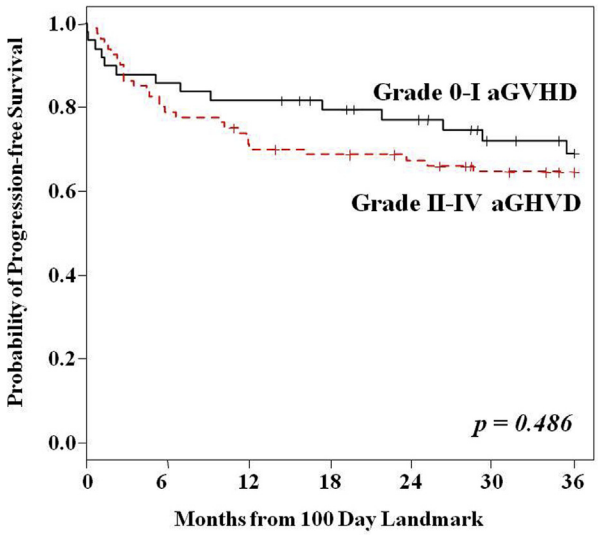

Figure 1.

with a median time to sys.IS cessation of 1.2 years (range 0.5-5.6) post-DCBT. Of 103 progression-free survivors at 1-year, 26 (25%) were on high, 26 (25%) on intermediate, 18 (17%) on low dose sys.IS, & 33 (32%) were on no sys.IS. The number of patients on any sys.IS decreased to 30% in evaluable progression-free survivors at 2-years, & 18% at 3-years. A total of 84/129 (65%) patients survive progression-free to date from the day 100 landmark with 24 having died of TRM (17 GVHD-related), 1 from relapsed sarcoma, & 20 have relapsed/progressed. The 3-year incidence of TRM according to maximum day 100 aGVHD grade was 11% (95%CI: 4-22) in grade 0-I & 24% (95%CI: 15-34) in grade II-IV patients, $p = 0.14$. The 3-year incidence of relapse was 20% (95%CI: 10-34) in grade 0-I & 11% (95%CI: 6-20) in grade II-IV patients, $p = 0.54$. Overall, there was no difference in the 3-year PFS of 69% (95%CI: 56-84) in those whose day 100 aGVHD grade was 0-I when compared to the 65% (95%CI: 55-76) PFS in patients whose aGVHD grade was II-IV (Figure).

Conclusions: In patients alive at day 100, most will achieve sustained cessation of sys.IS despite initial aGVHD. Moreover, while the contribution of aGVHD to TRM is significant, there was no statistical difference in overall TRM in the GVHD groups. Finally, grade 0-I versus II-IV aGVHD had no impact on long-term PFS. Thus, despite an approximate 50% incidence of grade II-IV aGVHD in DCBT recipients at our center (Ponce et al, *BBMT* 2013), long-term PFS is not impacted in day 100 survivors & the majority of patients are off IS after 2 years post-allograft.

505

Inhaled Cyclosporine Solution for the Treatment of Bronchiolitis Obliterans Following Hematopoietic Stem Cell Transplantation (HSCT) or Lung Transplantation

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Bronchiolitis Obliterans Syndrome (BOS) is a late pulmonary complication of both lung and HSCT resulting in obstructive lung disease. For the latter, BOS is thought to be a manifestation of chronic graft versus host disease (cGVHD). The mainstay of therapy is systemic immunosuppression, which increases the risk of infection and reduces graft versus tumor effects. We investigated whether targeted, local delivery of inhaled cyclosporine could improve or stabilize lung function in BOS patients.

HSCT and lung transplant recipients with BOS were eligible if they met the following inclusion criteria: FEV1<75% predicted, FEV1 decline >10% compared to pre-transplant FEV1, no evidence of pulmonary infection as causative etiology, and one of the following: FEV1/FVC ratio <70%, air-trapping seen on CT scan or RV ≥120%, or evidence of cGVHD affecting at least one other organ system. Subjects received cyclosporine inhalation solution (CIS) 150 mg via nebulizer 3 times weekly for 6 weeks before dose escalation to 300mg three times weekly. Pharmacokinetic and lung deposition studies were performed. The primary endpoint was change in FEV1 at study completion (average of week 18 and 19) compared to study baseline.

