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Treatment of chronic graft-versus-host disease in 2011

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Abstract

Purpose of review—This article summarizes recent reports on the risks, pathogenesis and treatment of chronic graft-versus-host disease (GVHD).

Recent findings—Chronic GVHD remains an elusive disorder to characterize and to treat. Recent evidence on tolerance induction by regulatory T cells and on B cells involvement shed some insights in the pathogenesis of chronic GVHD. In a recent large comparative study, the overall risk profiles for acute and for chronic GVHD were similar, but risks factors were not changed after adjustment for prior acute GVHD, supporting the concept that chronic GVHD is not an end stage of acute GVHD. Glucocorticoids remain the standard initial treatment of chronic GVHD, but the outcomes are not satisfactory, particularly for patients with high-risk features. Many treatments for chronic GVHD including extracorporeal photopheresis, rituximab, sirolimus, mycophenolate mofetil, imatinib, pentostatin and infusion of mesenchymal stem cells have been reported in several retrospective and relatively small phase I/II studies with a wide range of overall responses.

Summary—No current therapies used for chronic GVHD have been approved by the Food and Drug Administration. Large well-designed prospective studies are warranted to establish better treatments. Targeted therapies based on the pathogenesis of chronic GVHD may lead to better outcomes.

Keywords

chronic graft-versus-host disease; risk factor; pathogenesis; treatment

Introduction

Chronic graft-versus-host disease (GVHD) remains a major complication of allogeneic hematopoietic cell transplantation involving multiple sites and occurring in approximately 50% of transplant recipients [1]. Patients with chronic GVHD require prolonged immunosuppressive treatment for an average of 2 to 3 years from the initial diagnosis, with 10% of those surviving at least for 7 years still requiring immunosuppressive treatment at that time or beyond [2]. Glucocorticoids with or without calcineurin inhibitors (i.e., cyclosporine or tacrolimus) remain the standard initial treatment, but significant side effects and unsatisfactory outcomes, particularly for patients with high-risk features of chronic GVHD, support the need for more effective and less toxic therapies. This article summarizes recent reports on the risks, pathogenesis and treatment of chronic GVHD in the past 2 years. Reports of less than 8 patients were not included. Since recent publications include only relatively small prospective and retrospective studies, previously reported randomized or larger studies are also reviewed to put into perspective the therapeutic options commonly used today.

Risk factors and pathogenesis of chronic GVHD

Risk factors for acute GVHD and for chronic GVHD defined by the NIH consensus criteria [3] were compared in a recent large study [4]. Whereas overall risk profiles were similar for acute GVHD and for chronic GVHD, notable differences were a greater impact of female donor into a male recipient on chronic GVHD compared to acute GVHD and the strong associations of mobilized peripheral blood cells and of older patient age with increased risks for chronic GVHD but not for acute GVHD. Risk factors associated with chronic GVHD were not changed after adjustment for prior acute GVHD (Figure 1), supporting the conclusion that chronic GVHD was not simply an end stage of acute GVHD [4].

The pathogenesis of chronic GVHD remains elusive, but recent murine and human studies have provided some insights. First, alloreactive T cells are known to be important in the initiation of chronic GVHD. Thus the traditional treatment of chronic GVHD has been immunosuppressive agents that target T cells. This strategy is supported by the decreased incidence of chronic GVHD reported with anti-T-cells globulin given as prophylaxis before transplantation [5,6]. Second, evidence for B cell involvement in the immunopathophysiology of chronic GVHD has been reported as summarized in several review articles [7–10]. Autoantibodies have been detected in some patients with chronic GVHD, but direct evidence for the causal relationship of these antibodies in GVHD pathogenesis has not yet been demonstrated, except for the stimulatory anti-platelet derived growth factor alpha receptor (PDGFR) antibodies reported in patients with chronic GVHD [7]. The potential involvement of stimulatory anti-PDGFR antibodies, at least in the sclerotic chronic GVHD phenotype, is based on reported activities of these antibodies in the induction of PDGFR phosphorylation, reactive oxygen species generation, and increased α -actin and collagen expression, leading to fibrosis. Such observations have prompted recent interest in imatinib, a tyrosine kinase inhibitor of PDGFR, c-KIT, BCR-ABL, DDR1, and DDR2, to treat patients with chronic GVHD [11–13].

