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Have we improved in preventing and treating acute GVHD?

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Abstract

Purpose of review—Acute graft vs. host disease (GVHD) is a considerable source of morbidity and mortality following allogeneic hematopoietic cell transplantation (HCT). Accordingly, progress in the prevention and primary therapy of this complication is needed to improve patient outcomes.

Recent findings—Guided by insights into acute GVHD pathogenesis, investigators have explored novel cellular and pharmacologic approaches to acute GVHD prevention that demonstrates promise. While pan-T cell depletion has reduced GVHD, novel strategies that selectively deplete alloreactive T cells or modulate the balance of effector T cells and regulatory T cells offer promise to selectively abrogate acute GVHD while retaining protection from primary disease relapse and infectious complications.

Summary—Divergent approaches in the primary therapy of acute GVHD have explored both combination approaches with standard dose glucocorticoids and additional immunosuppressive agents and conversely steroid-sparing approaches including topical agents such as beclomethasone or sirolimus as a steroid-free approach to acute GVHD therapy. Mature results of high quality clinical trials are needed to determine the optimal therapy that results in effective control of the syndrome and limited toxicity. These complementary outcomes represent the therapeutic goal for future investigation in acute GVHD therapy.

Keywords

Graft-versus-Host Disease (GVHD); Hematopoietic Cell Transplantation (HCT); regulatory T cells (Tregs)

Introduction: Prevention of acute graft-versus-host disease

Acute graft vs. host disease (GVHD) is a major source of morbidity and mortality following allogeneic hematopoietic cell transplantation (HCT). As current pharmacologic strategies are insufficient to prevent acute GVHD, [1,2] investigators continue to exploit approaches that affect GVHD immunobiology to improve patient outcomes. A triphasic conceptual model of GVHD pathogenesis introduced 20 years ago simplifies a complex network: Tissue damage from conditioning therapy, activation of host antigen presenting cells and donor T cells resulting in differentiation, migration, and an effector phase in which T cells mediate tissue

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damage by releasing inflammatory cytokines including Tumor necrosis factor (TNF)-α and Interleukin (IL)-1, and cytotoxic moieties. More recent investigation demonstrated the importance of regulatory mechanisms, including regulatory T cells (Tregs). Pre-clinical models demonstrated their potential for abrogating acute GVHD, and clinical correlative data has suggested a relationship between the incidence and severity of GVHD and circulating Tregs. Hence, there is great interest in the clinical translation of such potential for the prevention of acute GVHD.

Brunstein, et al have expanded umbilical cord blood donor Treg using anti-CD3/CD28 beads and IL-2, and have examined the safety of infusion of these cells in a phase I study (n = 23).[3] Median expansion was 211-fold, and the median post-expansion proportion of CD4+CD127-FoxP3+ cells was 64% (range 31%–96%). Dose escalation was performed up to 30×10^5 Treg/kg. Patients received initially cyclosporine (CSA)/mycophenolate mofetil (MMF), and later sirolimus (SIR)/MMF. Grade II–IV acute GVHD was 43%, compared to historical control of 61% (p = 0.05). These data substantiate the feasibility of ex-vivo Treg expansion. Further work is needed to examine the efficacy of this approach.

Sirolimus promotes peripheral Treg expansion while suppressing effector T cells. *Rodriguez, et al* have expanded available data on tacrolimus (TAC)/SIR in GVHD prevention with the publication of a phase II study (n = 85) after one of three conditioning regimens in matched sibling HCT. Grade II–IV acute GVHD was 43% (37–50%), and III–IV was 19%. The 2 year incidence of chronic GVHD was 46%. NRM was low at 4.8% (2–12%) at 100 days, and 10.2% (6–18%) at 2 years. These data provide further evidence in support of TAC/SIR for GHVD prevention. More conclusive evidence for the benefit of TAC/SIR compared to TAC/MTX will result from the national Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) trial (http://clinicaltrials.gov/ct2/show/NCT01106833).