16 subjects have been enrolled (median age: 45 years; range: 14-73); 14 had HSCT-associated BOS, and 2 had lung-transplant-associated BOS. The median time from BOS diagnosis to study enrollment was 9 months (range: 2-37). The median FEV1 at study entry was 1.1 liters (range: 0.5-2.11). One patient suffered a severe adverse event with CIS (cough, bronchospasm, and dyspnea requiring hospitalization). Adverse events associated with CIS occurred in 11/12 patients and included grade 2 (range 1-3) cough, bronchospasm, and dyspnea that occurred primarily during inhalation.

Of the 12 evaluable subjects, 4 subjects went off-study (patient choice) prior to completion of the 18 weeks, and were considered non-responders. Responses were observed in 5/10 subjects (50%) with BOS following HSCT. Among responding patients who had an improvement in their FEV1, 3 were also able to decrease their systemic steroid dose (Figure 1). The median peak systemic absorption of cyclosporine was 99

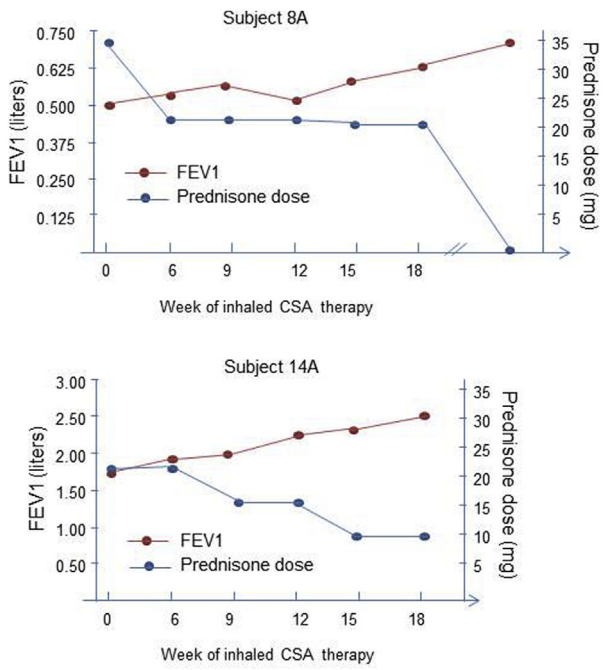

Figure 1. FEV1 and prednisone dose for Subject 8A and 14A

mcg/L (range: 32-263) 20 minutes post-CIS inhalation. Lung deposition studies showed the total deposited dose averaged 13% (range: 4-20%) of the inhaled dose. Of note, 5 subjects who showed a clinical benefit on study were subsequently enrolled onto a CIS extension protocol.

Conclusion: These data are the first to establish that CIS is safe and can stabilize or improve lung function in HSCT recipients with severe BOS, allowing systemic immunosuppression to be reduced. Importantly, lung deposition studies revealed substantial delivery of CIS could be achieved in the airways with only minimal systemic absorption.

506

Early Post-Transplant Notch Signaling Activity Is Critical for the Differentiation of Pathogenic Alloantigen-Specific T Cells Mediating Acute Graft-Versus-Host Disease

