LEADING ARTICLE

Drugs 2002; 62 (6): 879-889
0012-6667/02/0006-0879/$30.00/0

Novel Pharmacotherapeutic Approaches to Prevention and Treatment of GVHD

David A. Jacobsohn[1] and *Georgia B. Vogelsang*[2]

1 Oncology and Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
2 Hematologic Malignancies, Department of Oncology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Acute and chronic graft versus host disease (GVHD) remain the major barriers to successful hematopoietic cell transplantation. The induction of GVHD may be divided into three phases: (i) recipient conditioning; (ii) donor T-cell activation; and (iii) effector cells mediating GVHD. This review examines GVHD prevention and treatment using this conceptual model as framework.

The various pharmacological agents discussed impact on different phases of the GVHD cascade. For example, keratinocyte growth factor and interleukin (IL)-11 are cytokines that may be useful in disrupting phase I of the GVHD cascade by blocking gastrointestinal tract damage, and lowering serum levels of lipopolysaccharide and tumour necrosis factor (TNF)-α. Cyclosporin, tacrolimus (FK-506) and sirolimus (rapamycin) are some of the main agents that disrupt phase II (donor T-cell activation). Mycophenolate mofetil and tresperimus probably act on this phase as well. Other novel drugs that affect phase II are tolerance-induction agents such as CTLA-4 and anti-CD40–ligand monoclonal antibodies, and preliminary results using CTLA-4 monoclonal antibody in GVHD prevention are encouraging. Examples of agents that disrupt phase III are the IL-2 receptor antagonist daclizumab and the anti-TNFα monoclonal antibody infliximab. These anti-cytokine antibodies have shown promising results in early studies.

The most effective approach to GVHD prevention will probably be a combination regimen where the three phases of the GVHD cascade are disrupted. Once GVHD has occurred, all three phases of the cascade are activated. Developments of combination therapy for treatment of both acute and chronic GVHD are likely to yield better results than monotherapy. The numerous new treatment modalities presented should improve the outlook for patients with acute and chronic GVHD.

This review aims at familiarising the reader with novel approaches to the prevention and treatment of graft-versus-host disease (GVHD). After explaining the clinical symptoms associated with GVHD, a well-supported model of GVHD is discussed to set the stage. The agents and how they potentially disrupt the GVHD cascade are then discussed. Prophylaxis is discussed first, then treat-

ment. Rather than grouping drugs by mechanism of action, the review is deliberately structured to provide information that would be immediately usable to the clinician.

1. Clinical Symptoms and Pathophysiology

Acute and chronic GVHD remain the major barriers to successful hematopoietic stem cell transplantation (SCT). Skin rash (which may progress to dermal-epidermal separation), hepatic dysfunction and abdominal cramping with diarrhoea characterise acute GVHD. Biopsies of affected organs show lymphocyte infiltration. Most centres now use the Keystone criteria (table I) for grading GVHD, although some may make minor modifications. The majority of patients with grade III to IV acute GVHD die of their disease.

Chronic GVHD usually begins at least 100 days after SCT but rarely may start earlier or over a year after SCT. It can evolve from acute GVHD (progressive – associated with high mortality), follow resolution of acute GVHD (quiescent), or start in patients without history of acute GVHD (*de novo*). Chronic GVHD mimics certain rheumatologic diseases such as systemic lupus erythematosus and Sjogren's syndrome. Most commonly, patients have skin involvement in the form of an erythematous lichenoid papular rash that may progress to thickened, sclerodermatous skin. Patients may develop fasciitis and contractures. Dryness and mucosal ulceration of the eyes and mouth are common. The respiratory tract, gastrointestinal (GI) tract and liver can also be affected.[2] Patients receiving peripheral blood stem cell transplants (PBSC) have a higher incidence of chronic GVHD than those receiving standard bone marrow transplant.[3]

The pathophysiology of acute GVHD may be divided into three phases (figure 1). This model allows us to understand which pathways can be blocked to prevent or treat GVHD. In the first phase, the conditioning regimen causes damage to the intestinal mucosa and liver that leads to activation of host cells and release of inflammatory cytokines such as tumour necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-1.[4] These cytokines upregulate major histocompatibility complex (MHC) antigens, thus enhancing their recognition by donor T cells.[5-9] In the second phase, donor T cells become activated and proliferate in response to host antigens, fueled by the inflammatory cytokines. Activation of T cells requires two signals: the first from the T-cell receptor-peptide–MHC interaction [10,11] and the second (costimulatory) from contact with antigen-presenting cells. The binding of B7 on the antigen-presenting cell to CD28 or CTLA-4 on the T cell usually carries out this signal. Another costimulatory signal is

Table I. Clinical staging and grading of acute graft-versus-host disease[1]

Stage or equivalent grade	Skin	Liver	GI tract
Stage			
1	Rash on <25% of skin	Bilirubin 2-3 mg/dl	Diarrhoea >500 ml/day or persistent nausea with positive biopsy
2	Rash on 25-50% of skin	Bilirubin 3-6 mg/dl	Diarrhoea >1000 ml/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dl	Diarrhoea >1500 ml/day
4	Generalised erythroderma with bulla formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus
Grade			
1	Stage 1-2	None	None
2	Stage 3 or	Stage 1 or	Stage 1
3		Stage 2-3 or	Stage 2-4
4	Stage 4 or	Stage 4	

GI = gastrointestinal.

