GVHD are a diagnosis of prior acute GVHD,^{25,26} and the use of corticosteroids at day 100.²⁷ The probability of chronic GVHD ranges from 59% to 85% among those with prior grade II–IV acute GVHD, up to 49% with prior grade I acute GVHD, and up to 28% for those who developed *de novo* chronic GVHD.

Other significant predictive factors for chronic GVHD are the use of non T cell-depleted bone marrow, male recipients of alloimmune female donors,²⁶ and older age of recipient or donor.^{28,29} In unrelated donor transplantation, donor age is an independent predictor of acute and chronic GVHD.³⁰ The use of busulfan has been associated with increased risk of chronic GVHD in one study,³¹ but other studies have not found an increased incidence of chronic GVHD for busulfan-containing regimens.^{32,33} Although there is general agreement that recipients of allogeneic peripheral blood stem cells (PBSC) do not develop more acute GVHD than those receiving marrow, whether the incidence of chronic GVHD is higher in PBSC recipients is controversial. Earlier studies reported the incidence of chronic GVHD to be higher,^{34,35} however, the recent randomized trials comparing marrow and peripheral blood source of

stem cells showed no difference in the rates of chronic GVHD.^{36,37} Nonmyeloablative regimens that include CAMPATH-1H appear to have a low risk of acute and chronic GVHD, although longer follow-up is needed.³⁸

Clinical manifestations

Although the clinical manifestations of chronic GVHD differ from acute GVHD, concordance among clinicians in making the diagnosis, grading the disease, and deciding when to treat remains a challenge.³⁹ Practical problems encountered by clinicians caring for patients with chronic GVHD include the recognition of uncommon manifestations of the disease, interpretation of symptoms and signs of chronic GVHD appearing earlier than 2 months after transplant, and the determination whether to treat chronic GVHD limited to skin. The classification of chronic GVHD,⁷ which is based on clinical and pathologic findings, is helpful in categorizing the severity of chronic GVHD. Patients with extensive disease will invariably require systemic immunosuppressive therapy while most patients with limited disease do not (see Table 1). A more refined prognostic model for chronic GVHD was recently reported, and staging of chronic GVHD based on this model may provide greater accuracy in assessing the outcomes of various treatments.⁴⁰

Clinical manifestations of chronic GVHD are similar to autoimmune collagen vascular diseases,^{41,42} such as oral ulcerations (lichen planus), keratoconjunctivitis sicca,⁴³ xerostomia,⁴⁴ polyserositis,⁴⁵ esophagitis and stricture,⁴⁶ vaginal ulceration and stricture,^{47,48} intrahepatic obstructive liver disease, obstructive pulmonary disease, scleroderma, morphea, fasciitis⁴⁹ and myositis.^{50,51}

Oral mucosal involvement

The oral mucosa is most frequently involved by chronic GVHD. The clinical findings range from erythema, leukoplakia, lichenoid lesions, ulcers, mucosal atrophy, cicatricial changes and xerostomia.⁵² The mucosal appearance can be confused with oral candidiasis. The typical histologic findings of oral chronic GVHD consist of diffuse and periductal lymphocytic infiltration in labial salivary glands, subepithelial lymphocytic infiltration, and epithelial changes in buccal mucosa, similar to findings seen in patients with Sjögren's syndrome.^{53–55} Involvement of major salivary glands invariably leads to severe xerostomia, rampant caries, periodontal disease, and occasionally sialadenitis.⁵⁶ Pilocarpine has been shown to relieve the symptoms of xerostomia.^{57,58} Nystatin suspension and clotrimazole troches should not be used in patients with severe xerophthalmia because the high sugar content of nystatin suspension can exacerbate caries and troches are poorly dissolved in the absence of saliva.

Skin and soft tissues

There are two main forms of cutaneous chronic GVHD, namely, lichenoid and sclerodermatous types.⁵⁹ Early in the

course of chronic GVHD, the lichenoid form predominates and typically involves the periorbital regions, ears, palms and soles. Rarely, lichenoid chronic GVHD may involve the glans penis and foreskin (causing phimosis),⁶⁰ and not infrequently involve the vaginal mucosa (resulting in stenosis).⁴⁷ Appearing later is the sclerodermatous form which may present as inflammatory plaques over the extremities. Frequently, the progression of sclerodermatous changes is insidious. Raynaud's phenomenon is rare in contrast to patients with progressive systemic sclerosis.⁴² Patchy areas of sclerotic plaques with bound-down consistency may occur on the trunk, especially over pressure surfaces (eg along the bra or waistline). Patients with truncal involvement by sclerodermatous GVHD may develop progressive restrictive lung disease due to diminished chest wall compliance. Skin sclerosis may be the product of excessive tissue repair resulting from immunologic injury by effector lymphocytes.⁶¹ Skin and subcutaneous involvement is often accompanied by dystrophic changes of the nails, including vertical ridges, onycholysis and telangiectasia of the nail fold.⁵⁹ Occasionally, fungal infection of the nail plate (onychomycosis) by dermatophytes and nondermatophytes may confound the clinical picture of chronic GVHD. Subungual accumulation of friable keratinous debris suggests the presence of onychomycosis.⁶²

