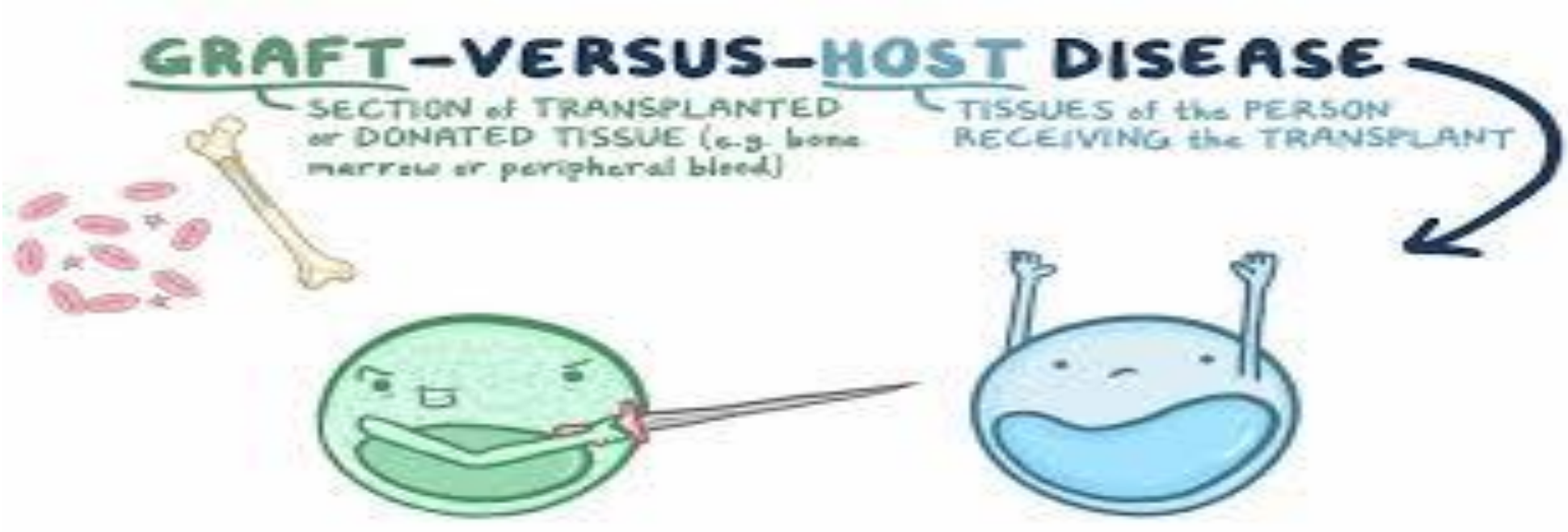
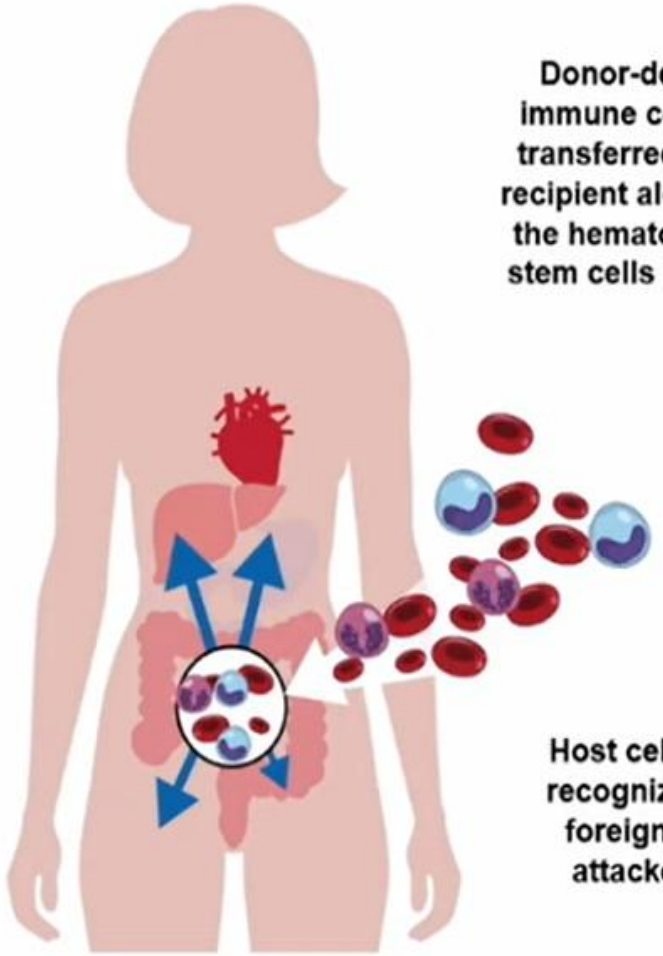