Preclinical studies have demonstrated that the transfer of cells treated with extra-corporeal phototherapy (ECP) with ultraviolet A radiation reverses established GVHD by increasing donor Tregs.[4] *Shaughnessy, et al* have aimed to exploit the effect of ECP on host antigen-presenting cells: Their phase II multicenter trial tested 2 consecutive days of ECP administered before HCT. CSA and methotrexate (MTX) were administered following ablative conditioning and infusion of peripheral blood stem cells (PBSC) or bone marrow (BM) from matched related (MRD) or unrelated donors (MUD) (n = 66).[5] Grade II–IV acute GVHD was 35% (23–48%), chronic GVHD at one year was 38% (21–47%), and overall survival (OS) at one year was 77% (64–86%). In comparison to historical controls not treated with ECP, there was no significant difference in outcomes. While these data do not support that pre-transplant ECP prevents acute GVHD, modulation of host antigen presentation remains a key area of investigation with potential for clinical translation.

As evidence supports a central role for donor T cells in acute GVHD pathogenesis, investigators have refined protocols for T cell depletion. *Jakubowski, et al* published a phase II trial of ex-vivo T cell depletion employing CD34 enrichment by the Miltenyi device in 35 unrelated donor transplants (PBSC 29, BM 6).[6] The median CD3+ cell dose was 1.52×10^3/kg. With no pharmacologic prophylaxis, the grade II-IV acute GVHD was 6%, chronic GVHD 29%, NRM 20% at 100 days and 29% and 1 year. Epstein-Barr Virus (EBV)-associated post-transplant lymphoproliferative disease (PTLD) occurred in 8.5% of the cases. With the highly intense conditioning, the relapse incidence was low, 6% at 4 years, despite a largely advanced disease cohort. *Devine, et al* have confirmed the efficacy of this protocol in HLA-matched sibling donor transplantation (n = 44) for acute myeloid leukemia (AML) in complete remission (CR)1 or CR2 in the BMT CTN 0303 trial.[7] T cell depleted allografts contained a median CD3+ dose of 6.6×10^3/kg. Without pharmacologic

prophylaxis, grade II–IV acute GVHD was 22.7% (10.2–35.3%), and grade III–IV was 4.5% (0–10.8%). Extensive chronic GVHD was 6.8% (0–14.4%) at 24 months. With median follow up of 34 months, the 36 month DFS was 58%, which is in keeping with DFS reported for AML in CR1 with comparable myeloablative approaches.[8] NRM was 14% (3.4–24%) by 12 months, and 23.2% (9.3–37.1%) by 36 months. These results demonstrate that subtotal depletion of donor T cells provides protection against GVHD. Risks inherent in this approach, including increased infectious risk and EBV associated PTLD, support alternate strategies to mitigate the GVHD risk.

Others have examined alternative pharmacologic prophylaxis strategies to improve on outcomes achieved with a calcineurin inhibitor and methotrexate. *Parmar, et al* have reported the results of a novel phase I/II, controlled, Bayesian adaptively randomized study employing a regimen of TAC/MTX (5 mg/m^2 on days +1, +3, +6, and only on day +11 in controls) and pentostatin (dose levels 0, 0.5, 1, 1.5, and 2 mg/m^2 administered on days +8, +15, +22, and +30) in mismatched related donors (n = 10) and MUD (n = 137).[9] Pentostatin doses of 1.0 and 1.5 mg/m^2 had the greatest success rates. However, grade II–IV acute GHVD incidence (35.7% vs. 55.6%, p = 0.085), chronic GVHD and OS did not significantly differ compared to control. It is not clear from these data that the addition of pentostatin has significantly improved protection from acute GVHD.

Our group conducted a phase II trial of TAC/MMF vs. TAC/MTX in recipients of MRD and MUD PBSC transplants to test the hypothesis that MMF administered for a year is more effective than a short course of MTX on days +1, +3, +6 and +11 in depleting allo-activated T cells.[10] There was no significant difference in the incidence of grade II–IV acute GVHD between the study arms (78 vs. 79%, p = 0.8). No significant differences were observed in depletion of replicating T cells. In total these findings suggest that substitution of MMF for MTX alleviates MTX-associated toxicity, but is not more effective than MTX in the prevention of severe acute GVHD, especially in unrelated donors.