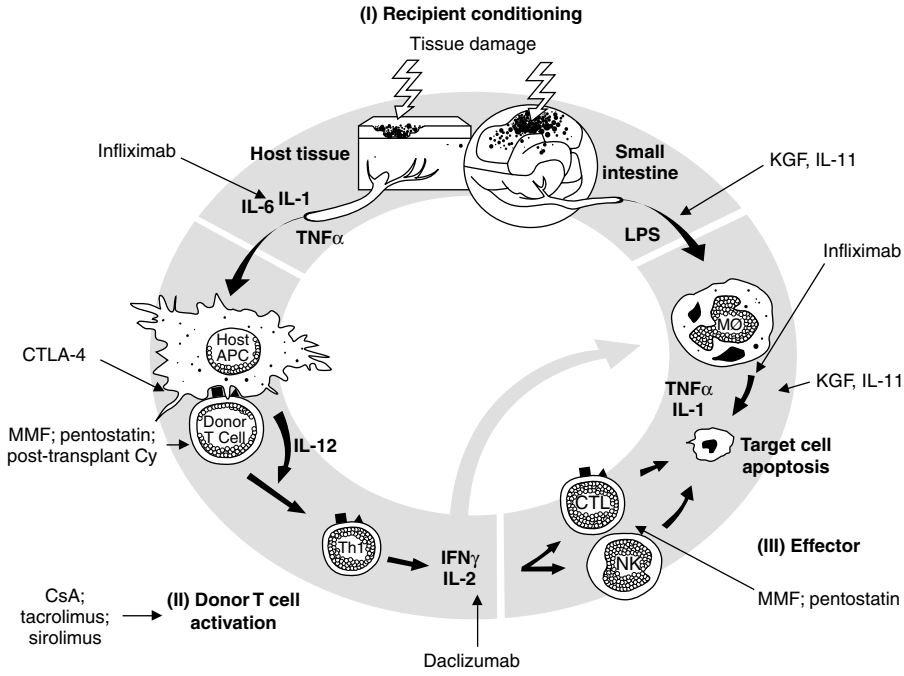

Fig. 1. Acute graft versus host disease (GVHD) pathophysiology and pharmacotherapeutic intervention. The three sequential phases of GVHD (I, II, III) are detailed. Agents discussed are shown in relation to the phases of GVHD they disrupt (Adapted from Hill and Ferrara,[13] © American Society of Hematology, with permission). **APC** = antigen-presenting cells; **CsA** = cyclosporin; **CTL** = cytotoxic T cells; **CTLA-4** = CTLA-4 monoclonal antibody; **Cy** = cyclophosphamide; **IL** = interleukin; **IFN** = interferon; **KGF** = keratinocyte growth factor; **LPS** = lipopolysaccharide; **MØ** = monocyte; **MMF** = mycophenolate mofetil; **NK** = natural killer cell; **Th1** = T helper-1 cell; **TNF** = tumour necrosis factor.

the binding of CD40 to its ligand. Signalling through the T-cell receptor in the absence of a second signal leads to tolerance, whereas absence of CTLA-4 leads to uncontrolled activation and cytokine production.[12] Blockade of the costimulatory signal would clearly be a potential way of preventing GVHD.

In the third phase, monocytes that have been primed by lipopolysaccharide (LPS) [secreted by damaged intestinal mucosa], IL-2 and IFNγ (from activated T cells), secrete IL-1 and TNFα. TNFα causes direct tissue damage and causes apoptosis via the TNFα–Fas pathway. IL-1 also leads to target cell apoptosis. In addition, cytotoxic T cells and natural killer (NK) cells, also activated by IFNγ and IL-2, lead to cellular damage.[12] IFNγ and IL-2 can also cause direct injury of skin and intestines.[14-16]

2. Graft versus Host Disease (GVHD) Prophylaxis

The intent of this review is to provide a description of new therapies in the context of the GVHD cascade to better comprehend where each agent may fit in within the scope of treatment. A key point is that for successful prophylaxis, it is likely that disruption of more than one phase of the GVHD cascade will be required. Figure 1 explains how each agent disrupts the GVHD cascade. It should be noted that certain drugs may affect more than one phase of the GVHD cascade. Table II

shows a summary of key GVHD prophylaxis studies.

2.1 Disruption of Phase I of the GVHD Cascade (Recipient Conditioning)

In animal models, IL-11 and keratinocyte growth factor (KGF) act as 'cytokine shields' and, when administered during the conditioning regimen, completely abolish GI tract GVHD. The agents decrease serum levels of LPS and TNFα. They appear to block GI tract damage in phase I, preventing amplification of the cascade. However, they preserve cytotoxic T cell and NK cell responses, maintaining the graft-versus-leukaemia effect. As shown in figure 1, these agents also block the activity of TNFα and IL-1 and therefore decrease target cell apoptosis in phase III.[13] Both of these agents are currently in clinical trials.

2.2 Disruption of Phase II of the GVHD Cascade (Donor T Cell Activation)

Before the introduction of cyclosporin, the first drug developed for purely immunomodulatory effects, lympholytic drugs such as methotrexate, antithymocyte globulin, cyclophosphamide and corticosteroids were used. Cyclosporin has complex effects on the immune system but basically acts by inhibiting IL-2 production.[23] Therefore, cyclosporin acts mainly on phase II of the GVHD cascade, preventing activation of T cells. This leads to disruption of phase III – decreasing activated cytotoxic T cells, NK cells and monocytes; therefore reducing target cell apoptosis. Short-course methotrexate (15mg/m^2 on day 1; 10mg/m^2 on days 3, 6, and 11) plus cyclosporin for 6 months has become the gold standard against which other GVHD prophylaxis is measured. [24] Controversy exists as to whether the addition of corticosteroids to the regimen decreases the incidence of acute GVHD.[25,26] However, the addition of methylprednisolone increases the risk of bacterial and fungal infections within the first 2 months after SCT.[27]

At some centres tacrolimus (FK-506) has replaced cyclosporin on the basis of two phase III trials that showed a slight decrease in grade II to IV acute GVHD with tacrolimus plus methotrexate compared with cyclosporin plus methotrexate. Overall disease-free survival is not different. Toxicities are similar except for nephrotoxicity, which is slightly higher in the tacrolimus group.[17,18] The mechanism of action of tacrolimus is similar to that of cyclosporin but it is a more potent calcineurin inhibitor,[28] allowing lower doses to be used.