In addition to antibody production, B cells possess important antibody-independent mechanisms such as antigen presentation, cytokine production, and immune regulation, which are thought to be involved in chronic GVHD [7,8]. Taken all together, targeting B cells with agents such as rituximab, other monoclonal anti-CD20 antibodies (ocrelizumab, GA101, and ofatumumab), anti-CD22 antibody (epratuzumab), and novel agents targeting at B cell-tropic factors (belimumab and anti-BR3 antibody) are of great interest for chronic GVHD and under active investigation in other more common autoimmune diseases [7].

Finally, new insights about regulatory T cells have generated enthusiasm for testing therapies thought to promote expansion of regulatory T cells such as extra corporeal photopheresis [14] and mammalian target of rapamycin inhibitors [15] instead of calcineurin inhibitors to induce tolerance. This approach is currently being studied in a large randomized clinical trial through the Bone Marrow Transplant Clinical Trials Group (BMT CTN 0801).

Indications for systemic treatment of chronic GVHD

Systemic therapy is generally considered for patients who meet criteria for moderate-to-severe global severity according to the NIH consensus criteria [3,16–18] (involvement of 3 or more organs, or with an organ score of 2 or greater in any single organ, or any lung involvement), or for those with less severe disease but with high-risk features (Table 1). Topical therapies may also be used as an adjunct to improve and hasten local response for patients requiring systemic therapy [3,19]. Symptomatic mild chronic GVHD is often treated with topical therapies alone. A comprehensive review of topical therapies has recently been summarized [19].

Initial treatment

No large prospective studies for initial treatment of chronic GVHD have been published in the 2 years period of this review. Prior randomized studies for treatment of newly diagnosed chronic GVHD have not demonstrated benefits of additional agents to glucocorticoids [20–24], except for lower rates of avascular necrosis when calcineurin inhibitor (CNI) was added to prednisone. The standard initial systemic treatment of chronic GVHD is administration of glucocorticoids (1 mg/kg/day) followed by taper to eventually reach an alternate-day regimen, with or without calcineurin inhibitor. Despite little evidence that initial combination therapy of CNI (i.e., cyclosporine, tacrolimus) with prednisone improves outcomes [23], the combination therapy is often considered in hopes to minimize toxicity from prolonged use of steroid [18,19]. Considering the poor outcomes with standard treatment, particularly in patients with high-risk features, and the significant toxicities of prolonged treatment with steroids, clinical trials should be considered as the first option for initial systemic treatment of chronic GVHD for eligible patients.

Secondary treatment

Secondary treatment is generally considered when chronic GVHD shows evidence of progression, when chronic GVHD shows no improvement despite treatment with the originally prescribed medications, when prednisone can not be tapered below 1.0 mg/kg/day within 3 months, when new clinical manifestations develop, or when symptoms worsen during a further taper of prednisone below 0.5 mg/kg/day [18]. There is no current standard of secondary treatment, and “trial-and-error” remains the major way to identify an effective treatment for each individual patient [25]. Table 2 summarizes secondary treatments for chronic GVHD. Below are the treatments reported in this review period.

Extracorporeal photopheresis (ECP)

Many retrospective and several prospective studies of ECP treatment have been reported. Flowers et al. [26] reported the results of a phase II randomized study in 95 patients with refractory chronic GVHD. In ECP arm, ECP was continued for 12 to 24 weeks in combination with immunosuppressive treatment. The median percentage improvement in total skin score showed no statistical difference between the arms, but a higher rate of skin response and a more evident reduction in steroid dose were observed in ECP arm. Perotti et al. [27] reported the results of a phase II study in 23 pediatric patients with steroid-refractory chronic GVHD. The overall response rate was 70%, and 78% of the patients were alive at their last follow-up. No transfusion was required before or after a median of 34 ECP sessions (range, 16 – 43), and no hypotensive or metabolic complications were recorded even among low-body-weight patients. In recent retrospective studies, Jagasia et al. and Lucid et al. reported similar overall response rates of 65% and 67%, respectively [28,29].

Rituximab

Cutler et al. [30] originally reported the results of a phase I/II study of weekly rituximab 375 mg/m² for 4 weeks in 21 patients. The clinical response rate was 70%, and patients with cutaneous or musculoskeletal manifestations had the highest probability of response. Antibody titers against H-Y antigens decreased during the treatment period, while titers against EBV and tetanus remained stable. Kim et al. [31] recently reported the results of a phase II study of weekly rituximab 375 mg/m² for 4 weeks followed by monthly rituximab for 4 months in 37 patients. The overall response rate was 86%, and the complete response rate was 22%. The response rates were higher in skin, mouth and musculoskeletal system than in other organs. Twenty-one patients (57%) maintained their response, and 6 patients (16%) had steroid treatment successfully withdrawn. The results were encouraging, but

infection and recurrent malignancy accounted for most of treatment failures. In another recent small study [32], the overall response rate was 43%, and no patients had a complete response. Severe manifestations involving the skin, fascia and eye did not respond to treatment, suggesting that efficacy for advanced chronic GVHD was limited. A recent meta-analysis of 111 patients reported that the pooled overall response rate was 66% [33].