Fasciitis is a rare presentation of chronic skin GVHD, involving the medial aspects of the proximal portion of extremities.⁴⁹ Inflammatory changes of the overlying skin and subcutaneous tissue simulating cellulitis may be pronounced. As the inflammation subsides, the skin and subcutaneous tissue is replaced with fibrotic tissue leading to dimpling appearance of the skin and contracture.⁵⁹

Xerophthalmia

Ocular involvement occurs in approximately 60% of patients with chronic GVHD. The most frequent ocular manifestations include keratoconjunctivitis sicca, cicatricial lagophthalmos, and sterile conjunctivitis and uveitis.⁶³ Xerophthalmia must be recognized early in order to avoid serious complications such as corneal epithelial defects and ulceration. The Schirmer's test should be routinely performed in all patients early in the onset of chronic GVHD. If xerophthalmia is present, aggressive use of topical lubricants should be initiated. Patients should be advised to wear protective eyewear outdoors especially on windy days. In more severe cases, punctal occlusion or cauterization, bandage soft contact lenses, and/or tarsorrhaphy may be needed.

Liver

Cholestasis predominates the clinical picture of chronic liver GVHD. However, isolated liver involvement by chronic GVHD, without the clinical signs and symptoms of other organ involvement, is uncommon. The severity of chronic liver disease correlates with the histopathologic findings on biopsy; namely, the presence of bridging necrosis indicates extensive chronic GVHD.^{25,64} Hepatic

failure resulting from progression of chronic GVHD is uncommon in long-term survivors. When hepatic failure occurs, the most frequent etiology is hepatitis C infection.⁶⁵

GI tract

Esophageal involvement in chronic GVHD results in dysphagia and retrosternal pain from mucosal desquamation with fibrosis, esophageal webs, distal peptic esophagitis, and stricture.⁶⁶ Gastrointestinal involvement is not usually a prominent manifestation of chronic GVHD, but occasionally may evolve from acute GVHD leading to gastrointestinal dysmotility and pseudo-obstruction.⁶⁷ In some patients, involvement of the small intestine by acute GVHD may lead to permanent damage, resulting in mechanical obstruction, diarrhea, stasis syndrome, and malabsorption.^{46,68,69}

Obstructive lung disease

Interstitial lung disease encompasses a broad range of etiologies, from regimen-related toxicity^{70,71} to infection⁷²⁻⁷⁴ and possibly to immunologic injury related to GVHD.⁷⁵ The occurrence of obliterative bronchiolitis, however, is limited to patients who develop chronic GVHD. Symptoms such as cough may begin 3 to 20 months after transplantation and then progress to dyspnea, progressive airflow obstruction, and finally respiratory failure.⁷⁶⁻⁷⁸ A high-resolution CT scan may be normal or show hyperinflation, bronchial dilatation, consolidation, hypo-attenuated areas and vascular attenuation.⁷⁹ Patients with obstructive lung disease due to chronic GVHD infrequently respond to therapy, although some patients may survive long term.⁸⁰

Neuromuscular and CNS involvement

Neuromuscular involvement in chronic GVHD is uncommon.⁸¹ Sensory⁸² and motor neuropathy,⁸³ myositis,⁸⁴ dermatomyositis⁸⁵ and myasthenia gravis⁸⁶⁻⁸⁸ have been reported to be associated with chronic GVHD. In most cases, neurologic complications after stem cell transplantation are the result of the toxicities of the preparative regimen.⁸¹ Neuropathy is frequently associated with treatment for GVHD, including thalidomide⁸⁹ and occasionally tacrolimus or cyclosporine.¹

Immunodeficiency

The most important complication associated with chronic GVHD is immunodeficiency, leading to susceptibility to wide ranges of opportunistic infections and frequently to death.⁹⁰⁻⁹⁴ Antimicrobial prophylaxis against *Pneumocystis carinii*, cytomegalovirus (CMV),⁹⁵ and pneumococcus is crucial in the prevention of potentially fatal infections.⁹⁶ Late onset CMV infection also occurs preferentially in patients with chronic GVHD, especially in the setting of corticosteroid usage.⁹⁷ Long-term CMV prophylaxis may

be needed in seropositive patients with chronic GVHD, especially those receiving immunosuppressive therapy. A comprehensive guideline for infectious prophylaxis in stem cell transplant recipients, including patients with chronic GVHD, has recently been published.⁹⁸