GVHD PROPHILAXIS

DR SAYRH PARKHIDEH

TALEGHANI HOSPITAL

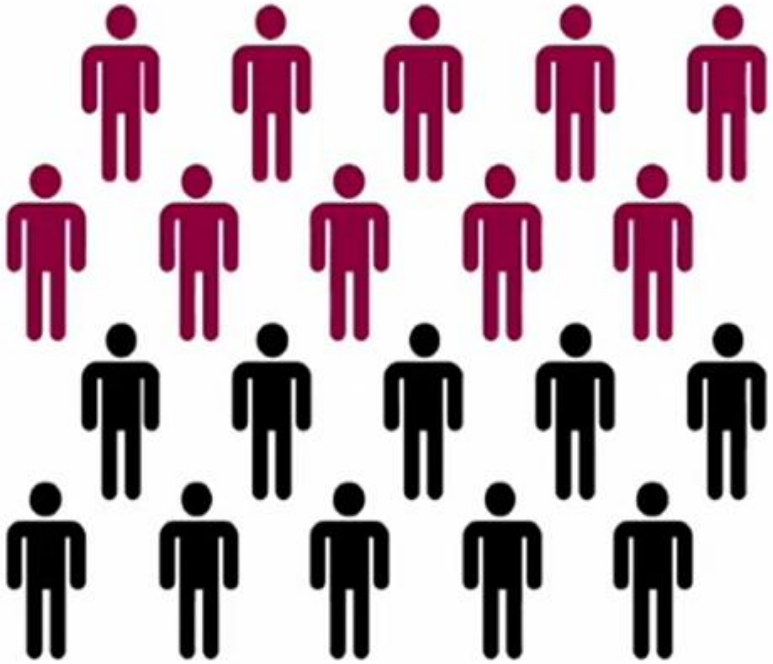
GvHD is a major complication of alloSCT



Donor-derived immune cells are transferred to the recipient along with the hematopoietic stem cells (graft)[1,2]

Host cells are recognized as foreign and attacked[1,2]

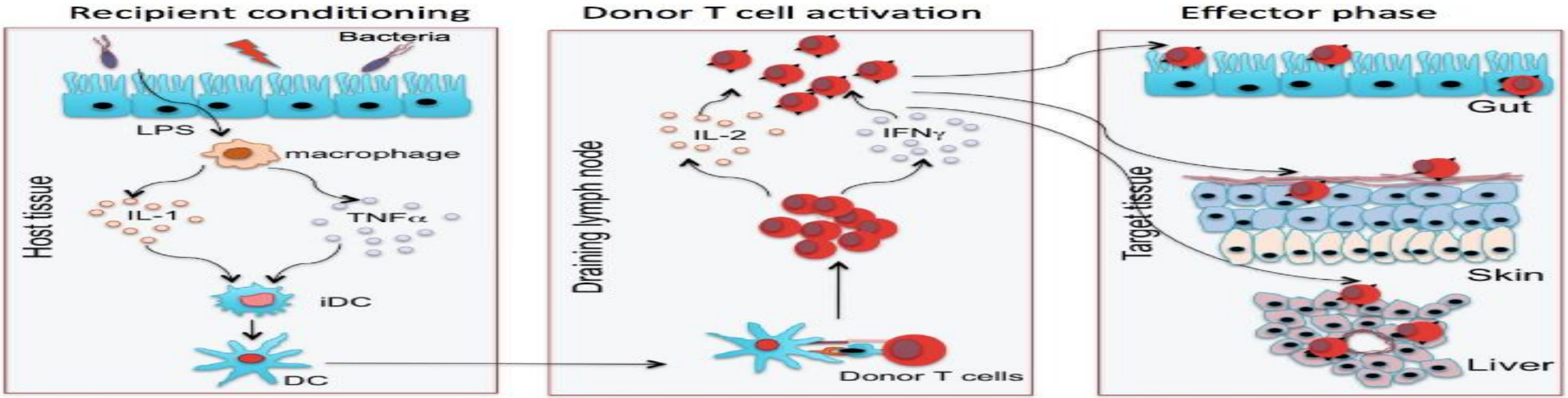
- Up to 50% of patients develop GvHD, despite immunosuppressive prophylaxis[3-5]



alloSCT, allogeneic stem cell transplant; GvHD, graft-versus-host disease.