Mycophenolate mofetil blocks synthesis of RNA and DNA by inhibition of inosine monophosphate dehydrogenase. Lymphocytes do not have a salvage pathway and die in the presence of mycophenolate mofetil.[29] The use of mycophenolate mofetil is appealing since it disrupts phases II and III, where lymphocytes play a key role. It is successful at preventing renal transplant rejection.[30]

Table II. Summary of clinical trials for prophylaxis of acute graft versus host disease (aGVHD)

Drugs	Setting	Incidence aGVHD	Reference
Tacrolimus plus methotrexate	HLA-identical donor marrow (unmodified); myeloablative	32% grade II-IV aGVHD	17
Tacrolimus plus methotrexate	Matched-unrelated donor marrow (unmodified); myeloablative	56% grade II-IV aGVHD	18
MMF/CsA	HLA-identical PBSC; nonmyeloablative	25% grade II-IV aGVHD	19
CTLA-4 antibody–cultured donor marrow; cyclosporin plus methotrexate prophylaxis	Mismatched marrow from parents/siblings; myeloablative	27% grade II-IV aGVHD; (only GI, no skin or liver)	20
Campath antibodies (*in vitro* treatment of marrow and *in vivo* during conditioning)	HLA-identical donor marrow; myeloablative	4% grade II-IV aGVHD	21
Daclizumab with cyclosporin plus methotrexate	Matched-unrelated donors; myeloablative	75% grade II-IV aGVHD (no difference from placebo)	22

CsA = cyclosporin**; GI** = gastrointestinal; **HLA** = human leucocyte antigen; **MMF** = mycophenolate mofetil; **PBSC** = peripheral blood stem cell.

In SCT, it has mainly been used for GVHD prophylaxis after nonmyeloablative transplants. Bornhauser and colleagues[19] reported 24 patients with malignancies who received busulfan, fludarabine and 200 cGy total body irradiation followed by human leucocyte antigen (HLA)-identical PBSC. GVHD prophylaxis was cyclosporin plus mycophenolate mofetil (1000mg orally twice daily on days 1 to 40). Only 25% of patients developed grade II to IV acute GVHD but it is too early to determine the long-term incidence of chronic GVHD.

Another promising agent is tresperimus (15-deoxyspergualin). One of the mechanisms of action of tresperimus is binding to HSP70 in T cells to inhibit nuclear factor kappa B (NF-κB) and thus prevent IL-2 activation.[31] This agent selectively induces anergy post-transplant and has been used to treat GVHD in animal models. A multicentre clinical trial using tresperimus as prophylaxis for GVHD in patients undergoing transplants for high-risk malignancies is ongoing.

Other interesting agents are those that induce tolerance by blocking the costimulatory signal (signal 2), namely CTLA-4 and anti-CD40–ligand monoclonal antibodies. These agents preserve T cell response to other antigens, thus minimising global immunosuppression. CTLA-4 monoclonal antibody binds to B7 molecules with high affinity and blocks signal 2 by preventing the binding of B7 on the antigen presenting cell to CD28 on the T cell.[32] These agents have significant appeal as they could potentially obliterate phase II of the cascade, therefore diminishing resultant target cell apoptosis. Guinan and colleagues[20] transplanted 12 patients with mismatched marrow, from parents or siblings, which was cultured with irradiated recipient cells and CTLA-4 monoclonal antibody before infusion. The preparative regimen consisted of total body irradiation, cyclosporin and methylprednisolone ± cytarabine; and GVHD prophylaxis was cyclosporin plus methotrexate. No patient died of GVHD, and of 11 evaluable patients, none had skin or liver GVHD and three had GI tract GVHD. Larger studies will follow given the encouraging initial results. Tolerance-induction drugs are likely to be more effective without cyclosporin or tacrolimus, since these agents prevent tolerance by blocking signal 1.[33]

Sirolimus (rapamycin) may play an important role in GVHD prophylaxis. In contrast to cyclosporin or tacrolimus, this agent inhibits mTOR, which is essential for T-cell proliferation, and thus leads to cell cycle arrest.[34] In animal models, sirolimus is synergistic with co-stimulatory blockade in producing allograft tolerance.[35] Thus, we will probably see this agent used with tolerance-induction regimens. Clinical trials are under way but no results have been reported in marrow transplants.

Finally, animal data from Johns Hopkins, Baltimore, Maryland, USA, indicate that in non-myeloablative transplants following fludarabine and total body irradiation, post-transplant cyclophosphamide (48 to 72 hours after transplant) inhibits acute GVHD mediated by T cells reactive to host MHC and minor H antigens.[36] The ability of cyclophosphamide to prevent GVHD without causing global immunosuppression is consistent with the selective toxicity of the drug to T cells recently activated by antigen recognition.[37] A clinical trial is currently underway examining the effect of different dosages of post-transplant cyclophosphamide.