Prophylaxis of chronic GVHD

Although there is no specific prophylactic therapy for chronic GVHD, the most important risk factor for the development of chronic GVHD is a prior diagnosis of acute GVHD. Pharmacologic approaches to the prevention of chronic GVHD have been disappointing. One recent prospective randomized double-blind study using thalidomide, an agent shown to have activity in the treatment of chronic GVHD, resulted in a paradoxical outcome of a higher incidence of chronic GVHD and a lower overall survival for those receiving thalidomide.⁹⁹ Tacrolimus reduces the inci-

dence of acute GVHD when used for GVHD prophylaxis, but does not influence the incidence of chronic GVHD.^{1,2} T cell depletion of stem cell grafts reduces the risk of both acute and chronic GVHD.^{26,100} Studies using Campath antibody have reported exceptionally low incidences of acute and chronic GVHD.^{38,101,102} Other methods of T cell depletion also report low incidences of chronic GVHD.^{100,103}

Treatment

The diversity of organ involvement, the chronic nature of the illness, and the hematologic and immunologic dysfunction associated with the syndrome all contribute to the difficulties in successfully treating chronic GVHD. The 'progressive' form of chronic GVHD evolves without a hiatus from active acute GVHD. Patients with progressive chronic GVHD are more likely to receive corticosteroids and tacrol-

Table 2 Agents used in the treatment of chronic GVHD

Author/Ref.	Study design	Patient characteristics	Treatment	No.	Response			Survival %
					CR	PR	% Response	
Sullivan <i>et al</i> ⁹⁰	Randomized	Extensive	Prednisone	63	21	18	62	61 at 5 years
			vs					
			Prednisone + Azathioprine	63	23	17	64	47
Sullivan <i>et al</i> ¹⁰⁵	Phase II	Extensive Platelets <100 000	Prednisone	38	6	6	32	26
			+ Cyclosporine	40 1st therapy	13	9	56	51 at 4 years
			+ Prednisone	21 salvage	4	11	71	67
Vogelsang <i>et al</i> ¹¹⁰	Phase II	High risk Refractory	Thalidomide	21 high risk	7	1	38	48 at 4 years
Parker <i>et al</i> ⁸⁹	Phase II	Refractory Extensive	Thalidomide	23 refractory	7	11	78	76
Browne <i>et al</i> ¹²³	Phase II	Refractory Extensive	Thalidomide	80	9	7	20	53
Vogelsang <i>et al</i> ¹¹⁵	Retrospective	Refractory/New Onset	PUVA	37	1	13	38	41 at 2 years
Marcellus <i>et al</i> ¹⁰⁸		Refractory Sclerodermatosis	Etretinate	35 refractory	16	15	77	27/40 Survival
Gaziev <i>et al</i> ¹²⁴	Retrospective	Moderate or Severe	CSA/MP/AZ CSA/MP/AZ/CY and/or MTX	5 <i>de novo</i>	32	20/32 Responder		Not mentioned
Lee <i>et al</i> ¹²⁵	Phase II	6 Limited 16 Extensive	Clofazimine	33	30	1	70	Not mentioned
Mookerjee <i>et al</i> ¹²⁶	Retrospective	Refractory	Mycophenolate Tacrolimus	11	4	6	81	mentioned
Carnevale-Schianca <i>et al</i> ¹⁰⁶	Phase II	Refractory Extensive GVHD	Tacrolimus	26	2	10	46	Not mentioned
Gilman <i>et al</i> ¹¹¹	Phase II	Steroid-resistant Steroid-dependent	Hydroxychloroquine	39	5	3	21	Not mentioned
Greinix <i>et al</i> ¹¹²	Not stated	Extensive	ECP	32	3	14	53	Not mentioned
Chiang <i>et al</i> ¹¹⁹	Prospective	Steroid-dependent	Etanercept (Enbrel)	15	Cutaneous 12/15 CR			64
Couriel <i>et al</i> ¹¹⁸	Prospective	Steroid-resistant	Infliximab (Remicade)	8 (7 evaluable)	Not stated	Not stated	100	Not mentioned
				22	Not stated	Not stated	Skin 57 GI 92	Not mentioned

imus or cyclosporine at onset, but are less likely to respond to these and other immunosuppressive therapies.^{3,40,104} By contrast, patients who develop chronic GVHD after an interval of response to treatment for acute GVHD (quiescent form) or patients who have never had acute GVHD (*de novo* form) are more likely to respond to therapy. In these latter situations, institution of tacrolimus or cyclosporine in combination with glucocorticoids is often effective.^{90,104,105} Some patients failing on cyclosporine may achieve complete and durable remission with tacrolimus.¹⁰⁶

