THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Graft-vs-Host Disease: Looking Ahead

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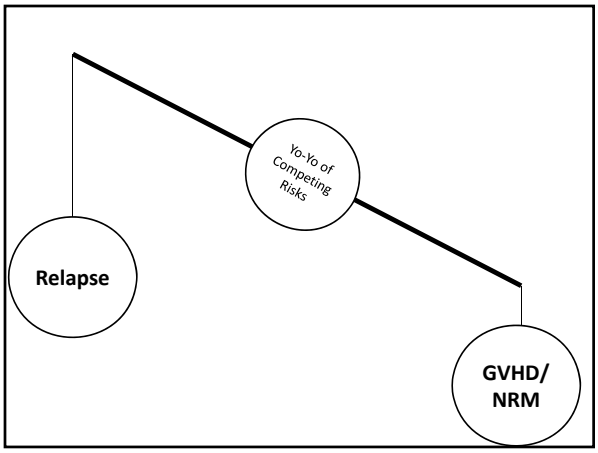
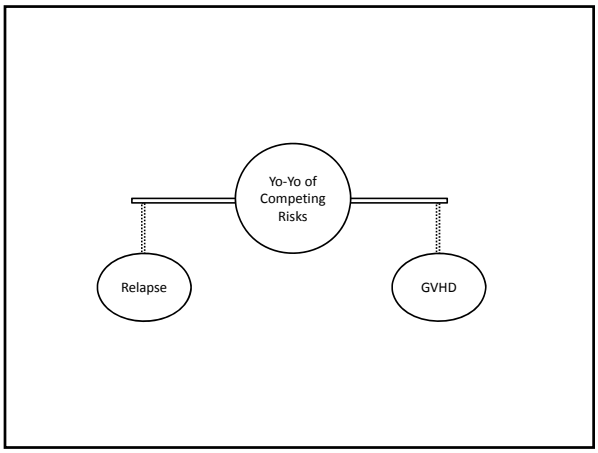
~~GVHD~~

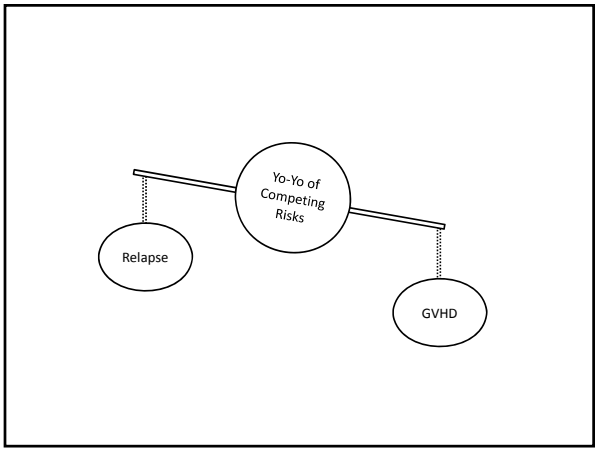
Disclosures: Therakos: Consulting, Speaker and Research Funding; Alexion: Consulting, Research Funding; Terumo BCT: Consulting; All therapeutics are off-label.

Learning Objectives

- Identify the Current Agents/ Methods for GVHD prophylaxis and upcoming trials in Phase 1, 2 and 3 testing
- Outline the Current "Standard Treatment" for Newly Diagnosed Acute GVHD
- Distinguish important factors important for identifying a patient with "Low Risk" and "High Risk" newly diagnosed acute GVHD and how research aims will differ for these two populations.
- Identify the Impact of Lower GI GVHD on non-relapse mortality (NRM) and the importance of institutional strategies/ pathways to evaluate and treat these patients.
- Compare limitations of performing drug trials in patients with chronic GVHD and recognize the current drug classes undergoing study consideration.




Yo-Yo of Competing Risks
Relapse
GVHD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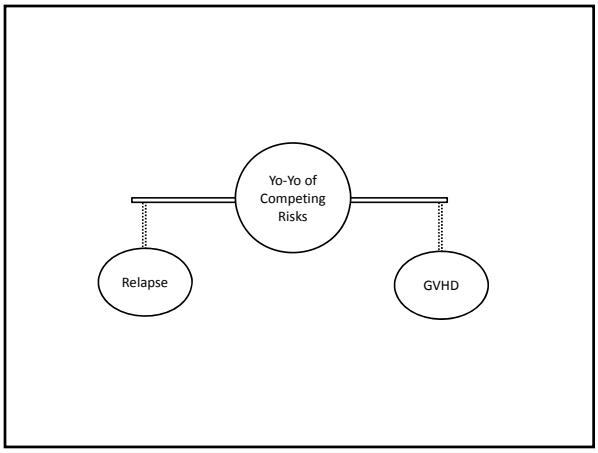
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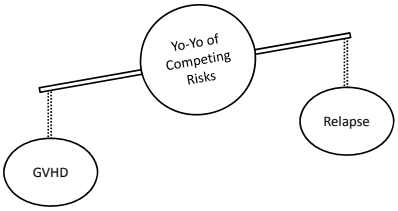


Looking Forward is Important; But One Must Know the Past First!!!

What is the impact of GVHD and GVHD Treatment on Disease Relapse?

A Truly Must Read for any Transplant Practitioner

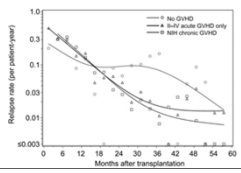
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Influence of immunosuppressive treatment on risk of recurrent malignancy after allogeneic hematopoietic cell transplantation

Yoshihiro Inamoto, Mary E. D. Flowers, Stephanie J. Lee, Paul A. Carpenter, Edus H. Warren, H. Joachim Deeg, Rainer F. Storb, Frederick R. Appelbaum, Barry E. Storer and Paul J. Martin

2011 118: 456-463

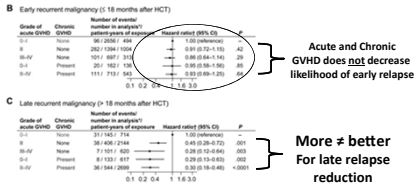
Risk of early and late recurrent malignancy according to GVHD condition.



- **Relapse Rates Gradually Fall for patients with either acute or chronic GVHD until at least 36 months.**
- **Patients with No GVHD, Relapse Rates fall for first 18 months, flat between 18 -> 30 months then fall again reaching similar rates to those with GVHD by 60 months**.

Inamoto Y et al. Blood 2011;118:456-463

Early (<18 months) and Late Relapse (>18 months) Rates based on Presence or Absence of Acute or Chronic GVHD

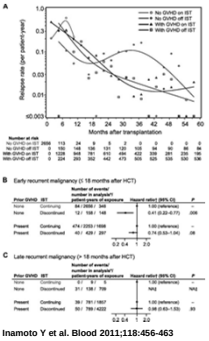


Acute and Chronic GVHD does not decrease likelihood of early relapse

More ≠ better For late relapse reduction

- Grade II, Grade III/IV Acute and Chronic GVHD are all associated with similar reductions in rates of late relapse.
- In those with Grade II-IV acute GVHD; subsequent development of chronic GVHD does not further reduce relapse.
- No interaction between donor type, HLA-mismatch, **disease risk category** and stem cell source.

Rates of recurrent malignancy and risk of early and late recurrent malignancy according to GVHD and immunosuppressive treatment conditions.



Inamoto Y et al. Blood 2011;118:456-463

- In patients with prior GVHD, the reduction in relapse persisted during immune suppressive therapy and after withdrawal.
  - ***Take Home Message: If patient Has GVHD- don't be in a hurry to stop IST and IST does not increase risk for relapse.***
- In patients who do not develop GVHD, relapse rates during immune suppressive therapy peak between 6-9 months post-SCT.
  - ***Take Home Message: If patient does not have GVHD taper immunosuppression per guidelines [MRD: ~ 3-4 months, MUD (others): ~ 6 months].***
- During the first 12 months, relapse rates in patients w/o GVHD who d/c immune suppression were lower than those who continue IST.
  - ***Take Home Message: same as above***

- After 24 months, patients with no h/o GVHD and who stopped IST have higher late relapse than those with prior h/o GVHD.
  - ***Take Home Message: GVHD protects from late relapse and unfortunately even if you stop IST promptly in patients with no h/o GVHD rates for late relapse remain higher.***
- Withdrawal of IST was not associated with a significantly decrease risk of late relapse in those with h/o GVHD.
  - ***Take Home Message: Once GVHD occurs, the withdrawal of IST does not add to benefit in reduction in relapse, i.e. don't be in too much of a hurry to stop IST in patients with GVHD.***

Alousi's Take Home Message

- *Forget the fact that untreated GVHD has high Mortality.*
- *Forget the fact that Dying of GVHD is no better (and probably worse) than Dying of Relapse.*
- *Forget the fact that Dying of GVHD is a terrible way to die.*
- **But don't forget . . . treating GVHD does not increase the likelihood of relapse.**

GVHD-Free, Relapse-Free Survival

- *How Do we Measure Success?*
  - ✓ Alive
  - ✓ In Remission
  - ✓ No High-Risk Acute GVHD (Grade III/IV)
  - ✓ No Chronic GVHD that needs systemic therapy

Happy Camper

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GVHD-Free, Relapse-Free Survival (GRFS)

Composite endpoint of graft–versus-host disease-free, relapse-free survival after allogeneic hematopoietic cell transplantation

by

Shernan G Holtan, Todd E DeFor, Aleksandr Lazaryan, Nelli Bejanyan, Mukta Arora, Claudio G Brunstein, Bruce R Blazar, Margaret L MacMillan, Daniel J Weisdorf

Blood Pre-published online January 15, 2015;
Volume 125 : doi:10.1182/blood-2014-10-609032

GRFS: New Composite Endpoint for Clinical Trials

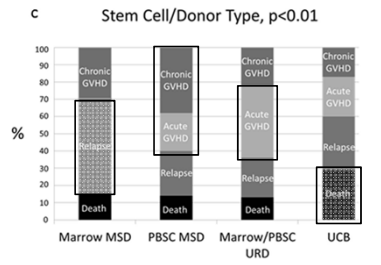
- Attempt to Measure "Cure" without "On-Morbidity".
- Data from CIBMTR estimates roughly a quarter of patients meet this endpoint @ 1 year.
- Minnesota Examined Risk Factors for GFRS in 907 adult and pediatric allo-HCT recipients for malignant diseases from 2000-2012.