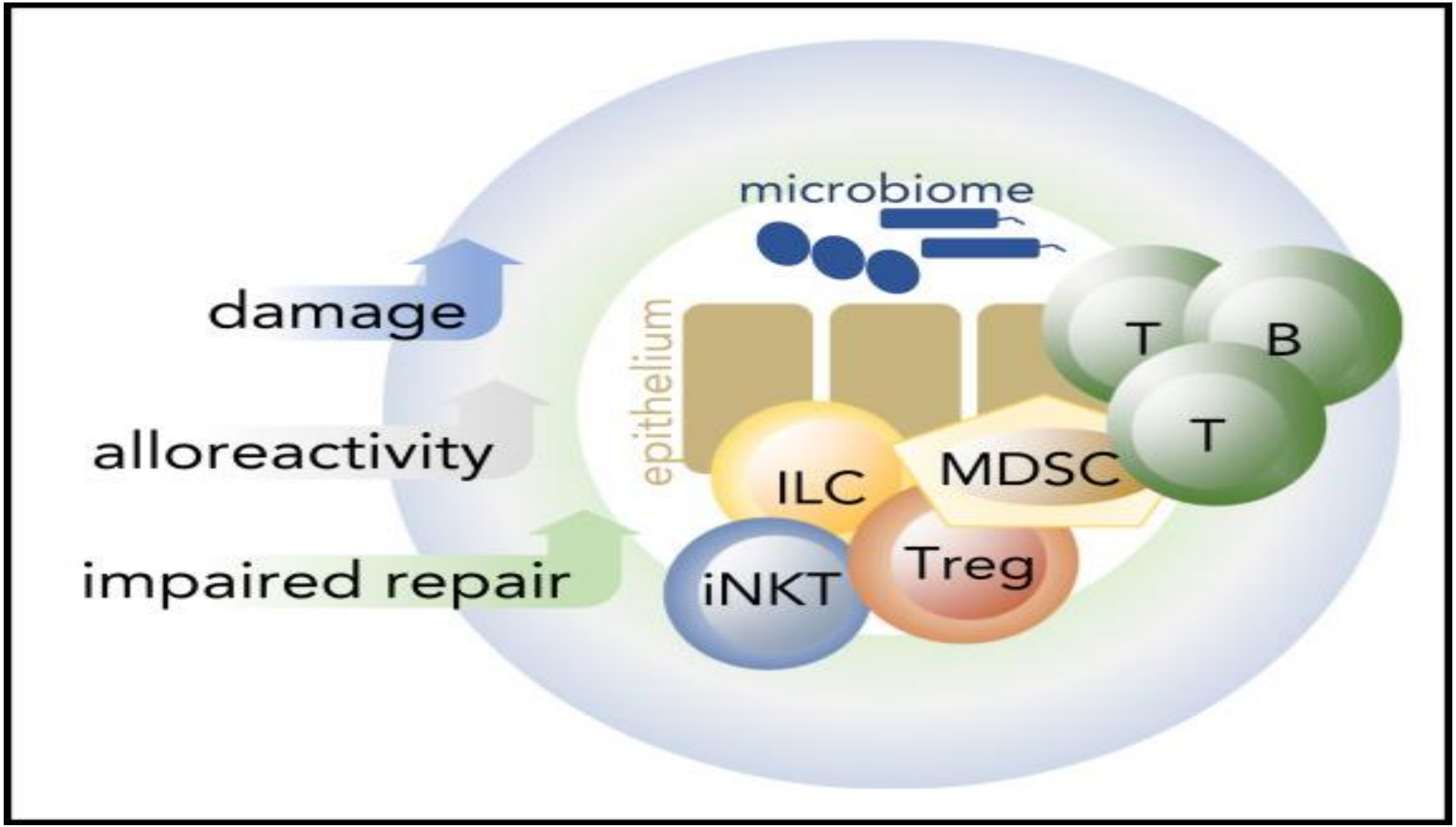
1. Ferrara JL, et al. Lancet. 2009;373:1550-61. 2. Spoerl S, et al. Blood. 2014;123:3832-42. 3. Zeiser R, Blazar BR. N Engl J Med. 2017;377:2167-79. 4. Jagasia M, et al. Immunotherapy. 2018;10:391-402. 5. Martin PJ, et al. Biol Blood Marrow Transplant. 2012;18:1150-63.