Luznik et al have pioneered GVHD prophylaxis with post-transplant high dose cyclophosphamide (CY, 50 mg/kg/d on days +3 and +4) based on its potent and selective activity against allo-activated donor T cells.[11] Based on murine preclinical data, Johns Hopkins investigators have first demonstrated the effectiveness of post-transplant CY in preventing GVHD after haploidentical marrow transplant. In a recent phase I–II Bayesian design trial (n = 117) including MRD and MUD, T replete marrow was transplanted following myeloablative busulfan (BU) and CY. With sole post-transplant CY prophylaxis, 43% developed grade II–IV acute GVHD, and 10% had grade III–IV. Impressively, the cumulative incidence of chronic GVHD was only 10% with median follow up of 26.3 months (Figure 1). NRM was only 9% at 100 days and 17% at 2 years. These data suggest that pharmacologic strategies targeting alloreactive donor T cells can mitigate acute and chronic GVHD risk and facilitate transplantation tolerance.

The performance of high quality clinical trials that modulate immunobiology of acute GVHD offer promise to advance the field and spare patients morbidity and mortality associated with the syndrome.

Therapy of acute graft-versus-host disease

Glucocorticoids (prednisone at ≥ 1–2 mg/kg for 7 to 14 days, followed by gradual dose reduction) have been considered the standard initial treatment for acute GVHD.[12] CRs occur in approximately 35% to 50% of the patients at day 28 of therapy.[12–14] The likelihood of GVHD treatment response decreases with increasing severity of the disease.[15,16] The response to primary therapy is of critical importance as it correlates with survival post transplant.[17]

If the manifestations of GVHD in any organ worsen over 3 days of treatment, or if the skin does not improve by 5 days while other organ manifestations are present, secondary therapy should be considered.[12] An additional immunosuppressive agent should be added,[18–20] as attempts to use higher initial doses of glucocorticoids [21] or prolonged steroid tapering failed to improve responses rates.[22] No consensus exists on the optimal treatment of patients with steroid refractory or dependent GVHD.

New immunosuppressive agents and/or strategies are required to improve management of GVHD and decrease its toxicities. Effective therapy for acute GVHD might improve CR rates and result in better survival after allogeneic HCT.[23] Few controlled studies have been conducted testing initial treatment of acute GVHD with novel agents in addition to glucocorticoids to improve GVHD response rates and survival. Initial attempts using anti-T cell antibodies in addition to standard GVHD therapy failed to improve response.[24–26] A randomized trial comparing prednisone (2 mg/kg/day) plus a humanized monoclonal antibody against the interleukin-2 receptor (daclizumab) against prednisone plus placebo for primary treatment of acute GVHD did not improve response rates. Furthermore, the combination resulted in significantly worse 100-day survival and 1-year OS due to increased relapse and GVHD related mortality.[27]

Levine et al tested the combination of methylprednisolone (2 mg/kg/day) plus a tumor necrosis factor α inhibitor, etanercept, as initial therapy in a pilot study [28] followed by a Phase II clinical trial.[29] Etanercept and glucocorticoids were significantly more likely to achieve CR after 4 weeks of treatment compared to an external control group treated with glucocorticoids alone (69% vs. 33%; P <.001), and response benefits persisted at 12 weeks (77% vs. 50%; P <.001). Difference in results was observed regardless of stem cell donor (related vs. unrelated), or conditioning regimen (myeloablative vs. reduced intensity) and/or organ involved (skin vs. liver vs. gastro-intestinal tract). Incidence of infections, malignancy relapse and/or flare of GVHD did not vary among compared groups. Combination therapy translated into a significantly improved survival at 6 months for unrelated recipients. [29]