Imatinib

Some case studies reported that imatinib improved symptoms in patients with sclerodermatous GVHD or bronchiolitis obliterans after allogeneic HCT as reviewed in a recent summary [25]. Olivieri et al. [11] performed a phase I/II study of imatinib for refractory chronic GVHD with fibrotic features, since their group found autoantibodies activating the PDGFR pathway in such patients. Imatinib was initiated at 100 mg/day and increased to 200 mg/day if tolerable. Response was observed in 15 of 19 patients (79%) at 6 months, and overall survival rate was 84% at 18 months. Imatinib was discontinued in 3 patients because of toxicity. This result was encouraging, but Stadler et al. [12] reported limited efficacy of similar treatment in 9 patients with a more advanced stage of lung disease and old age. In one retrospective study of 14 patients with refractory sclerotic chronic GVHD [13], the overall response rate was 50% and Rodnan scores were improved in some patients. Imatinib seems tolerable for patients with chronic GVHD, but further prospective studies are warranted to confirm its efficacy.

Pentostatin

Jacobsohn et al. [34] reported the results of a phase II study of intravenous pentostatin 4 mg/m² every 2 weeks for 6 to 12 months in 51 pediatric patients. The overall response rate was 53%, with a complete response rate of 14%. Thirteen patients (25%) discontinued pentostatin because of toxicities, including infection, leukoencephalopathy, autoimmune hemolytic anemia, and others. Responders showed a trend for a better survival rate than nonresponders. Pidala et al. [35] reported the results of a retrospective study of pentostatin for 18 patients with refractory chronic GVHD. The response rate and 1-year overall survival rate were 56% and 34%, respectively.

Mesenchymal stem cells (MSCs)

MSCs have been originally used for refractory acute GVHD [36], and some recent studies report their use for chronic GVHD. Weng et al. [37] reported the results of 19 patients treated with intravenous MSCs. The median dose of MSCs was 0.6×10^6 cells/kg, and infusions were given one to five times. The overall response rate was 74%, and the survival rate was 78% at 2 years. Perez Simon et al. [38] reported the results of 8 patients treated with intravenous MSCs. MSCs were infused at a dose of $1-2 \times 10^6$ cells/kg one to four times. One patient had a complete response, 3 had partial responses and five patients were alive at their last follow-up. These results seem encouraging, and randomized studies are warranted to prove its efficacy.

Mycofenolate mofetil (MMF)

Furlong et al. [39] and Onishi et al. [40] reported the results of retrospective studies of MMF for refractory acute and chronic GVHD. Symptoms of chronic GVHD resolved in more than half of the patients, and 26% of the patients were able to discontinue all immunosuppressive therapy at 3 years after MMF therapy. Both studies, however, reported a high incidence of toxicities (22% and 54%, respectively) such as infection and gastrointestinal discomfort.

Mammalian target of rapamycin inhibitors (mTOR-I)

The efficacy of sirolimus has been reported in several previous studies [25,41]. Unlike calcineurin inhibitors, sirolimus promotes the generation of regulatory T cells. Jedlickova et al. [42] reported the results of a retrospective study in 34 patients with severe sclerodermatous GVHD treated with sirolimus or everolimus. The overall response rate was 76%, and steroid could be tapered and stopped in a significant number of patients. Survival was 72% at 3 years. No difference in response was observed between sirolimus and everolimus. Common toxicities included infections, shortened prothrombin time, hyperlipidemia and impaired wound healing. Close monitoring of trough levels, blood counts and serum chemistry was necessary to prevent toxicities.