GRFS: New Composite Endpoint for Clinical Trials

- Roughly 30% of patients in this analysis were deemed GVHD and Relapse-Free Survivors @ 1 year (compared to DFS of ~50% and OS~60%).
- *In-other-words*, while roughly 60% of patients survive to 1 year, but only 1/3rd or so do so without major complication.

Stem Cell and Donor Type impacts GFRS: Dominant Contributors to Failure

- Sib Marrow: NO Acute GVHD III/IV, ↑ relapse
- Sib PB: ↑ Chronic GVHD; ↓ Relapse)
- MUD's: ↑ Acute GVHD III/IV
- Cords: ↑ Death without Relapse or GVHD



What Impacts GVHD- Relapse-Free Survival Incidences?

- Donor Type
- Age
- Disease Risk

} Not Modifiable

- Graft Type

} Modifiable

- Pediatric MRD who received Marrow had the highest GFRS; numbers too small to determine whether there was a difference in adult MUD or MRD recipients between Marrow and Peripheral Blood.

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Prevention of GVHD

~~GVHD~~

Overview GVHD Prophylaxis

- Standard GVHD Prophylaxis:
  - CNI + Short Course Methotrexate the most common regimen for myeloablative Allo HCT.
  - CNI + Mycophenolate Mofetil the most common prophylaxis for non-myeloablative Allo HCT and UCT.
- Despite the use of these regimens, 25-70% of recipients develop acute and/or chronic GVHD; main contributor to NRM.
- Can we improve upon this?
- Recent Attempts and Future Direction

BMT CTN Protocol 0402
A Phase III Randomized, Multicenter Trial of GVHD Prophylaxis Regimens After HLA-Matched, Related PBSCT

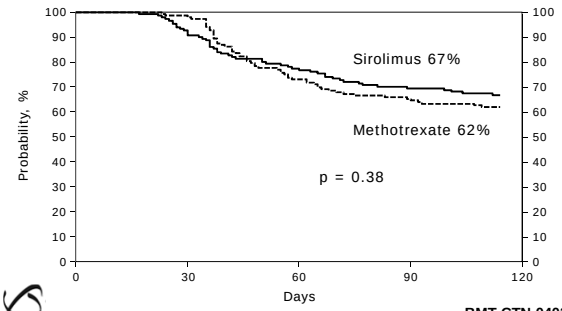
Sirolimus / Tacrolimus
Versus
Tacrolimus / Methotrexate

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Study Conduct

- ***Eligibility***:
  - AML/ALL in CR, CML CP/AP, MDS
  - Matched Sibling Donor (HLA-A, B, DRB1)
  - Age 2- 60
  - No prior transplant or uncontrolled infection
  - Adequate organ function
- ***Conditioning:***
  - Cy or VP-16 + TBI (>12 Gy)
  - Initially BuCy was included but removed due to excess toxicity
- ***Supportive Care:***
  - No planned G-CSF unless clinically indicated

Probability of Grade II-IV Acute GVHD-Free Survival



BMT CTN 0402

Study Findings

- ***Engraftment***: Tac/Siro results in quicker engraftment
  - Neutrophils: 14 vs. 16 days, p<0.001
  - Platelets: 16 vs. 19 days, p=0.03
  - Time to hospital Discharge Not Different
- **Incidence of Acute GVHD by Day 100:**
  - Grade II-IV: Siro/Tac 26% vs. Tac/MTX 34%, p=0.17
  - Grade III/IV: Siro/Tac 8% vs. Tac/MTX 15%, p=0.05
- **Chronic GVHD**: Higher for Tac/Siro (54% vs. 43%, p=0.044).
- **TRM by Day 100**, **DFS and OS @ 2 years**: identical.
- **Within the context of TBI-based, MAC MRD AHCT, Siro/Tac is a suitable alternative to Tac/MTX.**
- **Remains Unknown if Results would differ if MUD's were studied.**

Cutler et al. *Blood*. **144 (8): 1372-7. 2014.**

GVHD Prophylaxis: Current Strategies being Investigated

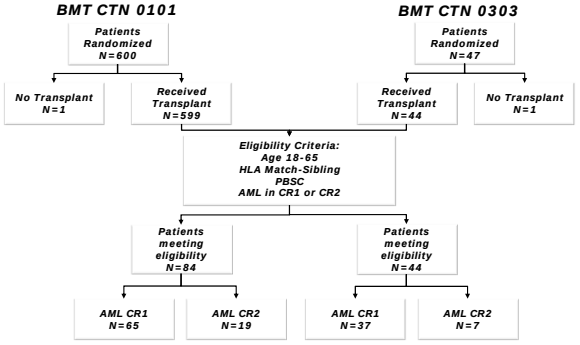
- Recent wealth of novel GVHD prevention strategies examined in early phase, single-center trials with encouraging results.
- In addition, two "older" methods of *ex vivo* and *in vivo* T-cell Depletion remain areas of active research.
- Current challenge will be in selecting the most promising approach to move forward into multi-center trials.

Ex Vivo T-cell Depletion: Evidence for and Against

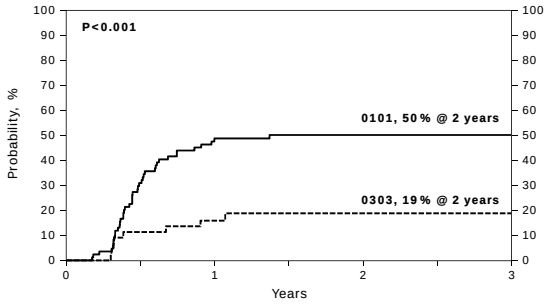
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Comparative Analysis of CD34+ Selected, T-Cell Depleted HLA-Matched Sibling Grafts on Allogeneic Hematopoietic Cell Transplantation for Patients with Acute Myeloid Leukemia in Complete Remission

Comparison Outline

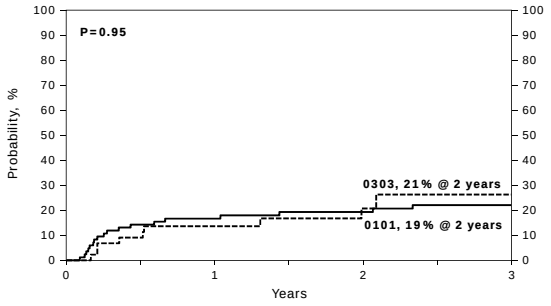


Cumulative Incidences of Chronic GVHD



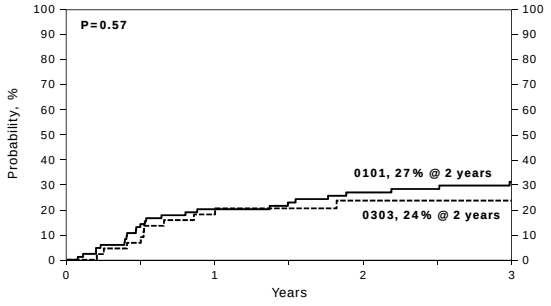
Pasquini et al. *JCO*. 30(26): 3194-201. 2012.

Cumulative Incidence of Treatment-related Mortality



Pasquini et al. *JCO*. 30(26): 3194-201. 2012.

Cumulative Incidence of Leukemia Relapse



Pasquini et al. *JCO*. 30(26): 3194-201. 2012.

CD34 Selected (TCD) AHCT: *Case For and Against*

Pros	Cons
▪ Consistently low rates of Acute GVHD ▪ **Lower rates of Chronic GVHD** ▪ Comparable TRM ▪ No apparent impact on DFS & OS for patients in CR1 ▪ If patients have same survival but less GVHD (especially chronic) isn't this desirable?	▪ Primarily studied/ applied to patients in first CR ▪ Requires Ablative Conditioning ▪ **So if acute and chronic is lower . . . *shouldn't TRM be less* (not the same)?** ▪ Death from poor immune reconstitution and toxicity from conditioning is no better than death from GVHD (death is death). ▪ Should the bar be lower GVHD which translates into **improved** OS?