Depletion of T cells is an effective way of preventing GVHD but leads to higher relapse rates. The multiple non-pharmacological modalities of depleting T cells[38,39] are beyond the scope of this paper. Campath-1M is a rat immunoglobulin (Ig)M antibody that recognises the human lymphocyte antigen CD52. Although the use of Campath-1M is an effective way of purging T cells *in vitro* by cell lysis, it leads to higher relapse rates secondary to ablation of the graft-versus-leukaemia effect.[40,41]

However, using *in vivo* with *in vitro* Campath antibodies has shown promising results. In 70 patients receiving HLA-identical transplants for acute myeloid leukaemia, T-cell depletion was accomplished with Campath-1M and immunosup-

pression consisted of *in vivo* Campath-1G 20mg/day over 5 days during conditioning. Campath-1G is a rat IgG2b CD52 antibody effective in depleting residual host T cells.[42] The incidence of acute GVHD was 4% and chronic GVHD was 3%. The risk of relapse or 5-year leukaemia-free survival was equal to historical controls receiving cyclosporin plus methotrexate.[21] Campath-1G has also been used in nonmyeloablative transplants with good results.[43] Although longer follow-up is needed to assess remission status and chronic GVHD incidence, the use of Campath antibodies in preparative regimens will be seen in future studies given positive initial results.

2.3 Disruption of Phase III of the GVHD Cascade (Effector)

Daclizumab or humanised anti-TAC antibody, the IL-2 receptor antagonist, was studied in a double-blind, placebo-controlled, multicenter trial as add-on prophylaxis to cyclosporin and methotrexate. Daclizumab did not prevent acute GVHD nor improve survival compared with placebo.[22] Other agents that disrupt phase III (i.e. infliximab) have not been studied in the context of prophylaxis. If shown to have some benefit in treatment, these agents should be further studied in this context.

3. Treatment of Acute GVHD

3.1 Primary Treatment

Once GVHD occurs, all phases of GVHD induction are active. Successful treatment will ultimately need to work on all phases. Most centres treat grade II to IV acute GVHD by continuing immunosuppression and adding methylprednisolone at 2 or 2.5 mg/kg/day. However, starting dosages range from 1 to >20 mg/kg/day.[44] Corticosteroids are tapered after control of GVHD. A rapid steroid taper (86 days) is just as effective as a slow taper (147 days) in terms of preventing flares of GVHD or chronic GVHD.[45] A few studies have reported outcomes with high-dose methylprednisolone (20 to 50mg/kg/day). Patients that responded to these dosages generally had a flare-up after dose reduction, and there were a number of deaths secondary to opportunistic infections.[46,47]

To our knowledge, there is one randomised trial comparing high- and low-dose methylprednisolone for the treatment of acute GVHD.[48] Patients receiving 2mg/kg/day and 10mg/kg/day had the same rate of response (70%) and the same 3-year actuarial survival (62%). Higher morbidity was observed with the higher dose. Therefore, there is no compelling argument to start with a high dose of corticosteroids. Initial response to corticosteroids, either low-dose or high-dose, is very predictive of future severity of GVHD and other transplant complications.

Table III shows a summary of key GVHD treatment studies. Several different anti–IL-2 receptor antibodies have been investigated as primary treatment of acute GVHD. A study of 69 patients who received treatment in 13 centres for acute GVHD showed no benefit in survival or response when adding an anti–IL-2 receptor antibody (inolimomab; BT-563) to methylprednisolone and cyclosporin, despite successful trials of this antibody in salvage therapy.[49]

The study with daclizumab is more promising. Daclizumab is a humanised monoclonal IgG1 that incorporates the complementarity-determining regions of a murine monoclonal antibody raised against the human IL-2 receptor-α chain.[56,57] Forty-three patients received treatment at diagnosis of severe acute GVHD or after corticosteroid failure. The dose of daclizumab was 1mg/kg and was given on days 1, 8, 15, 22 and 29 (regimen 1) to 24 patients and on days 1, 4, 8, 15 and 22 (regimen 2) to 19 patients. All patients were treated concurrently with methylprednisolone 2mg/kg/day. If there was no improvement within the first week, antithymocyte globulin was added. At day 43, the response rate was 51%. Responses were better in skin than in GI tract or multiorgan GVHD. Regimen 2 yielded a higher complete response rate. Although the drug was well tolerated, three patients developed Epstein-Barr virus (EBV) lymphoproliferative disease.[50] Future trials need to study daclizumab in the absence of antithymocyte glob-

Table III. Summary of clinical trials in the treatment of acute graft versus host disease (aGVHD)

Drugs	Setting	Response	Reference
Daclizumab	Most HLA-non identical transplants; most steroid-refractory	51% response at day 43	50
CD5 immunotoxin plus methylprednisolone	HLA-identical & unrelated transplants; primary treatment	44% CR at 6 weeks (same as placebo)	51
Anti-CD2 monoclonal antibody (salvage treatment)	HLA-identical & unrelated transplants; all steroid-refractory	55% improvement in overall aGVHD grade	52
Recombinant human IL-1 receptor	HLA-identical & unrelated transplants; all steroid-refractory	57% improvement in overall aGVHD grade	53
Infliximab	HLA-identical & unrelated transplants; most steroid-refractory	74% overall (CR&PR)	54
Pentostatin	HLA-identical & unrelated transplants; all steroid-refractory	67% overall (CR&PR)	55

CR = complete response; **HLA** = human leucocyte antigen; **IL** = interleukin; **PR** = partial response.

ulin (since 40% of patients in this trial received antithymocyte globulin) to understand the independent contribution of this agent to acute GVHD therapy.