Limitations and lessons about reported secondary GVHD treatments

Current literature regarding secondary GVHD is not of high quality. Most studies rely on the unfounded assumption that any improvement after the study intervention must have been caused by the study intervention. Major deficiencies in virtually all studies are the lack of a suitable comparison group that can serve as a valid historical benchmark, the absence of a formal statistical hypothesis, and the absence of consistent treatment due to variation in the selection of patients. In addition, most studies also use response at any time as the endpoint, as opposed to response at a fixed time point after enrollment. To address to lack of uniformity in evaluating and reporting responses in chronic GVHD, the NIH consensus conference developed new criteria for responses in clinical trials [43]. Jacobsohn et al. [44] recently reported an 80% agreement between the NIH and the Hopkins skin scales, although the NIH scale appeared less sensitive to detect early response in patients with sclerotic cutaneous manifestations. Validation studies are in progress worldwide to determine the clinical significance of the NIH responses criteria. One problem in determining efficacy of a therapy in chronic GVHD is that early responses may not translate in durable or major late outcomes. Martin et al. [45] compared short-term response and long-term outcomes after initial treatment of chronic GVHD with MMF, and demonstrated that early response did not necessarily predict subsequent tolerance without recurrent malignancy.

Conclusion

No current therapies used for chronic GVHD have been approved by the Food and Drug Administration in the United States. Thus clinical trials represent the first option to consider for eligible patients. New insights regarding the pathogenesis of chronic GVHD have started to emerge, and novel strategies such as therapies that target at B cells, expand T regulatory cells and target the processes implicated in fibrosis are under active investigations and could lead to future advances in treatment of chronic GVHD. Well-designed prospective studies are warranted to establish better treatments for patients with chronic GVHD.

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Key points

- Glucocorticoids (1 mg/kg/day followed by taper to eventually reach an alternate-day regimen) remain the standard initial treatment of chronic GVHD, but the outcomes are not satisfactory, particularly for patients with high-risk features.
- Several therapies have been reported for secondary treatment for chronic GVHD, but most studies in the current literature are not rigorous.
- Emerging insights in the pathogenesis of chronic GVHD have resulted in novel target therapies that might lead to better outcomes.
- Large and well-designed prospective clinical trials are needed to establish better treatments for chronic GVHD.

Figure 1.
 Risk factors for NIH chronic GVHD before and after adjustment for prior acute GVHD [4]

Table 1

Indication for systemic treatment according to severity and high-risk features of chronic GVHD

NIH Global severity	Maximal severity in all organs	Number of organs	High-risk feature ^a	Systemic treatment
Mild	1 (0 for lung)	≤ 2	Absent	No
			Present	Yes ^b
Moderate	1 (0 for lung)	≥ 3	Present or absent	Yes ^b
	2 (1 for lung)	Any		
Severe	3 (2 for lung)	Any	Present or absent	Yes

^aThrombocytopenia $<100 \times 10^3/\mu\text{L}$, progressive onset, or total serum bilirubin $>2 \text{ mg/dL}$ at onset.

^bThe benefits of graft-versus-tumor effect and the risk of chronic GVHD require careful consideration particularly for patients with high risk of recurrent malignancy.

Table 2

Secondary treatment for chronic GVHD

Treatment	Study type	No. of patients	% Overall Response	Overall Survival	Reference
<i>Therapies reported during the two years review period</i>					
Extracorporeal photopheresis (ECP)	Phase II	23	70	78%	[27]
	Retrospective	43	65	70%/1-yr	[28]
	Retrospective	9	67		[29]
Rituximab	Phase II	37	86	72%/1-yr	[31]
	Meta-analysis	111	66		[33]
Imatinib	Phase I/II	19	79	84%/1.5-yr	[11]
	Phase I/II	9	22	78%/1.5-yr	[12]
	Retrospective	14	50	75%/1.5-yr	[13]
Pentostatin	Phase II	51	53	60%/3-yr	[34]
	Retrospective	18	56	34%/1-yr	[35]
Mesenchymal stem cells infusions (MSC)	Phase I/II	19	74	78%/2-yr	[37]
	Phase I/II	8	50		[38]
Mycophenolate mofetil	Retrospective	23	26 ^a	96%/1-yr	[39]
	Retrospective	11	64	67%/1-yr	[40]
mTOR inhibitor	Retrospective	34	76	72%/3-yr	[42]
<i>Other therapies summarized in recent reviews</i>					
Calcineurin inhibitor					20 – 82% overall response rates reported
High-dose methylprednisolone					
Methotrexate					
Thalidomide					
Hydroxychloroquine					
Clofazimine					
Thoracoabdominal irradiation					
Alefacept					
Infliximab					

mTOR, mammalian target of rapamycin.

^dResponse was defined as discontinuation of all immunosuppressive treatment by 3 years.