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Blocking Notch signaling after allogeneic bone marrow transplantation prevents acute graft-versus-host disease (GVHD) in mice, with key roles for Notch1/2 receptors and Delta-like-1/4 ligands (Dll1/4) (Zhang, *Blood* 2011; Tran, *JCI* 2013). To investigate the consequences of Notch inhibition in alloantigen-specific T cells, we identified a short 2-day window of Notch activity early after transplantation during which Notch blockade is critical for maximal prevention of acute GVHD. We describe new mechanistic models to study alloantigen-specific T-cells within this window, and provide insights into early events associated with Notch blockade. In a MHC-mismatched model, transgenic C57Bl/6 $CD4^+$ 4C T-cells directly recognizing host $I\text{-}A^d$ alloantigens induced lethal GVHD in BALB/c recipients. 4C $CD4^+$ T-cells were sensitive to Notch blockade, which resulted in the downregulation of Notch target genes in and impaired production of inflammatory cytokines, concordant with findings in polyclonal responses (Zhang, *Blood* 2011; Tran, *JCI* 2013). Nonetheless, serial analysis revealed preserved 4C $CD4^+$ T-cell activation, proliferation and expansion upon Dll1/4 blockade. In the B10.D2→BALB/c MHC-matched model of sclerodermatous GVHD, donor-derived $CD4^+Vb3^+$ T-cells, responding to a Mtv6-encoded BALB/c superantigen, demonstrated massive expansion and dominant Th1 polarization of $Vb3^+$ T-cells in lymphoid tissues and the liver. Despite this, Notch blockade in $Vb3^+$ T-cells inhibited cytokine production, but preserved activation and proliferation. These findings document dissociated effects of Notch inhibition on proliferation and cytokine production in alloantigen-specific T-cells, allowing further focused evaluation of Notch signaling functions in alloimmunity.

507

Is There a Stronger Graft-Versus-Leukemia Effect Using HLA-Haplo-Identical Donors Compared to HLA-Identical Sibling Donors?

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Purpose: Haplo-identical transplants are increasingly used in hematopoietic stem cell transplantation (HSCT). Do haplo-identical transplants have a stronger graft-versus-leukemia (GVL) effect?

Patients and Methods: We analyzed 10,679 patients with acute leukemia undergoing HSCT from an HLA-matched sibling donor (MSD, n=9,815), or a haplo-identical donor (≥2 HLA-antigen disparity, n=864) between 2007–2012, reported to the European Group for Blood and Marrow Transplantation. In a Cox regression model, acute and chronic GVHD were added as time-dependent variables.

Results: In the multivariate analysis, there was no difference in relapse probability between recipients of haplo-identical or MSD grafts. This was seen in T-cell replete and T-cell depleted grafts analyzed separately. Factors of importance for relapse among T-cell replete grafts included remission status at HSCT, Karnofsky score ≤80, acute GVHD ≥grade II, and chronic GVHD ($p<10^{-5}$). Among patients receiving T-cell depleted grafts, advanced disease ($p<10^{-5}$) and second remission (p=0.01) compared to first remission were the strongest factors for leukemic relapse. Non-relapse mortality was significantly higher in the haplo group versus MSD transplants among patients receiving T-cell repleted grafts or T-cell depleted grafts ($p<10^{-5}$). Subsequently, leukemia-free survival was superior in the MSD group of T-cell replete grafts ($p<10^{-5}$) and T-cell depleted grafts (p=0.0006).

Conclusion: Risk of relapse was the same in patients with acute leukemia in haplo-identical transplant recipients compared with MSD transplants, suggesting a similar GVL effect.

508

Case Report: 52 Year-Old Male 11 Months after MUD for Angionimmunoblastic T Cell Lymphoma Developed Acute Fibrinous Organizing Pneumonitis Successfully Treated with Etanercept Suggesting TNF Alpha in the Pathogenesis in This Sub-Type of Pulmonary GVHD

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Introduction: We describe a case of a 52-year-old man with history of refractory angioimmunoblastic T-cell lymphoma 11 months after matched unrelated allogeneic hematopoietic cell transplant with acute fibrinous organizing pneumonitis successfully treated with high dose steroids, tacrolimus, and 8 doses of etanercept.

Case presentation: A 52-year-old Caucasian male with a history of refractory stage IV angioimmunoblastic T-cell lymphoma treated with CHOP, ICE and Romidepsin followed by ATG/TBI matched unrelated allogeneic hematopoietic cell transplant (HCT) in March 2013. He had an uncomplicated course with the exception of mild classic chronic GVHD of skin treated with topical steroids. Eleven months after HCT, he was off