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1301: The PROGRESS II Trial: Prevention and Reduction of GVHD and Relapse Enhancing Survival after Stem Cell Transplantation

Comparison of Two CNI-Free Prophylaxis Regimens: Post-CY versus CD34-Selection in Patients with Acute Leukemia in Remission receiving Myeloablative Conditioning

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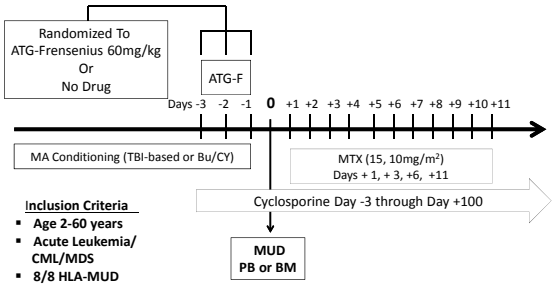
National Heart Lung and Blood Institute

In Vivo T-cell Depletion: Evidence for and Against

Finke et al. Lancet Oncology. 10(9): 855-64. 2009



Finke et al. Lancet Oncology. 10(9): 855-64. 2009

	Acute GVHD III/IV or Death by Day 100	Acute GVHD II-IV	Acute GVHD III/IV	Chronic GVHD @ 2 -years	NRM @ 2-years	Relapse @ 2 years
ATG-F	21%	33	11.7	30.8%	19.6%	28.9%
No ATG-F	34%	51	24.5	58.8%	28.9%	23.6%
HR (95% CI)	0.59 (0.3-1.7)	0.56 (0.36-0.87)	0.5 (0.25-1.01)	0.34 (0.21-0.55)	0.68 (0.38- 1.22)	1.18 (0.69-2.03)
P-Value	0.1	0.011	0.054	0.001	0.20	0.55

- Primary Endpoint of Acute GVHD III/IV Day 100 Survival: NS
- More EBV PTLD in ATG-F Arm (5 vs. 1 cases)
- Encouraging reduction in Acute and Chronic GVHD
- No apparent impact on relapse
- Randomized Study currently underway in the U.S.A.

Caution!!!
Benefit of ATG may not apply Broadly
Results of CIBMTR Analysis:

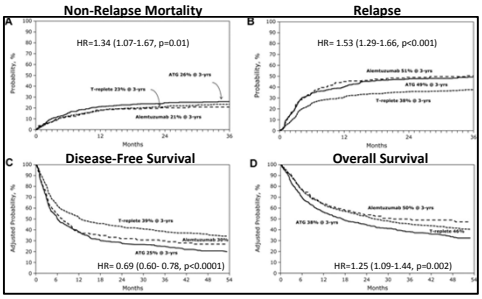
Impact of anti–T-cell antibodies on the outcome of RIC HCT for hematologic malignancies:

ATG-containing vs. T-cell Replete Regimens

	HR (95% CI)	P-value
Acute GVHD II-IV	0.88 (0.74-1.04)	0.12
Acute GVHD III/IV	0.86 (0.69-1.08)	0.19
Chronic GVHD	0.69 (0.59-0.81)	<0.001

Soiffer R J et al. *Blood.* 117: 6933-70. 2011.

Impact of anti–T-cell antibody infusion on outcomes in Reduced Intensity Conditioned HCT.



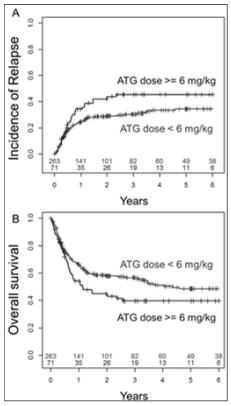
Soiffer R J et al. Blood 2011;117:6963-6970

ASH 2014 Updates: ATG for Prophylaxis

- *Prevention of Chronic GVHD after HLA-matched Sibling PB +/- ATG 10mg/kg days -3 to -1(Neovii®) before MAC: Prospective, Multi-center, Phase III.* **Bonifazi et al.**
  - Engraftment Delayed in ATG arm.
  - No difference in Acute GVHD (1-IV or III/IV).
  - Less Chronic GVHD @ 2 years (36% versus 73%, p<0.0001).
  - No apparent difference in TRM, RFS or OS.
- *Thymoglobulin Decreases the Need for IST @ 12 months after MA and NMA Conditioned MUD HCT: CBMTG 0801: A RCT.* **Walker et al.**
  - PB or BM Allowed, MA or NMA Allowed.
  - Dose of rabbit- ATG was 4.5mg/kg.
  - Freedom from IST @ 1 year was twice as high in ATG –arm (37% vs. 17%, p=0.0001).
  - Benefit seen in MA and NMA groups.
  - No difference in NRM, Relapse or OS.

ASH 2014 Updates: ATG for Prophylaxis

- *Higher Dose of ATG (rabbit ATG) increases the Risk of Relapse in AML Patients undergoing MRD HCT in CR1: An Analysis from the Acute Leukemia Working Party of EBMT.* **Devillier et al.**
  - EBMT Registry Data, AML CR1, PB and RIC.
  - High Dose ATG >/=6mg/kg (median 7.5mg/kg) vs. Low Dose ATG <6mg/kg (median dose 5mg/kg).
  - Dose did not appear to impact the rates of Acute GVHD II-IV, Chronic GVHD or NRM.
  - Cum Incidence of Relapse was higher in high-dose ATG group (HR 2.3, p=0.003) leading to worst LFS and OS.

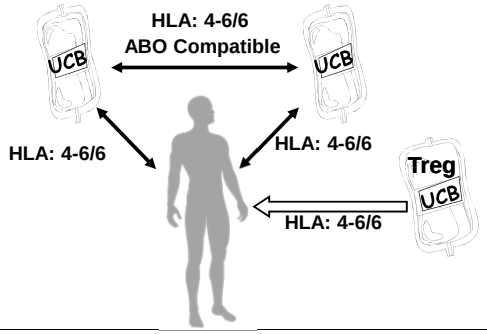


Devillier et al. ASH. 2014

New Approaches: Cellular Therapy with Regulatory T-cells (Tregs) to Reduce GVHD

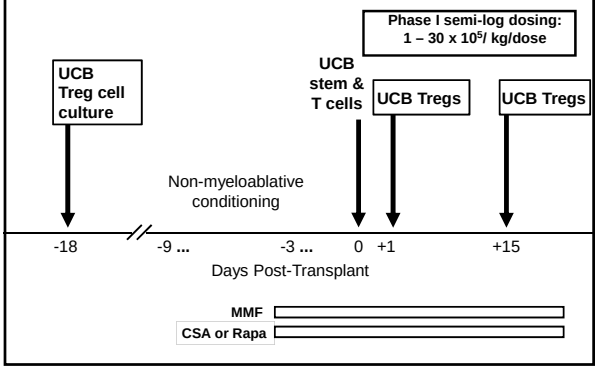
The University of Minnesota Experience in Umbilical Cord Transplantation

Patient Eligibility: Phase I UCB Treg Trial in UCB Transplant Recipients



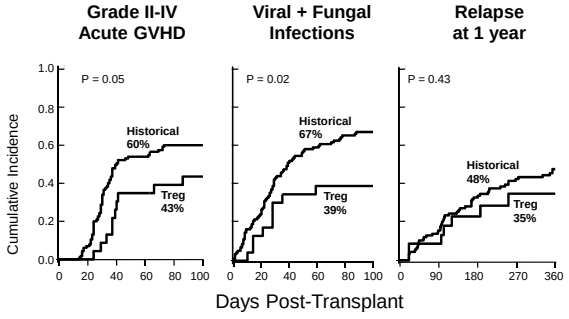
Brunstein, C., *Blood* 117:1061-70, 2011

Phase I Treatment Plan for Human UCB Tregs



Major Outcomes of Phase I Treatment Plan

Primary Endpoint: No Dose-Limiting Toxicities Seen

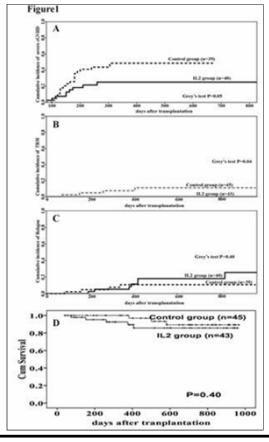


Future Direction: Tregs

- University of Minnesota is planning a f/up phase 1 trial utilizing a new expansion method to achieve $T_{effector}$: T_{reg} ratios approaching that found beneficial in mouse models.
- Similar Trial planned at MDACC.

ASH 2014: Increasing Tregs a Pharmacologic Strategy

- Zhao et al. *Low Dose Interleukin-2 Therapy Could Prevent Chronic GVHD: A Randomized Study.*
  - Preclinical work suggested that low dose IL-2 may preferential expand NK cells and Tregs following allo HCT.
  - Performed a Randomized Control Trial to see if this would translate into prevention of Chronic GVHD.
  - Treatment started on Day 60.
  - Preliminary Analysis of 88 randomized patients (short follow-up, majority less than 1 year).
  - *Less Severe Chronic GVHD and TRM in treatment group.*
  - *Appeared to Expand Regulatory Treg and NK cells while not affecting conventional T cells, Th1 T-cells or TH17 T-cells.*



Zhao et al. ASH. 2014.