Two randomised studies of antithymocyte globulin for initial therapy of grade II to IV GVHD showed no difference in efficacy between antithymocyte globulin and prednisone,[58] nor between antithymocyte globulin plus prednisone and prednisone alone.[59] In fact, given the very high risk of infectious complications with antithymocyte globulin use, this drug has a minimal role in GVHD, particularly for primary treatment. Furthermore, results from a phase III trial comparing methylprednisolone plus placebo versus methylprednisolone plus a CD5-specific immunotoxin (xomazyme) yielded similar outcomes in both groups.[51]

3.2 Salvage Therapy

The response to salvage therapy after failure to initial therapy (i.e. progression after 3 days, no change after 7 days, or incomplete response after 14 days of corticosteroid therapy) is usually very poor. The most common agents used as salvage therapy are antithymocyte globulin, monoclonal antibodies and higher dosages of corticosteroids.[44,60] The review of the experience at Johns Hopkins' with antithymocyte globulin shows that of 69 patients who received antithymocyte globulin for steroid-refractory GVHD, 59% had improvement in skin, 15% in liver, and 32% in GI tract. However, the survival rate was very poor: median survival for grade II – 4.1 months, grade III – 3.6 months, and grade IV – 2.7 months. Ninety-five percent of deaths were attributed to infection.[61] Given these data, antithymocyte globulin should not be considered standard therapy for steroid-refractory GVHD.

In an attempt to give more selective immunosuppression, many investigators have explored the use of monoclonal antibodies. Use of an anti-CD2 monoclonal antibody gave a response rate of 55% in patients with steroid-resistant GVHD.[52] Results from a pilot study testing a recombinant human IL-1 receptor demonstrate a 57% response rate in patients with acute GVHD.[53] These results should be interpreted with caution as there were few patients enrolled and results from larger studies have not been reported.

A promising agent is infliximab, an anti-TNFα monoclonal antibody licensed for the treatment of Crohn's disease and rheumatoid arthritis. At the MD Anderson Cancer Center, Houston, Texas, USA, close to 75% of patients (n = 32) with acute GVHD demonstrated a response to intravenous infliximab 10mg/kg weekly for 4 weeks. A majority of these patients had steroid-refractory disease. The drug appears to work best for skin and GI tract GVHD and much less so for liver.[54] A multicentre, randomised trial is under way to evaluate the efficacy of this drug. When used for treat-

ment, infliximab probably impacts phase III mostly. Potentially, this drug could also be used prophylactically by decreasing MHC antigen presentation thus affecting donor T-cell activation (phase I/II).

Finally, pentostatin, a purine analogue that appears to be less myelosuppressive than fludarabine, is being explored at Johns Hopkins for the treatment of acute GVHD. Being a lympholytic agent, this drug is likely to affect both phase II and III of the GVHD cascade. Out of 15 patients with steroid-refractory acute GVHD, seven achieved a complete response and three patients achieved a partial response (overall response 67%). Responses are mostly in the skin and gut, and less so in the liver.[55] The goal of our study is to determine a rational dose administration schedule before advancing the drug in clinical trials. It is most likely that dose administration schedules different from chemotherapeutic regimens will be optimal.

4. Treatment of Chronic GVHD

4.1 Standard Therapy

Although there is no specific 'standard therapy', it seems that most centres start with prednisone and cyclosporin for the treatment of chronic GVHD. One regimen that appears to improve survival in patients with high-risk features such as thrombocytopenia and extensive skin involvement is alternate-day prednisone and cyclosporin.[62] At our institution, patients are evaluated every 3 months and therapy is continued for 3 months after maximal response. The 3-month time frame for evaluation of response to a given therapy is based on our own observation that 90% of patients who are ultimately going to respond to therapy will show signs of response at that point.[63]

4.2 Salvage Regimens

An agent initially shown by Vogelsang to have a role in chronic GVHD is thalidomide. The response of patients with high-risk chronic GVHD to thalidomide appears to be 20 to 30%.[64,65] Unfortunately, the adverse effects (particularly sedation and constipation) are intolerable to many patients and the drug has therefore fallen out of favour with other newer agents being preferred. Another agent sometimes used in patients with steroid-refractory chronic GVHD is azathioprine. However, given its myelosuppressive effects and high incidence of infections, it is best avoided.[66]

We are currently studying, in a phase II trial, the combination of mycophenolate mofetil and tacrolimus. A retrospective review of 26 patients with refractory chronic GVHD who received treatment with this steroid-sparing combination showed that it was well tolerated, and nearly half the patients showed an objective response.[67]

A study using pentostatin is also under way at Johns Hopkins. Patients are receiving 4mg/m^2 intravenously every 2 weeks for 6 months. Of 17 patients treated so far, there have been objective responses in 65%.[68] Particularly encouraging is that some heavily pre-treated patients with sclerodermatous skin and fascial changes showed dramatic responses. The goal after this study is to incorporate this agent as front-line treatment of chronic GVHD to avoid corticosteroids and their toxicities.

4.3 Additional Treatment Considerations

Etretinate and acitretin are synthetic retinoids used in dermatological conditions. In a case series of 32 patients, these drugs induced improvement in about 65% of patients with sclerodermatous chronic GVHD when added on to a chronic GVHD regimen.[69] The mechanism of action of the retinoids is not likely to involve modulation of the immune response to foreign antigen.

