

Novel Pharmacotherapeutic Approaches to Prevention and Treatment of GVHD

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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 trespersimus 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-TNF α 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.

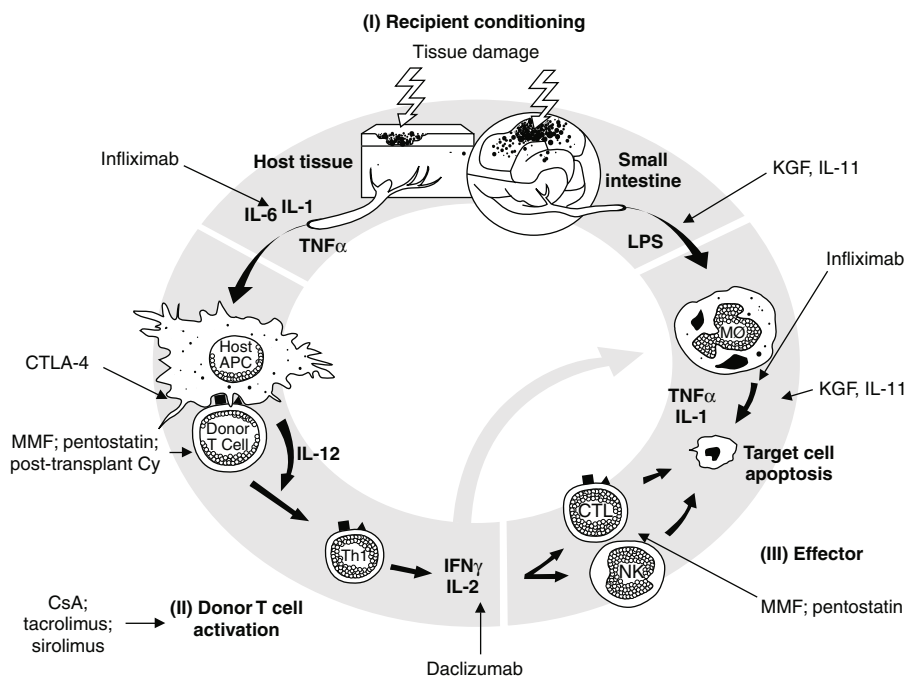


Fig. 1. Acute graft versus host disease (GVHD) pathophysiology and pharmacotherapeutic intervention. The three sequential phases of GVHD (I, II, III) are detailed. Agents discussed are shown in relation to the phases of GVHD they disrupt (Adapted from Hill and Ferrara,^[13] © American Society of Hematology, 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 IFN γ (from activated T cells), secrete IL-1 and TNF α . TNF α causes direct tissue damage and causes apoptosis via the TNF α -Fas pathway. IL-1 also leads to target cell apoptosis. In addition, cytotoxic T cells and natural killer (NK) cells, also activated by IFN γ and IL-2, lead to cellular damage.^[12] IFN γ 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 TNF α . 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 TNF α 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/m² on day 1; 10mg/m² 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 (<i>in vitro</i> treatment of marrow and <i>in vivo</i> 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- κ B) 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 $\pm$ 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 en-

couraging 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 reduc-

tion, 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 im-

provement 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-TNF α 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/m² 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.

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