HDAC Inhibitors & Experimental GVHD

- Histone deacetylase inhibitors (HDACi) remodel chromatin, regulate gene expression, and have demonstrable efficacy as anti-cancer agents.
- HDACi reduce pro-inflammatory cytokines, increase regulatory T cell numbers, and attenuate experimental GVHD.
- HDAC inhibition in murine model reduced GVHD with no apparent impact on GVL.

Reddy, PNAS 2004; Leng, Exp Hematol 2006; Tao, Nat Med 2007; Reddy JCI 2008.

Pre-clinical Study of SAHA for GVHD Prevention

- In the mouse model of GVHD where BALB/c mice are transplanted into C57BL/6 after TBI.
- Treating the mice with nanomolar concentrations of SAHA from days+3 to +7 post BMT reduced:
  - inflammatory cytokines,
  - reduced clinical severity scores of GVHD
  - improved survival when compared to control.
- SAHA did not appear to inhibit donor T-cell proliferative or cytotoxic responses.
- Concluded SAHA may reduce GVHD while preserving GVL.

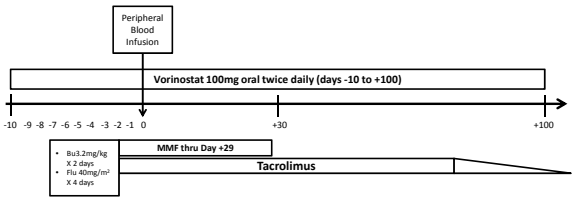
Reddy et al. *PNAS*. 101:3921-6. 2004.

Phase II Study: Targeting Histone Deacetylases for GVHD Prevention

- Safety and Efficacy of vorinostat for reduction in GVHD in patients undergoing matched related donor RIC AHCT.
- **Controls:** Comprised of similarly treated patients using standard GVHD prophylaxis (Tac/MMF).
- **PRIMARY ENDPOINT:** Cumulative incidence of grade 2-4 acute GVHD by day 100 with a target risk of 25%.

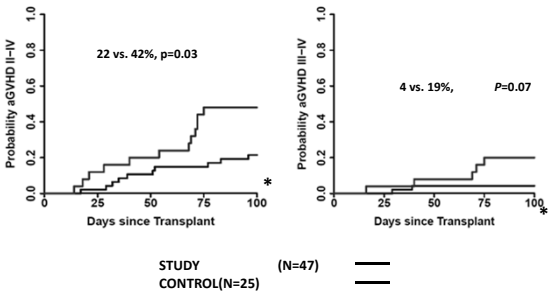
Choi et al. *Lancet Oncol*. 15:87-95. 2014

Vorinostat for GVHD Prophylaxis Treatment Schema



Presented at ASH 2012 by Choi et al.

Phase II Study: Vorinostat for GVHD Prevention



Choi et al. *Lancet Oncol*. 15:87-95. 2014

Post-Transplant Cyclophosphamide (Cy) as sole GVHD Prophylaxis

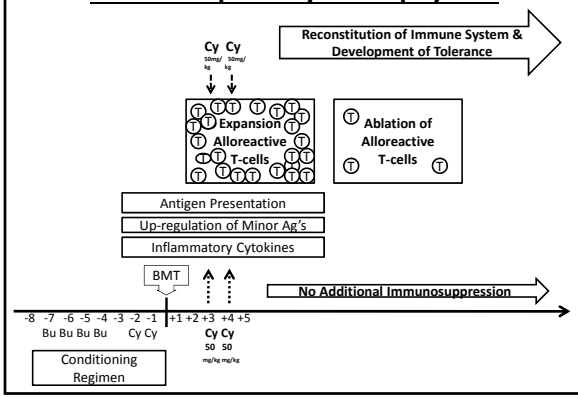
- Researchers at Johns Hopkins Cancer Center have explored methods for GVHD prophylaxis that avoids prolonged immunosuppression.
- Hypothesized that by avoiding prolonged exposure to calcineurin inhibitors would result in quicker immune reconstitution.
- In so doing, they predicted that the main post-transplant complications, GVHD and infections, would be minimized.

Post-Transplant Cyclophosphamide (Cy) as sole GVHD Prophylaxis

- Cy Lacks toxicity to hematopoietic stem cells and spares Tregs which express aldehyde dehydrogenase.
- In mouse models they were able to demonstrate that timed use of post-transplant Cy depletes allo-reactive T-cells and minimizes graft failure and GVHD.
- Previous work has shown that targeting allo-reactive T-cells leads to immunotolerance.
- Basic principle: antigen stimulation → proliferation of T-cells → selective elimination of proliferating allo-reactive T-cells.

Luznick et al. *Blood*. 115:3224-30. 2010.

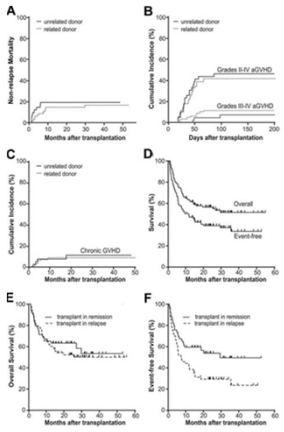
Post-Transplant Cy as Prophylaxis



Post-Transplant Cyclophosphamide (Cy) as sole GVHD Prophylaxis

- 117 patients with various hematologic malignancies treated.
- Incidence of Acute GVHD II-IV and III-IV was 43% and 10%.
- Day 100 NRM was 9%.
- Low infection Rates.
- Chronic GVHD incidence was 10%.
- Only 3 patients remained on immunosuppression at last follow-up.

Luznick et al. *Blood*. 115:3224-30. 2010.



Luznick et al. *Blood*. 115:3224-30. 2010.

Can Post-transplant CY be used with less intense Conditioning?

MD Anderson Protocol 2008-0261: Reduced Intensity Bu/Flu followed by Post-transplant Cy for Older-age / Frail Pts with Hematologic Malignancies

Alousi. ASH. 2012.
Alousi et al. *BBMT*. In press. 2015

Treatment Plan

Day -8	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day-1	0	+1	+2	Day +3	Day +4
BU Test Dose 32mg/m²	Rest	BU	BU	BU	BU							
		FLU 40 mg/m2	FLU 40 mg/m2	FLU 40 mg/m2	FLU 40 mg/m2						CY** 50 mg/kg	CY** 50 mg/kg
					ATG*	ATG*	ATG*					
								BMT ***				

* Only MUD's received ATG
** No additional immunosuppression unless developed GVHD
*** Bone Marrow preferred (but not mandated) over Peripheral Blood HCT

Alousi. ASH. 2012.
Alousi et al. *BBMT*. In press. 2015

Post-transplant CY vs. Matched-Controls** Tacrolimus/MTX in RIC HCT

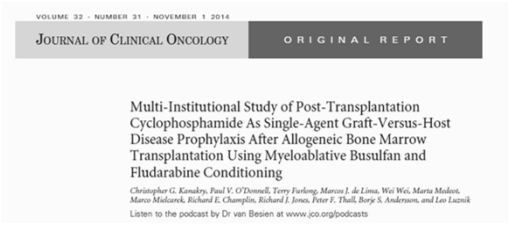
	Post-Transplant CY (n=37)* % (95% CI)	Tacrolimus/MTX (n= 37) % (95% CI)	Hazard Ratio	P Value
Acute GVHD Gd II-IV	46% (32-65)	19% (10-37)	3.2	0.009
Acute GVHD Gd III/IV	14% (6-32)	0		0.02
Chronic GVHD @ 1 yr	20% (10-39)	22% (12-40)	1.0	0.9
NRM @ 2 years	35% (23-54)	13% (6-30)	3.3	0.04
OS @ 2 years	30% (16-45)	52% (35-67)	1.9	0.04

* 49 patients enrolled for which matching could be done for 37/47 (non-matched patient outcomes did not differ).

** Patient matching using a computer generated algorithm matching in order of priority: Age, Diagnosis, Disease Status, Donor Type, Graft Source

Alousi. ASH. 2012.
Alousi et al. *BBMT*. In press. 2015

Two Trials of Bu/Flu followed by Post-CY: Kanakry et al. vs. Alousi et al.


VOLUME 32 · NUMBER 31 · NOVEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Multi-Institutional Study of Post-Transplantation Cyclophosphamide As Single-Agent Graft-Versus-Host Disease Prophylaxis After Allogeneic Bone Marrow Transplantation Using Myeloablative Busulfan and Fludarabine Conditioning

Christopher G. Kanakry, Paul V. O'Donnell, Terry Furlong, Marcos J. de Lima, Wei Wei, Marta Medeot, Marco Mielcarek, Richard E. Champlin, Richard J. Jones, Peter F. Thall, Borje S. Andersson, and Leo Luznik

Listen to the podcast by Dr van Besien at www.jco.org/podcasts

- Bu/Flu MA: AUC 5,000 (**vs. 4,000**)
- Median Age: 49 years (**vs.62 years with a median CMI of 3**)
- Acute GVHD II-IV: 51% (**vs. 53%**)
- Acute GVHD III/IV: 15% (**vs. 22%**)
- Chronic GVHD: 14% (**vs. 18%**)
- Relapse: 22% (**vs. 26%**)
- OS @ 2 years: **67% (vs. 33%)**

- Identical Rates of GVHD but differing Survival
- Impact of Higher rates of Acute GVHD in older, more frail population.
- NRM related to GVHD differs based on patient population.