Clofazimine is an antimycobacterial drug with anti-inflammatory activity that, in a recent phase II trial, yielded an approximately 50% response rate in patients with skin involvement, flexion contractures or oral manifestations. The drug was added on, in most cases, to the immunosuppressive regimen of the patient.[70]

Hydroxychloroquine is an antimalarial agent that down-regulates MHC. It also appears to have a role in treating sclerodermatous chronic GVHD and does not lead to skin drying, flaking or ulceration (as seen with acitretin).[71] A phase III trial of

initial therapy of patients with chronic GVHD (cyclosporin plus prednisone with or without hydroxychloroquine) is starting through the Children's Oncology Group, Arcadia, California, USA.

Finally, certain nonpharmacologic approaches may be helpful in chronic GVHD. PUVA (psoralens; 8-methoxypsoralen plus ultraviolet A radiation) is particularly useful in patients with systemic lichenoid disease.[72,73] Extracorporeal photopheresis is also being explored for chronic GVHD. In one report of 15 patients, skin, liver and oral manifestations of steroid-refractory chronic GVHD improved.[74] The optimal schedule is not known. Nevertheless, it is important to remember that these approaches can be particularly useful when systemic immunosuppression should be minimised.

5. Conclusion

Acute and chronic GVHD remain difficult problems to treat. The most effective approach is likely to be a combination regimen where the three phases of the GVHD cascade are disrupted. For example, we could envision a prophylactic regimen consisting of a cytokine shield such as KGF to block GI tract damage and CTLA-4 monoclonal antibody with sirolimus to prevent T-cell activation by tolerance without global immunosuppression.

Once GVHD has occurred, all three phases of the cascade are activated. Developments of combination therapy for treatment of both acute and chronic GVHD are therefore likely to yield better results than monotherapy. Incorporating steroid-sparing agents, such as infliximab and pentostatin, would be ideal to avoid the long-term sequelae associated with corticosteroids. The numerous new treatment modalities discussed should improve the outlook for patients with acute and chronic GVHD.

Acknowledgements

Dr Jacobsohn receives funding through NIH/NCI Grant number 5K12CA01709. Drs Jacobsohn and Vogelsang are running the Pentostatin GVHD clinical trials (sponsored by SuperGen, Inc.) at Johns Hopkins, Baltimore, MD, USA.

References

1. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995; 15: 825-8
2. Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. Hematol Oncol Clin North Am 1999; 13: 1091-112
3. Cutler C, Giri S, Jeyapalan S, et al. Acute and chronic graft-versus-host disease after allogeneic peripheral- blood stem-cell and bone marrow transplantation: a meta-analysis. J Clin Oncol 2001; 19: 3685-91
4. Xun CQ, Thompson JS, Jennings CD, et al. Effect of total body irradiation, busulfan-cyclophosphamide, or cyclophosphamide conditioning on inflammatory cytokine release and development of acute and chronic graft-versus-host disease in H-2- incompatible transplanted SCID mice. Blood 1994; 83: 2360-7
5. Cavender DE, Haskard DO, Joseph B, et al. Interleukin-1 increases the binding of human B and T lymphocytes to endothelial cell monolayers. J Immunol 1986; 136: 203-7
6. Chang RJ, Lee SH. Effects of interferon-gamma and tumor necrosis factor-alpha on the expression of an Ia antigen on a murine macrophage cell line. J Immunol 1986; 137: 2853-6
7. Leeuwenberg JF, Van Damme J, Meager T, et al. Effects of tumor necrosis factor on the interferon-gamma-induced major histocompatibility complex class II antigen expression by human endothelial cells. Eur J Immunol 1988; 18: 1469-72
8. Pober JS, Gimbrone Jr MA, Lapierre LA, et al. Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. J Immunol 1986; 137: 1893-6
9. Thornhill MH, Wellicome SM, Mahiouz DL, et al. Tumor necrosis factor combines with IL-4 or IFN-gamma to selectively enhance endothelial cell adhesiveness for T cells. The contribution of vascular cell adhesion molecule-1-dependent and -independent binding mechanisms. J Immunol 1991; 146: 592-8
10. Sette A, Alexander J, Grey HM. Interaction of antigenic peptides with MHC and TCR molecules. Clin Immunol Immunopathol 1995; 76: S168-71
11. Sakihama T, Smolyar A, Reinherz EL. Molecular recognition of antigen involves lattice formation between CD4, MHC class II and TCR molecules. Immunol Today 1995; 16: 581-7
12. Ferrara JL, Levy R, Chao NJ. Pathophysiologic mechanisms of acute graft-vs.-host disease. Biol Blood Marrow Transplant 1999; 5: 347-56
13. Hill GR, Ferrara JL. The primacy of the gastrointestinal tract as a target organ of acute graft-versus-host disease: rationale for the use of cytokine shields in allogeneic bone marrow transplantation. Blood 2000; 95: 2754-9
14. Nestel FP, Price KS, Seemayer TA, et al. Macrophage priming and lipopolysaccharide-triggered release of tumor necrosis factor alpha during graft-versus-host disease. J Exp Med 1992; 175: 405-13
15. Mowat AM. Antibodies to IFN-gamma prevent immunologically mediated intestinal damage in murine graft-versus-host reaction. Immunology 1989; 68: 18-23
16. Dickinson AM, Sviland L, Dunn J, et al. Demonstration of direct involvement of cytokines in graft-versus-host reactions using an in vitro human skin explant model. Bone Marrow Transplant 1991; 7: 209-16
17. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-