In patients with extensive chronic GVHD and a platelet count $\leq 100 \times 10^9/l$, the addition of azathioprine to prednisone actually resulted in poorer survival than those treated with prednisone alone (5 year survivals of 47% and 61%, respectively).⁹⁰ Patients with extensive chronic GVHD who had platelet counts $\leq 100\,000/\mu l$, most of whom had the 'progressive' form, had the poorest survival (5 year survival of 26%). A subsequent trial using alternate day cyclosporine and prednisone has shown improvement in this subset of patient with extensive chronic GVHD with thrombocytopenia.¹⁰⁵ Clinical trials using immunomodulatory approaches in the treatment of chronic GVHD are summarized in Table 2.

Despite the widely employed combination of steroids and cyclosporine or tacrolimus, the outcome of treatment in patients with extensive chronic GVHD remains unsatisfactory. Oral lichen planus often responds to immunosuppressive therapy. Involvement of limited scleroderma of the distal extremities is also more likely to respond to immunosuppressive therapy, but generalized scleroderma carries a poor prognosis.⁴⁰ Patients with bronchiolitis obliterans have an extremely poor prognosis independent of other clinical manifestations of chronic GVHD.^{77,78,107} They respond poorly to corticosteroids and other immunosuppressive therapy and progress over months to years to become oxygen dependent, culminating in respiratory failure.

Other agents that have been studied in the past decade are etritenate,¹⁰⁸ thalidomide,^{89,109,110} hydroxychloroquine,¹¹¹ extracorporeal photopheresis,^{112,113} UVB,¹¹⁴ and PUVA.¹¹⁵ Cutaneous involvement most frequently responds while pulmonary disease rarely responds to any of these treatments. The difficulty of conducting clinical trials in patients with chronic GVHD has been illustrated in a recent randomized double-blind study comparing thalidomide to placebo.¹¹⁶ Contrary to earlier reports,^{89,110} thalidomide was poorly tolerated, leading to early discontinuation of this agent in most patients. Furthermore, frequently reported side-effects in the placebo arm underscore the problem of interpretation of signs and symptoms not truly related to drug therapy but rather to chronic GVHD or other concurrent treatments. Heterogeneity of patient populations in these clinical trials also complicates the comparison of treatment outcomes across various series. The recent development of a prognostic model of chronic GVHD may help investigators improve future clinical trials in patients with extensive chronic GVHD.⁴⁰

The recent recognition of tumor necrosis factor (TNF) as an effector molecule in GVHD has drawn attention to the use of monoclonal antibodies and receptor antagonists for the treatment of GVHD.^{75,117} Both a humanized chim-

eric antibody against TNF (infliximab) and a TNF antagonist (etanercept) have been studied in patients with chronic GVHD. Preliminary reports reveal high response rates even for lung involvement.^{118,119} Further studies of TNF blockade to treat chronic GVHD are warranted.

The recognition of a possible pathogenetic link between autoantibodies and various autoimmune disorders has unveiled a new paradigm for the treatment of chronic GVHD.²⁰ A recent study designed to deplete B lymphocytes with an anti-CD20 monoclonal antibody has reported sustained improvement for patients with rheumatoid arthritis.¹²⁰ We had the opportunity to test this hypothesis by administering the anti-CD20 chimeric monoclonal antibody (rituximab) in a patient with severe chronic GVHD-associated thrombocytopenia.¹²¹ This patient had a dramatic response with complete recovery of her platelet count and concurrent improvement of other clinical signs of chronic GVHD, despite discontinuation of all other immunosuppressive agents. Improvement of myasthenia gravis associated with extensive chronic GVHD has also been reported.¹²² Further study of this innovative approach is underway.

In conclusion, chronic GVHD remains one of the most important challenges in allogeneic transplantation. Survival and quality of life in long-term survivors of allogeneic stem cell recipients depend on new innovative approaches to treat this chronic debilitating condition. Modulation of cytokines, depletion of autoantibody-producing B cells with monoclonal antibody, and other immunomodulatory agents are being investigated for their role in the treatment of chronic GVHD. Other supportive care measures such as antimicrobial prophylaxis, symptomatic control of sicca syndrome, skin care, psychological support, and physical rehabilitation are equally important in minimizing catastrophic infectious complications and improving the quality of life.

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