Post-CY

- Post-transplant CY may need to be combined with additional immunosuppression when used with less intensive conditioning and/or older/frailer patients.
- Post-transplant CY has combined with Tacrolimus/MMF
  - Studied in recipients of T-cell replete bone marrow grafts from haploidentical donors following non-myeloablative conditioning with low rates of GVHD.
  - Incidence of Acute GVHD II-IV 34%
  - Incidence of Extensive Chronic GVHD 5%.

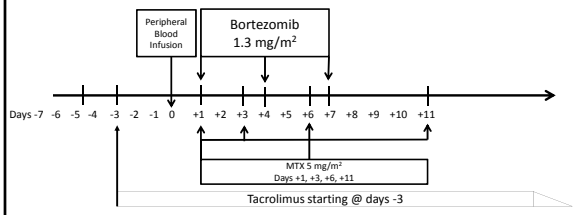
Luznik et al. *BBMT*. 14: 641-50. 2008.

Bortezomib for GVHD Prevention

- Proteasome inhibitor bortezomib has immunomodulatory properties that may be beneficial as GVHD prophylaxis.
- Researchers at the Dana-Farber performed a Phase I/II study in 45 recipients of T-cell replete, peripheral blood grafts from 1 or 2-loci MM Unrelated Donors following RIC.
- Bortezomib was given on Days +1, +4, +7 in combination with Tacrolimus/Methotrexate.

Koreth et al. *JCO*. 30: 3202-8. 2012

Bortezomib for GVHD Prophylaxis Treatment Schema



Koreth et al. *JCO*. 30: 3202-8. 2012.

Bortezomib for GVHD Prevention

- Acute GVHD II-IV and III/IV @ Day 180= 22% and 7%.
- Chronic GVHD @ 1 –year= 29%.
- NRM @ 2-years= 11% with minimal toxicity from study drug.
- GVHD and Survival outcomes compared favorably to a contemporaneous Cohort who received a 8/8 MUD PB HCT with Sirolimus-based GVHD prophylaxis at their center.

Koreth et al. *JCO*. 30: 3202-8. 2012

Prevention of GVHD through Controlling T-cell Trafficking to GVHD target tissues

Modified Billingham's Criteria: Requirements for GVHD

- Graft must contain immunocompetent cells.
- Host cells must have antigens (proteins) for which the graft cells recognize as foreign.
- The host must be unable to mount an attack against the graft (must be immunosuppressed).
- ***Effector cells have to traffic to GVHD organs.***

Background for Maraviroc Phase I/II Trial

- Chemokine Receptor 5 and its natural ligands CCL3/4 and 5 have been implicated in the pathogenesis of GVHD and solid organ rejection.
- Maraviroc (MVC) is the first drug in the class of CCR5 antagonists.
- Noncompetitive, slowly reversible small-molecule antagonist that prevents signaling by all three ligands.
- Drug is licensed for use in combination therapy for patients infected with a HIV subtype which is dependent solely on the CCR5 co-receptor to enter cells (CCR5-tropic HIV).

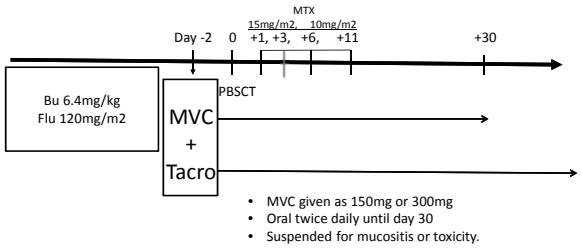
Reshef R et al. *N Engl J Med*. 367:135-45. 2012.

Background Studies for Phase I/II Study

- Hypothesized that MVC use early after allogeneic HCT might inhibit lymphocyte trafficking and decrease the incidence of acute GVHD (especially Gut and Liver).
- Good Safety Profile
  - No effect on T cell function.
  - In vitro tests on CD8+ T cells exposed to CMV peptide in presence or absence of MVC demonstrated no impact on antigen-specific proliferation and cytotoxicity.
  - No impact stem cell proliferation.

Reshef R et al. *N Engl J Med*. 367:135-45. 2012.

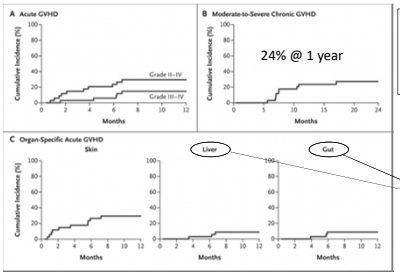
Treatment Schematic: Phase I/II Study



- MVC given as 150mg or 300mg
- Oral twice daily until day 30
- Suspended for mucositis or toxicity.

Reshef R et al. *N Engl J Med*. 367:135-45. 2012

Clinical Trial Outcomes of Acute GVHD, Moderate-to-Severe Chronic GVHD, and Organ-Specific Acute GVHD.



24% @ 1 year

- Gd II-IV: 14.7%
- Gd III/IV: 2.9%
- Day 180 Gd II-IV: 24%
- Day 180 III/IV: 6%

- Minimal GI and Liver GVHD

Reshef R et al. N Engl J Med 2012.

BMT CTN Protocol 1203
A Randomized, Multi-center, Phase II Trial Comparing Novel Approaches for Prevention of Graft-versus-Host Disease

- Age > 18 years
- All Diseases
- Marrow Remission or Chemosensitive tumor
- MRD or MUD Donors
- Peripheral Blood
- RIC/NMA Conditioning

Post-transplant Cy + Tacrolimus/ MTX

Maraviroc + Tacrolimus/ MTX

Bortezomib + Tacrolimus/ MTX

Prospectively Matched CIBMTR Cohort

Acute GVHD Therapy

Therapy of Acute GVHD

- Grade I (Less than 50% BSA Rash):
  - Initial therapy is usually topical steroids alone.
  - Systemic Steroids given for rash that persists/ worsens or new organ.
- Isolated Upper GI GVHD:
  - High response Rate with Prednisone 1mg/kg followed by rapid taper with or without non-absorbable steroid.

Therapy of Acute GVHD

- Grade II-IV Acute GVHD:
  - Standard Therapy: Methylprednisone (or Prednisone) @ 2mg/kg.
  - Day 28 RR is approximately 55%, worst for Lower GI versus other organs.
  - What is the appropriate steroid starting dose?
  - No improvement in response rate or outcome by addition of 2nd agent.
    - ATG
    - Anti-interleukin-2 Receptor Antibodies (Daclizumab)
    - Anti-TNF alpha agent (infliximab)
    - Mycophenolate mofetil

Initial Dose of Steroids for Acute GVHD

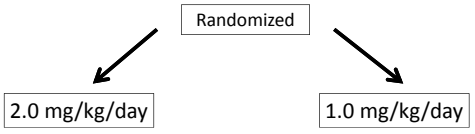
- Prospective randomized study of high versus low dose steroids:
  - Grade IIa AGVHD (Upper GI GVHD, Stool Volume < 1 liter, rash <50% and no liver involvement)

Prednisone-equivalent dosing

Mielcarek. ASH. 2013

Initial Dose of Steroids for Acute GVHD

- Prospective randomized study of high versus low dose steroids:
  - Grade IIb to IV AGVHD (Rash ≥ 50% BSA, Stool Volume > 1 liter and any liver involvement)



Prednisone-equivalent dosing

Mielcarek. ASH. 2013

No Impact on Reduction in Cumulative Dose

- Primary Outcome: 33% Reduction in Day 42 Cumulative Dose of Steroids.
  - Grade IIa Cohort: 1mg/kg vs. 0.5mg/kg/day Initial Dose 27mg/kg vs. 22 mg/kg (18% reduction, p=0.08)
  - Grade IIb-IV Cohort: 2mg/kg vs. 1mg/kg/day Initial Dose 41mg/kg vs. 38mg/kg (7% reduction, p=0.4)

Mielcarek. ASH. 2013

No Impact on Reduction in Cumulative Dose

- Secondary Outcomes:
  - Measures of prednisone toxicity (infections, hyperglycemia)
  - possible harm (progression to Grade III/IV GVHD, secondary therapy for refractory GVHD, non-relapse mortality, recurrent malignancy).
- Grade IIb-IV Cohort:
  - No difference in NRM, Relapse and OS.
  - Patients who started treatment with lower-dose prednisone were more likely to require secondary systemic immunosuppressive therapy than those who started treatment with higher-dose prednisone (41% vs 7%, p=0.001)
  - Trend suggested an increase in the risk of progression to Grade III-IV acute GVHD (19% vs 7%, p=0.2).
  - The risks of infection and measures of glycemic control were not affected by initially assigned prednisone dose.

Mielcarek. ASH. 2013

Conclusions:

- Acute GVHD Limited to Upper GI GVHD and Skin Rash <50%.
  - Patients started on 0.5mg/kg/day vs. 1mg/kg/day:
    - Trend for lower cumulative dose of steroids
    - No impact on secondary outcomes (benefit or adverse effect).
- Rash >50%, Stool > 1 Liter and/or Liver Involvement.
  - **2mg/kg/day should remain the starting dose.**
    - No Reduction in Cumulative Dose
    - Worst secondary Outcomes (much more likely to need secondary therapy and trend for progression to higher grade GVHD).

Incorporation of Biomarkers to Identify High-Risk Patients with New Onset GVHD

Who are the patients identified as High-Risk?