The BMT CTN reported the results of a randomized, phase 2 multicenter trial to evaluate the efficacy of 4 agents, each in combination with glucocorticoids as initial therapy for acute GVHD.[30] Patients were randomized to methylprednisolone 2 mg/kg/day plus either etanercept, MMF, denileukin diftitox (denileukin), or pentostatin. Day-28 CR rates were 26%, 60%, 53%, and 38%, respectively. The corresponding rates of severe infections were 48%, 44%, 62%, and 57%, and the 9-month OS rates were 47%, 64%, 49%, and 47%, respectively. Patients who received MMF for GVHD prophylaxis (24%) were randomized only to a non-MMF arm, creating an allocation bias. Non-MMF arms included 30%–34% patients previously treated with MMF as GVHD prophylaxis. Since pre-treatment with MMF affects GVHD responsiveness,[31] the allocation bias raised the concern that patients with less responsive acute GVHD were preferentially allocated to non-MMF arms and biased the results in favor of MMF. Despite this caveat, efficacy and toxicity data of this BMT CTN trial [30] indicated that MMF plus glucocorticoids might be the most promising of the four regimens, and therefore it was selected for comparison against glucocorticoids alone in a phase 3 trial that is currently open to accrual (BMT CTN Protocol 0802- http://clinicaltrials.gov/ct2/show/NCT01002742).

Primary treatment of GHVD using glucocorticoids as backbone for acute GVHD treatment provides also a template to test investigational (non-FDA approved) agents. Our group is currently testing the efficacy of a novel histone deacetylase inhibitor, panobinostat, in addition to glucocorticoids in a prospective phase I/II clinical trial (http://clinicaltrials.gov/ct2/show/NCT01111526).

Prolonged exposure to glucocorticoids is associated with complications that impair quality of life and increase risk of infections. In addition, methylprednisolone used in combination with CSA for GVHD prophylaxis resulted in a higher incidence of chronic GVHD (44% vs. 21%; P=.02) vs. CSA alone.[32] These data indicate that despite effectiveness in suppressing GVHD in some patients, glucocorticoids may interfere with signals required for development of immune tolerance.

Glucocorticoid dose-finding, prospective controlled clinical trials for the treatment of GVHD are few in the literature. A prospective randomized trial has shown that glucocorticoids at doses higher than 2 mg/kg/day do not offer benefits for treatment of acute GVHD. [21] Mielcarek et al have conducted a retrospective analysis to evaluate the efficacy of lower glucocorticoid doses for the treatment of acute GHVD. [33] Outcomes were compared between low-dose (1 mg/kg/day; n=347) and standard dose (2 mg/kg/day; n=386) prednisone or equivalent. Groups differed in degree of donor/recipient HLA matching, stem cell sources, timing of GVHD therapy and GVHD grading among others. Multivariate analysis after adjusting for GVHD-associated factors revealed no differences in OS, relapse, secondary GVHD therapy and non-relapse mortality for patients with grades I–II GVHD, and reduced risk of invasive fungal infections in the low-dose prednisone group.

Systemic glucocorticoid-sparing approaches have been initially tested by McDonald et al in the treatment of upper intestinal GVHD with nausea, vomiting and diarrhea ≤1 L/day. Beclomethasone dipropionate (BDP), a topically active non-absorbable glucocorticoid, was administered for 30 days in a single center trial, achieving GVHD control without recurrence and allowing faster taper of systemic glucocorticoids than usual.[34] Follow up randomized placebo-controlled multicenter trial testing oral BDP (8 mg for 50 days) in addition to short course of glucocorticoids (1–2 mg/kg/day, tapered on day 10 to a physiological dose by day 16), has confirmed that BDP allows a rapid steroid taper. Primary endpoint time to treatment failure by study day 50 was not reached but day 80 efficacy, day 200 and 1 year survival was significantly better in the BDP group. [35] Ongoing Phase III confirmatory trial is currently accruing subjects testing the primary endpoint of occurrence GVHD treatment failure during the 80 study period, encompassing a 50-day treatment and a 30-day observation period http://clinicaltrials.gov/ct2/show/NCT00926575). Additional glucocorticoid-sparing strategies have tested low dose MTX combined with low dose methylprednisolone (0.5 mg/Kg/day followed by taper on day 5 and cessation at about day 30) for the treatment of acute GVHD with encouraging results.[36] In summary, these studies established the proof of principle that steroids-sparing approaches are feasible and should be further explored to reduce morbidity and improve OS after HCT.