host disease prophylaxis after HLA-identical sibling bone marrow transplantation. Blood 1998; 92: 2303-14
18. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood 2000; 96: 2062-8
19. Bornhauser M, Thiede C, Schuler U, et al. Dose-reduced conditioning for allogeneic blood stem cell transplantation: durable engraftment without antithymocyte globulin. Bone Marrow Transplant 2000; 26: 119-25
20. Guinan EC, Boussiotis VA, Neuberg D, et al. Transplantation of anergic histoincompatible bone marrow allografts. N Engl J Med 1999; 340: 1704-14
21. Hale G, Zhang MJ, Bunjes D, et al. Improving the outcome of bone marrow transplantation by using CD52 monoclonal antibodies to prevent graft-versus-host disease and graft rejection. Blood 1998; 92: 4581-90
22. Anasetti C, Lin A, Nademanee A, et al. A phase II/III randomized, double-blind, placebo-controlled multicenter trial of humanized anti-TAC for prevention of acute graft-versus-host disease (GVHD) in recepients of marrow transplantation from unrelated donors [abstract]. Blood 1995; 86: 621a
23. Simpson D. Drug therapy for acute graft-versus-host disease prophylaxis. J Hematother Stem Cell Res 2000; 9: 317-25
24. Storb R, Deeg HJ, Pepe M, et al. Methotrexate and cyclosporine versus cyclosporine alone for prophylaxis of graft-versus-host disease in patients given HLA-identical marrow grafts for leukemia: long-term follow-up of a controlled trial. Blood 1989; 73: 1729-34
25. Chao NJ, Schmidt GM, Niland JC, et al. Cyclosporine, methotrexate, and prednisone compared with cyclosporine and prednisone for prophylaxis of acute graft-versus-host disease. N Engl J Med 1993; 329: 1225-30
26. Deeg HJ, Lin D, Leisenring W, et al. Cyclosporine or cyclosporine plus methylprednisolone for prophylaxis of graft-versus-host disease: a prospective, randomized trial. Blood 1997; 89: 3880-7
27. Sayer HG, Longton G, Bowden R, et al. Increased risk of infection in marrow transplant patients receiving methylprednisolone for graft-versus-host disease prevention. Blood 1994; 84: 1328-32
28. Sigal NH, Dumont FJ. Cyclosporin A, FK-506, and rapamycin: pharmacologic probes of lymphocyte signal transduction. Annu Rev Immunol 1992; 10: 519-60
29. Lipsky JJ. Mycophenolate mofetil. Lancet 1996; 348: 1357-9
30. Mycophenolate mofetil in cadaveric renal transplantation. US Renal Transplant Mycophenolate Mofetil Study Group. Am J Kidney Dis 1999; 34: 296-303
31. Nadler SG, Dischino DD, Malacko AR, et al. Identification of a binding site on Hsc70 for the immunosuppressant 15-deoxyspergualin. Biochem Biophys Res Commun 1998; 253: 176-80
32. Linsley PS, Brady W, Urnes M, et al. CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med 1991; 174: 561-9
33. Kirk AD, Burkly LC, Batty DS, et al. Treatment with humanized monoclonal antibody against CD154 prevents acute renal allograft rejection in nonhuman primates. Nat Med 1999; 5: 686-93
34. Sehgal SN. Rapamune (Sirolimus, rapamycin): an overview and mechanism of action. Ther Drug Monit 1995; 17: 660-5
35. Li Y, Li XC, Zheng XX, et al. Blocking both signal 1 and signal 2 of T-cell activation prevents apoptosis of alloreactive T cells and induction of peripheral allograft tolerance. Nat Med 1999; 5: 1298-302
36. Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after non-myeloablative conditioning with fludarabine, low-dose total body irradiation, and post-transplant cyclophosphamide. Blood 2001; 98: 3456-64
37. Eto M, Mayumi H, Tomita Y, et al. Intrathymic clonal deletion of V beta 6+ T cells in cyclophosphamide- induced tolerance to H-2-compatible, Mls-disparate antigens. J Exp Med 1990; 171: 97-113
38. Filipovich AH, Vallera DA, Youle RJ, et al. Graft-versus-host disease prevention in allogeneic bone marrow transplantation from histocompatible siblings. A pilot study using immunotoxins for T cell depletion of donor bone marrow. Transplantation 1987; 44: 62-9
39. Noga SJ, Donnenberg AD, Schwartz CL, et al. Development of a simplified counterflow centrifugation elutriation procedure for depletion of lymphocytes from human bone marrow. Transplantation 1986; 41: 220-9
40. Apperley JF, Mauro FR, Goldman JM, et al. Bone marrow transplantation for chronic myeloid leukaemia in first chronic phase: importance of a graft-versus-leukaemia effect. Br J Haematol 1988; 69: 239-45
41. Hale G, Cobbold S, Waldmann H. T cell depletion with CAMPATH-1 in allogeneic bone marrow transplantation. Transplantation 1988; 45: 753-9
42. Cobbold S, Martin G, Waldmann H. Monoclonal antibodies for the prevention of graft-versus-host disease and marrow graft rejection. The depletion of T cell subsets in vitro and in vivo. Transplantation 1986; 42: 239-47
43. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. Blood 2000; 96: 2419-25
44. Ruutu T, Niederwieser D, Gratwohl A, et al. A survey of the prophylaxis and treatment of acute GVHD in Europe: a report of the European Group for Blood and Marrow, Transplantation (EBMT). Chronic Leukaemia Working Party of the EBMT. Bone Marrow Transplant 1997; 19: 759-64
45. Hings IM, Filipovich AH, Miller WJ, et al. Prednisone therapy for acute graft-versus-host disease: short- versus long-term treatment. A prospective randomized trial. Transplantation 1993; 56: 577-80
46. Bacigalupo A, Van Lint MT, Frassoni F, et al. High dose bolus methylprednisolone for the treatment of acute graft versus host disease. Blut 1983; 46: 125-32
47. Kanojia MD, Anagnostou AA, Zander AR, et al. High-dose methylprednisolone treatment for acute graft-versus-host disease after bone marrow transplantation in adults. Transplantation 1984; 37: 246-9
48. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low- dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. Blood 1998; 92: 2288-93
49. Cahn JY, Bordigoni P, Tiberghien P, et al. Treatment of acute graft-versus-host disease with methylprednisolone and cyclosporine with or without an anti-interleukin-2 receptor monoclonal antibody: a multicenter phase III study. Transplantation 1995; 60: 939-42
50. Przepiorka D, Kernan NA, Ippoliti C, et al. Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for