Answer:

Patients with or who will develop Unresponsive lower GI GVHD.

* Slides and Data Compliments of John Levine EEBMT. 2014. *(Lancet Oncology In Press)*

ANN ARBOR SCORES BIOMARKERS AND GI GVHD

- TNFR1: TNFα amplifies GI injury
  Schmaltz Blood 2003
- ST2 and its ligand IL33 regulate inflammatory bowel disease activity
  Pastorelli PNAS 2010
- REG3α protects intestinal epithelial cells from damage
  Ogawa Inflamm Bowel Disease 2003
- 80% of GVHD-related NRM occurs in pts with poorly responsive GI GVHD
  unpublished data (UM/Regensburg)

* Slides and Data Compliments of John Levine EEBMT. 2014. *(Lancet Oncology In Press)*

Acute GVHD Clinical Grade and Biomarker Grade (called Ann Arbor) @ GVHD Onset

Acute GVHD Clinical Grade (Glucksberg Grading)	Ann Arbor I (Biomarker Grade)	Ann Arbor II (Biomarker Grade)	Ann Arbor III (Biomarker Grade)
Grade I (n=51)	23%	59%	18%
Grade II (n=183)	25%	56%	19%
Grade III/IV (n=69)	26%	49%	25%
Total: 303 patients	25%	55%	20%

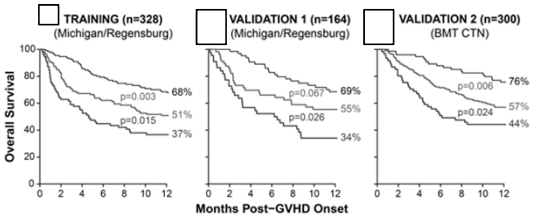
Biomarker Grading Can Outperform Clinical Grading by Identifying Seemingly Low-Risk Patients who are Actually High-Risk and vice-versa

GVHD BIOMARKER SCORES

- Goal: Identify high risk patients at **onset** (not max)
  - 3 biomarkers: TNFR1, ST2, REG3α
- Onset GVHD samples
  - 492 UM and Regensburg pts (training and validation)
  - 300 BMT CTN pts (multicenter validation)
- Use of 6 mo NRM as clean objective endpoint
  - Statistical model in training set (n=328) provides NRM probability for each patient
- Rank order the probabilities and identify thresholds that stratify patients such that 6m NRM:
  - **Ann Arbor 1: ≤10%**
  - **Ann Arbor 2: 10%-40%**
  - **Ann Arbor 3: ≥40%**
- Correlate scores with d28 treatment response
- Validate thresholds in two independent cohorts

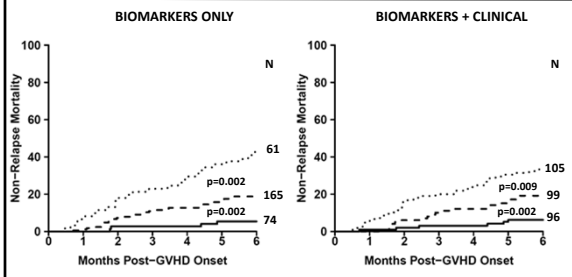
* Slides and Data Compliments of John Levine EEBMT. 2014. *(Lancet Oncology In Press)*

ANN ARBOR GVHD SCORES



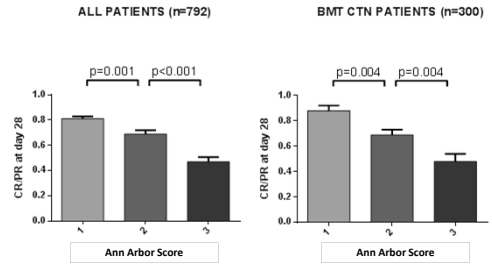
* Slides and Data Compliments of John Levine
EEBMT. 2014. *(Lancet Oncology In Press)*

BMT CTN (n=300)



* Slides and Data Compliments of John Levine
EEBMT. 2014. *(Lancet Oncology In Press)*

TREATMENT RESPONSE



* Slides and Data Compliments of John Levine
EEBMT. 2014. *(Lancet Oncology In Press)*

SUMMARY

- Identifies a high risk population across clinical severity presentations
  - Ann Arbor 3 GVHD = ~22% of mild, moderate, or severe GVHD
- Ann Arbor 3 enriches for HR GI GVHD
- Incorporating clinical grading into the algorithm does not improve stratification but increases size of strata 1 and 3
- (Similar effect on strata size can be achieved by adjusting thresholds in the biomarkers only algorithm)

* Slides and Data Compliments of John Levine
EEBMT. 2014. *(Lancet Oncology In Press)*

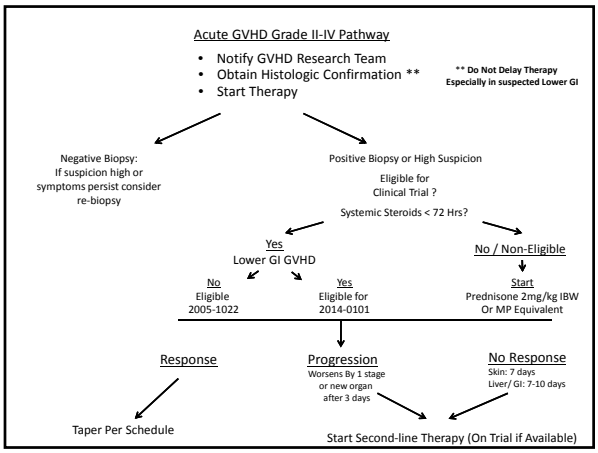
Evaluation of GI GVHD

- Have an institutional pathway for patients with suspected GI GVHD.
- Admit when need to expedite work-up or for severe symptoms (unable to tolerate diet, severe diarrhea resulting in dehydration).
- Flex Sigmoid with Random Rectal Biopsies correlates with Pathology from Proximal Bowel.
- EGD (with duodenal biopsy) + Flex Sig has highest yield.*
- Do not give Prep with flex sig as can induce grade 1 histologic changes in path.

* Alousi & Ross. *BMT*. 47: 321-2. 2012
Ross et al. *Am J Gastroenterol*. 103: 982-9.2005

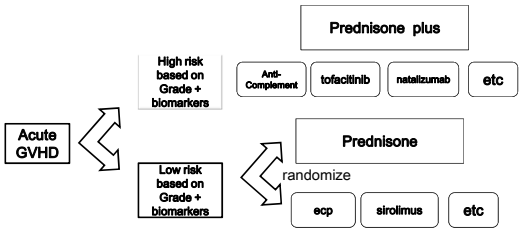
Most Important Slide of Lecture!!

Do Not Delay Therapy for Lower GI GVHD



ACUTE GI GVHD

- **Assessment**
  - History and Physical
  - Consider Admission to Expedite Work-up and Treatment
  - Strict I/O
  - Measurement and evaluation of stool
- **Diagnosis**
  - GI Consult
  - Upper endoscopy and/or flex sigmoidoscopy / colonoscopy
  - **DO NOT** wait for completion of these procedures to start systemic therapy
  - Stool culture for: *C.difficile*
- **Interventions**
  - Diet as tolerated
  - Dietary consult: Diet As Tolerated *(Lack if Evidence for GVHD Graduated Diet)*
  - Perianal skin care: Sitz baths and NDX cream (nystatin, zinc oxide, lidocaine)
  - Physical Therapy consult
  - Endocrine consult
- For lower GI GVHD +/- upper GI GVHD: SYSTEMIC THERAPY – Clinical Trial
  - ****Contact GVHD attending or research nurse****
  - **First-line therapy:** Prednisone 2 mg/kg/day PO as two divided doses or methylprednisolone equivalent IV/PO (based on IBW).
  - Continue tacrolimus IV or PO as clinically appropriate
  - **Suggested Second-line therapy**: MMF, Pentostatin, ECP, Infliximab/Etanercept
- **Supportive care options to consider:**
  - Loperamide +/- dipenoxylate/atropine
  - Octreotide 250 to 500 mcg IV q 8 hrs if diarrhea volume > 500 ml after 24 hours of loperamide and/or diphenoxylate/atropine or tincture of opium
  - Stop octreotide as soon as diarrhea has resolved, but re-assess every 4 to 7 days
  - If no response at 4 to 7 days continuing octreotide is **NOT** recommended
  - Budesonide 3 mg PO TID



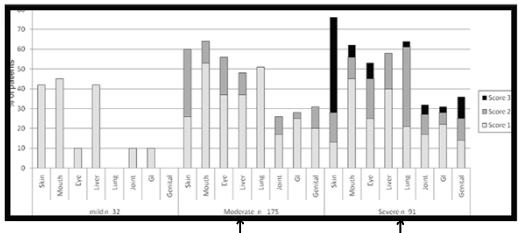
- The overall trial design depends on assignment to a high or low risk group based on GVHD grade and biomarkers.
- High risk patients will be treated with prednisone, and new agents will be serially studied by addition to standard prednisone therapy.
- Low risk patients will be randomized between a prednisone monotherapy or one of several single agent non-steroid alternatives.

Chronic GVHD

Who Needs Systemic Treatment?