Summary

Our group has experience using solely SIR, an inhibitor of mammalian mTOR, as primary treatment of acute GVHD in patients deemed high risk for steroid toxicity.[37] SIR is quite effective in GVHD prevention and its anti-tumor activity might decrease relapse after transplantation.[38] Treatment of grades I–III acute GVHD affecting primarily skin and gut (n=32) resulted in a CR rate of 50% with a favorable toxicity profile.[39] Response to treatment was achieved at median of 14 days (range 5–28 days) (Figure 2). Those patients requiring glucocorticoids achieved CR with prednisone doses of only 0.5–1 mg/kg/day suggesting a potential steroid-sparing effect. Prospective clinical trials are needed to address the definitive role of SIR alone for acute GVHD treatment.

With divergent efforts in acute GVHD therapy, namely combination therapy with traditional glucocorticoid doses vs. steroid-sparing approaches, mature results from high quality trials are needed to direct best practice that optimizes efficacy while sparing toxicity.

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Key points

- Animal models predict that GVHD prevention and operational tolerance require tipping the balance in favor of regulatory T cells, against effector T cells.
- Adoptive Treg transfer and sirolimus both favor regulatory T cells and have clinical activity in GVHD prevention and treatment.
- Post-transplant high-dose cyclophosphamide is effective in eliminating alloreactive effector T cells and has clinical activity in GVHD prevention.
- Glucocorticoids prevent or least delay transplantation tolerance.
- Glucocorticoid-sparing approaches, such as non-absorbable enteric steroids, have improved patient survival.

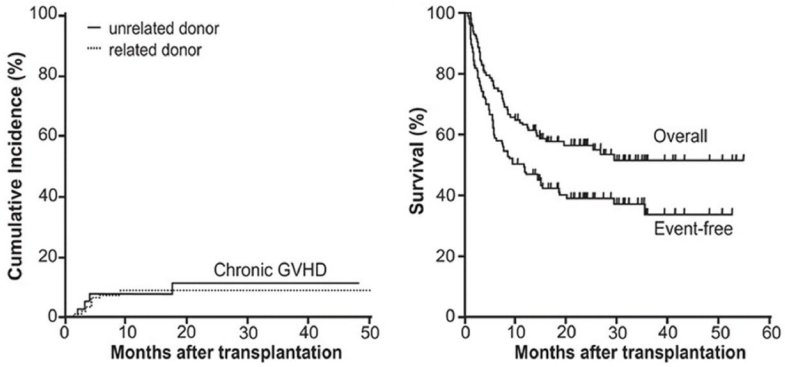

Figure 1.
Cumulative incidence of chronic GVHD and survival outcomes following post-HCT high dose cyclophosphamide (reprinted from *Luznik, et al*, Blood 2010)

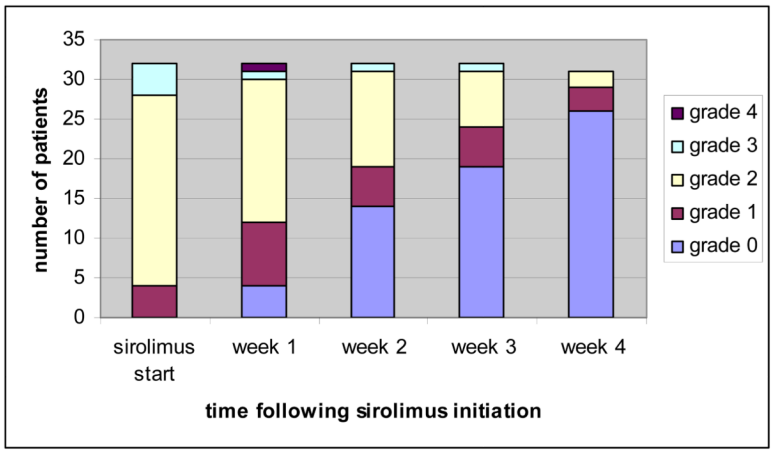

Figure 2.
Response to sirolimus as sole primary therapy of acute GVHD (reprinted from *Pidala, et al,* Haematologica, 2011)