treatment of acute graft-versus-host disease. Blood 2000; 95: 83-9
51. Martin PJ, Nelson BJ, Appelbaum FR, et al. Evaluation of a CD5-specific immunotoxin for treatment of acute graft- versus-host disease after allogeneic marrow transplantation. Blood 1996; 88: 824-30
52. Przepiorka D, Phillips GL, Ratanatharathorn V, et al. A phase II study of BTI-322, a monoclonal anti-CD2 antibody, for treatment of steroid-resistant acute graft-versus-host disease. Blood 1998; 92: 4066-71
53. McCarthy Jr PL, Williams L, Harris-Bacile M, et al. A clinical phase I/II study of recombinant human interleukin-1 receptor in glucocorticoid-resistant graft-versus-host disease. Transplantation 1996; 62: 626-31
54. Couriel DR, Hicks K, Giralt S, et al. Role of tumor necrosis factor-alpha inhibition with infliximAB in cancer therapy and hematopoietic stem cell transplantation. Curr Opin Oncol 2000; 12: 582-7
55. Margolis J, Jacobsohn D, Phelps M, et al. Pentostatin: A novel treatment for steroid refractory acute GVHD [abstract]. Blood 2000; 96: 400a
56. Queen C, Schneider WP, Selick HE, et al. A humanized antibody that binds to the interleukin 2 receptor. Proc Natl Acad Sci U S A 1989; 86: 10029-33
57. Junghans RP, Waldmann TA, Landolfi NF, et al. Anti-Tac-H, a humanized antibody to the interleukin 2 receptor with new features for immunotherapy in malignant and immune disorders. Cancer Res 1990; 50: 1495-502
58. Doney KC, Weiden PL, Storb R, et al. Treatment of graft-versus-host disease in human allogeneic marrow graft recipients: a randomized trial comparing antithymocyte globulin and corticosteroids. Am J Hematol 1981; 11: 1-8
59. Cragg L, Blazar BR, Defor T, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. Biol Blood Marrow Transplant 2000; 6: 441-7
60. Deeg HJ, Henslee-Downey PJ. Management of acute graft-versus-host disease. Bone Marrow Transplant 1990; 6: 1-8
61. Margolis J, Davidson R, Doherty J, et al. Poor outcome in steroid refractory GVHD with ATG treatment [abstract]. Blood 1999; 94: 152a
62. Sullivan KM, Witherspoon RP, Storb R, et al. Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft-v-host disease. Blood 1988; 72: 555-61
63. Wingard JR, Piantadosi S, Vogelsang GB, et al. Predictors of death from chronic graft-versus-host disease after bone marrow transplantation. Blood 1989; 74: 1428-35
64. Parker PM, Chao N, Nademanee A, et al. Thalidomide as salvage therapy for chronic graft-versus-host disease. Blood 1995; 86: 3604-9
65. Vogelsang GB, Farmer ER, Hess AD, et al. Thalidomide for the treatment of chronic graft-versus-host disease. N Engl J Med 1992; 326: 1055-8
66. Sullivan KM, Witherspoon RP, Storb R, et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. Blood 1988; 72: 546-54
67. Mookerjee B, Altomonte V, Vogelsang G. Salvage therapy for refractory chronic graft-versus-host disease with mycophenolate mofetil and tacrolimus. Bone Marrow Transplant 1999; 24: 517-20
68. Jacobsohn DA, Margolis J, Chen AR, et al. Pentostatin: A promising treatment for refractory chronic GVHD [abstract]. Blood 2001; 98: 399a
69. Marcellus DC, Altomonte VL, Farmer ER, et al. Etretinate therapy for refractory sclerodermatous chronic graft-versus- host disease. Blood 1999; 93: 66-70
70. Lee SJ, Wegner SA, McGarigle CJ, et al. Treatment of chronic graft-versus-host disease with clofazimine. Blood 1997; 89: 2298-302
71. Gilman AL, Chan KW, Mogul A, et al. Hydroxychloroquine for the treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2000; 6: 327-34
72. Vogelsang GB, Wolff D, Altomonte V, et al. Treatment of chronic graft-versus-host disease with ultraviolet irradiation and psoralen (PUVA). Bone Marrow Transplant 1996; 17: 1061-7
73. Aubin F, Brion A, Deconinck E, et al. Phototherapy in the treatment of cutaneous graft-versus-host disease. Our preliminary experience in resistant patients. Transplantation 1995; 59: 151-5
74. Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. Blood 1998; 92: 3098-104

Correspondence and offprints: Dr *David A Jacobsohn*, Pediatric Oncology/CMSC800, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287, USA.
E-mail: jacobda@jhmi.edu