Chronic GVHD manifestations based on Global Severity Score	Systemic Treatment Needed
Mild	
• ≤ 2 sites involved (no lung), all with mild scoring on Global Severity Score (asymptomatic or symptoms not interfering function), no high risk features*	No
• ≤ 2 sites involved (no lung), all with mild scoring on Global Severity Score (asymptomatic or symptoms not interfering function), but with high-risk features*.	Yes
• ≤ 2 sites but one is lung.	Yes
• > 2 sites.	Yes
Moderate or Severe	
Any site	Yes
* High-risk feature: Platelets < 100,000, skin involvement > 50% BSA, Progressive-Onset Chronic GVHD (already being treated with steroids > 0.5mg/kg) at chronic manifestation onset.	

Individual organ severity scoring within global severity categories



More than 90% of Patients will have Moderate Or Severe Chronic GVHD Based On NIH Severity Scoring

Arai S et al. Blood 2011;118:4242-4249

Treatment of Chronic GVHD

- Steroids 1mg/kg +/ - CNI
- No FDA Approved Therapy for Chronic GVHD
- Previous Randomized Study of MMF closed early due to higher death (and trend for higher relapse) in MMF arm compared to steroids alone
  - Martin et. al. *Blood*. 113: 5074-82. 2009.
- Large Case Series for ECP in chronic GVHD.
- Randomized study of ECP/ steroids versus steroids, what was learned?
  - Flowers et al. *Blood*. 112: 2667-74. 2008.
  - Greinix et al. *BBMT*. 17:1775-82. 2011.

Prospective, Randomized Control Trial of ECP in Chronic GVHD

- Only published prospective, randomized control trial of ECP in chronic GVHD.
- This single-blind, multicenter study randomized 100 patients in a 1:1 ratio to ECP therapy in addition to conventional immunosuppression *versus* conventional immunosuppression alone.
- Eligible patients received at least 2 weeks of steroids and were considered steroid-refractory, dependent or intolerant.

Flowers M E D et al. Blood 2008;112:2667-2674

Prospective, Randomized Control Trial of ECP in Chronic GVHD

- ECP was administered on 3 days for the first week, and then twice weekly (on consecutive days) through 12 weeks.
- Patients in the ECP arm who responded were allowed to continue with 2 ECP sessions every 4 weeks until week 24.
- Control arm patients were allowed to cross-over to ECP if progressed or after completion of 12 weeks.

Flowers M E D et al. Blood 2008;112:2667-2674

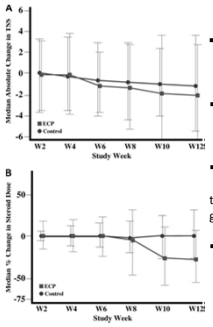
Prospective, Randomized Control Trial of ECP in Chronic GVHD

- The primary objective of was to determine the effect of ECP treatment on the cutaneous manifestations of cGVHD at week 12.
- Skin was the only organ studied in primary study.
- Non- (or *poorly*) validated Total Skin Score was used as primary measure of response.
- Blinded, trained expert assessed baseline and 12 week evaluation.

Flowers M E D et al. Blood 2008;112:2667-2674

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Improvement in Total Skin Score (TSS) and reduction in steroid dose through week 12.

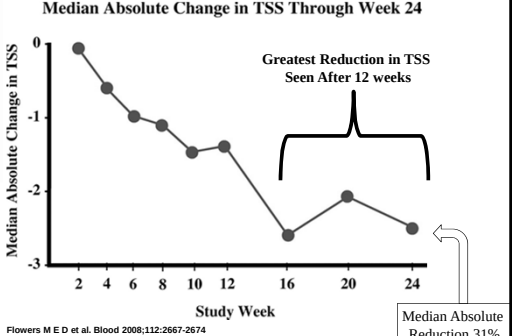


- Median changes in TSS from baseline until week 12: **ECP(14.5%)** and **control (8.5%)** arms were not statistically different (p=.48).
- **25.0% (n 12) of ECP-patients** and **12.8% (n 6) of control-patients** had a >/= 50% reduction in steroids (*P* .13).
- % of patients having both a 50% or > reduction in daily steroid dose and a 25% or > reduction in the TSS was higher in the ECP group than the control group (**8.3%; 4 patients** vs **0%; 0 patients**; *P* .04).
- **20.8% the ECP-patients** and **6.4% of the control-patients** had a 50% or > reduction in steroid dose and a daily dose of < 10 mg/day (*P* .04).

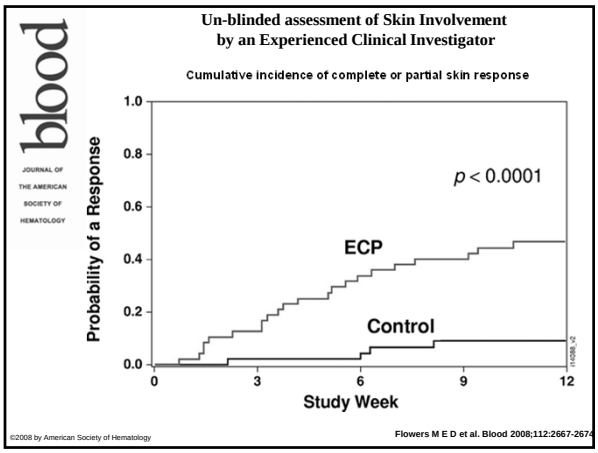
Flowers M E D et al. Blood 2008;112:2667-2674

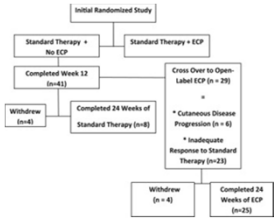
blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Median absolute change in TSS through week 24 in ECP Patients.



Flowers M E D et al. Blood 2008;112:2667-2674





Disposition of patients enrolled in initial randomized and crossover open-label ECP study.

Hildegard T. Greinix , Koen van Besien , Ahmet H. Elmaagacli , Uwe Hillen , Andrew Grigg , Robert Knobler , Dennis...

Progressive Improvement in Cutaneous and Extracutaneous Chronic Graft-versus-Host Disease after a 24-Week Course of Extracorporeal Photopheresis—Results of a Crossover Randomized Study

Biology of Blood and Marrow Transplantation, Volume 17, Issue 12, 2011, 1775 - 1782

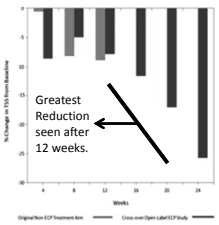


Figure 2 Comparison of percent decrease in total skin score (TSS) between patients of initial non-ECP standard therapy and crossover open-label ECP treatment.

Hildegard T. Greinix , Koen van Besien , Ahmet H. Elmaagacli , Uwe Hillen , Andrew Grigg , Robert Knobler , Dennis...

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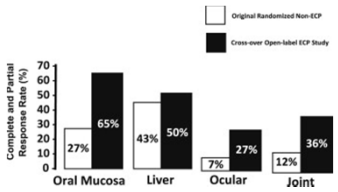
http://dx.doi.org/10.1016/j.bbmt.2011.05.004



Complete and partial response of extracutaneous manifestations during standard non-ECP therapy and after crossover to adjunct ECP: comparison of results after 12 weeks.

Hildegard T. Greinix , Koen van Besien , Ahmet H. Elmaagacli , Uwe Hillen , Andrew Grigg , Robert Knobler , Dennis..

Progressive Improvement in Cutaneous and Extracutaneous Chronic Graft-versus-Host Disease after a 24-Week Course of Extracorporeal Photopheresis—Results of a Crossover Randomized Study

Biology of Blood and Marrow Transplantation, Volume 17, Issue 12, 2011, 1775 - 1782

How Do We Know if Our Chronic GVHD Therapy is Working?

How do we measure response?

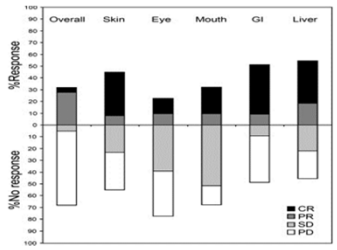
Clinical Benefit of Response in Chronic Graft-versus-Host Disease

Inamoto / Lee et al.
on behalf of the Chronic GVHD Consortium.
Biology of Blood and Marrow Transplant. 18: 1517-24. 2012

Chronic GVHD Patient Consortium

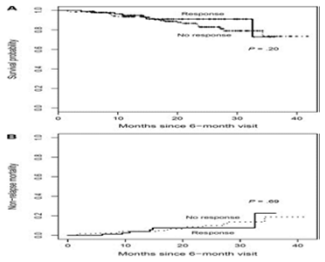
- 283 patients prospectively assessed.
- Roughly 80% “Overlap”/ 20% “Classic” Chronic
- Median age was 51 years (2-79)
- Skin, Mouth, liver, lungs and Eyes most commonly involved.
- 28% severe, 59% moderate and 13% mild chronic GVHD based on NIH Severity Classification.

Calculated response overall and in individual organs at 6 months after enrollment, according to the provisional algorithm



Clinical Benefit of Response in Chronic Graft-versus-Host Disease
Yoshihiro Inamoto , Paul J. Martin ,et al.
Biology of Blood and Marrow Transplantation.2012

Survival outcomes according to overall response at 6 months. (A) OS. (B) NRM.



Inamoto , Lee, et al
Clinical Benefit of Response in Chronic Graft-versus-Host Disease
Biology of Blood and Marrow Transplantation. 2012. 1517 – 1524.

NIH Consensus Response Does not Translate into improvement in QOL

QOL Measure	Clinical Meaningful Change	Prevalent Cases		Incident Cases	
		Estimated Difference	P-value	Estimated Difference	P-value
SF-36 PCS	4.8	0.9	0.62	1.2	0.52
SF-36 MCS	5.2	0.9	0.64	0.1	0.95
FACT-BMT	9.9	5.4	0.09	2.3	0.48
HAP-MAS	6.3	4.0	0.14	21.9	0.50
HAP-AAS	8.3	3.5	0.24	1.0	0.74

Inamoto , Lee, et al
Clinical Benefit of Response in Chronic Graft-versus-Host Disease
Biology of Blood and Marrow Transplantation. 2012. 1517 – 1524.

How Do we Assess Response?
Answer: We have No Idea !!

- "Physician Knows Best": not stringent, too subjective.
- NIH Global Severity Response Assessment: too stringent and inadequately captures clinically meaningful responses.

Challenging (if not impossible) to show benefit in a randomized study in Chronic GVHD when there is no valid end-point:

How does one define (show) response (benefit)?

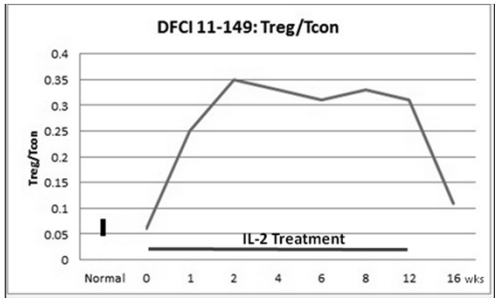
Looking Ahead: We need to know how to study this disease!!!

Thinking Ahead: Strategies for Increasing Tregs in Patients with Chronic GVHD

- ECP
- Rapamycin
- Ex-vivo Expanded Tregs
- Low-dose IL-2

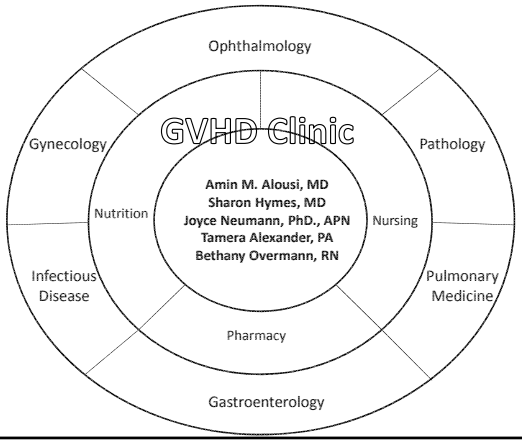
ASH 2014: *Low-Dose IL-2 for Steroid Refractory Chronic GVHD: Phase 2 and Long Term Efficacy, Safety and Immune Correlates.* **Koreth et al.**

- 35 Patients with St.-Refractory chronic GVHD, Median 4 organs involved, Median of 2 concurrent therapies at enrollment, median dose of steroids was Prednisone 20mg.
- Dose 1x 10^6 IU/m^2/day Sub-Q for 12 weeks.
- Well tolerated: 2 patients withdrew; 5 patients (out of 35) requiring dose reduction.
- Objective Response Rate at week 12 was 21/33 patients with 2 patients progressing.



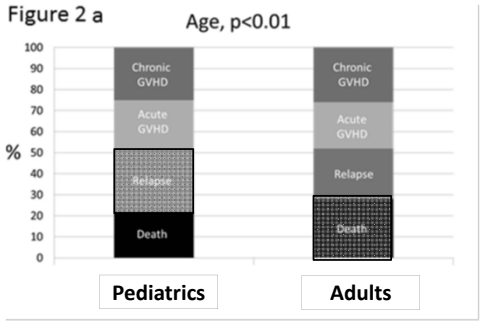
"It Takes a Whole Medical Center to Care for a BMT Patient"

- Gynecology
- Nursing
- Pharmacy
- Pulmonary Medicine
- Radiology
- Pathology
- Dermatology
- Ophthalmology
- Transfusion Services
- Gastroenterology
- Infectious Disease
- Nutrition

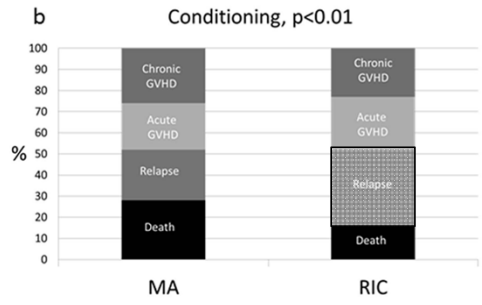


The M.D. Anderson Cancer Center

Impact of Age on GFRS: Pediatrics- Relapse Accounts for Higher Amount of Failures; Adults- Death without Relapse or GVHD



Conditioning Impact on GFRS: Relapse Accounts for Higher Amount of Failures in RIC



Patient Characteristics

Characteristic	ECP + Steroids N=48	Control Arm N=47
Median Age, years	41	43
Corticosteroid-status		
• Corticosteroid-dependent	28 (58%)	25 (53%)
• Corticosteroid-refractory	7 (15%)	5 (11%)
• Corticosteroid-intolerant	13 (27%)	17 (36%)
Median days from BMT to cGVHD (range)	140 (69-637)	129 (70-1389)
Median days from cGVHD to randomization (range)	569 (35-2743)	630 (1-2253)
Onset type of cGVHD, n (%)		
• Progressive	28 (58%)	25 (53%)
• Quiescent	5 (10%)	6 (13%)
• de novo	15 (32%)	16 (34%)
TSS at baseline, median (range)	9.4 (0.6-23.6)	9.2 (1.0-20.7)

Flowers M E D et al. Blood 2008;112:2667-2674

Patient Characteristics (continued)

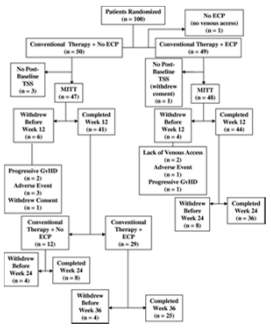
Characteristic	ECP + Steroids N=48	Control Arm N=47
Extracutaneous GVHD involvement, n (%)		
• Ocular	27 (56.3%)	28 (59.6%)
• GI	2 (4.2%)	9 (19.1%)
• Liver	14 (29.2%)	14 (29.8%)
• Lung	9 (18.8%)	7 (14.9%)
• Oral mucosa	30 (62.5%)	30 (63.8%)
• Joints	18 (37.5%)	16 (34%)
Median duration (wks) of corticosteroid usage for cGVHD before study entry (range)	50 (2.7-426)	55 (1.9-319)

Flowers M E D et al. Blood 2008;112:2667-2674

blood

JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Disposition of patients enrolled into the study.



Flowers M E D et al. Blood 2008;112:2667-2674

Audience Response Question #1

Which of the following statements is true regarding the interaction of gvhd, gvhd therapy and relapse:

A. Acute GVHD III/IV is associated with less relapse than lower grades acute gvhd.
B. Patients who have both acute and chronic gvhd have a lower likelihood of relapse than patients with just acute or chronic.
C. GVHD protects from early relapse (relapse which occurs in the first 18 months post-HCT.
D. Treating patients who have GVHD does not increase their risk of relapse.

Audience Response Question #2

GVHD-Free, Relapse-Free Survival [GRFS] is a new composite endpoint which defined as being Alive, in Remission, without history of Grade III/IV Acute GVHD and without Chronic GVHD that requires systemic treatment. At 1-year, what is the estimated likelihood that a recipient of an allogeneic HCT will meet this definition:

A. 15-25%
B. 25-35%
C. 35-50%
D. 50-65%

Audience Response Question #3

With respect to anti-thymocyte globulin (ATG) for GVHD prophylaxis, which is a true statement:

A. Fresenius ATG has been shown to lower the incidence of chronic GVHD in a randomized, control trial in recipients of MUD grafts following myeloablative conditioning.

B. It is clearly been shown that the benefits of ATG extend to all forms of conditioning intensity (ablative versus non-myeloablative).

C. Outcomes are the same regardless of the dose of rabbit ATG as long as the total dose is less than 10mg/kg.

D. All the above are true.

Audience Response Question #4

With respect to initial dose of corticosteroids in patients with newly-diagnosed acute GVHD, a single-center, randomized trial of 1mg/kg versus 2mg/kg for patients with grades IIb and higher (rash more than 50%, stool output more than 1 liter/day and/ or any liver involvement) showed that patients randomized to 1mg/kg experienced which of the following:

A. Less toxicity (infections and need for insulin).

B. Lower Cumulative Dose of Steroids.

C. Higher likelihood of needing a second-line therapy.

D. Less likely to progress to higher grade acute GVHD.

Audience Response Question #5

Which is true regarding treatment of patients with chronic GVHD:

A. The 2005 NIH Consensus Guidelines for measuring response to therapy have been validated and shown to correlate with non-relapse mortality and quality-of-life.

B. Newer strategies are focusing on methods of increasing regulatory T-cells (T regs) to promote tolerance.

C. Patients with 2 organs involved, all classified as mild severity on NIH scoring generally are treated with systemic steroids.

D. All of the above.