Pathophysiology of Graft versus Host Disease



Pathophysiology of aGvHD

Phase 1: recipient-conditioning tissue damage	Phase 2: donor T cell activation	Phase 3: target tissue destruction
• Conditioning regimens damage tissues	• Host APCs activate donor T cells	• T cells migrate to target tissues and cause tissue destruction
• Inflammatory cytokines, such as TNF-α, IL-1, and IL-6, are released	• T cells proliferate and differentiate into different subsets	• Th1 cells promote proliferation and differentiation of CTLs and stimulate NK cells, inducing apoptosis via effector molecules (e.g. perforin, granzymes, IFN-γ)
• Host APCs are activated		


damage
alloreactivity
impaired repair
microbiome
epithelium
T
B
T
ILC
MDSC
Treg
iNKT

Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria

Mary E. D. Flowers,[1,2] Yoshihiro Inamoto,[1] Paul A. Carpenter,[1,3] Stephanie J. Lee,[1,2] Hans-Peter Kiem,[1,2] Effie W. Petersdorf,[1,2] Shalini E. Pereira,[1] Richard A. Nash,[1,2] Marco Mielcarek,[1,2] Matthew L. Fero,[1,2] Edus H. Warren,[1,2] Jean E. Sanders,[1,3] Rainer F. Storb,[1,2] Frederick R. Appelbaum,[1,2] Barry E. Storer,[1,4] and Paul J. Martin[1,2]

[1]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA; and Departments of [2]Medicine, [3]Pediatrics, and [4]Biostatistics, University of Washington School of Medicine, Seattle, WA

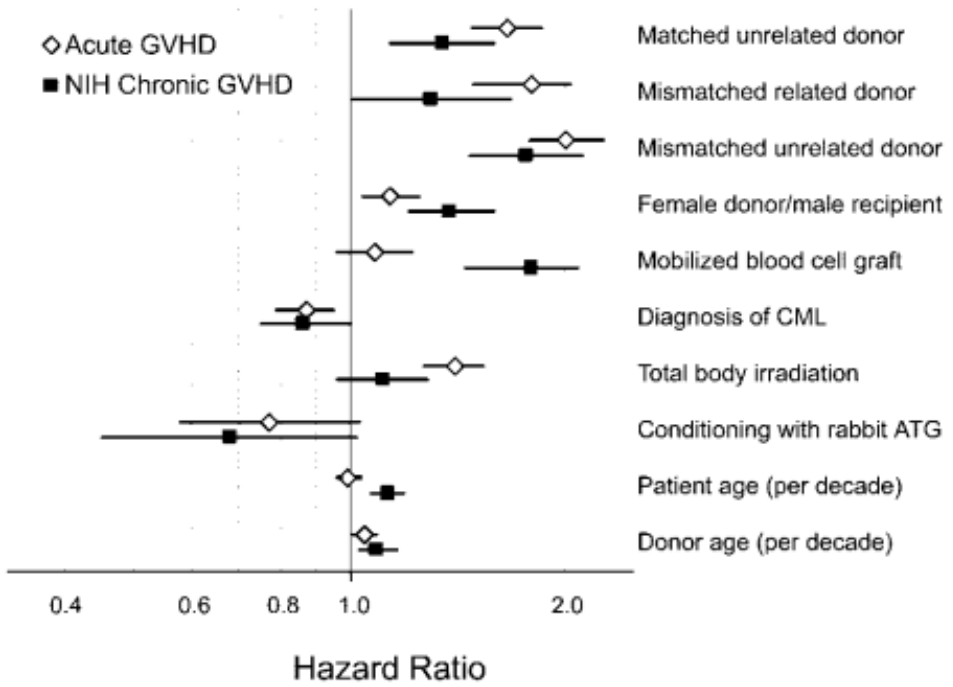
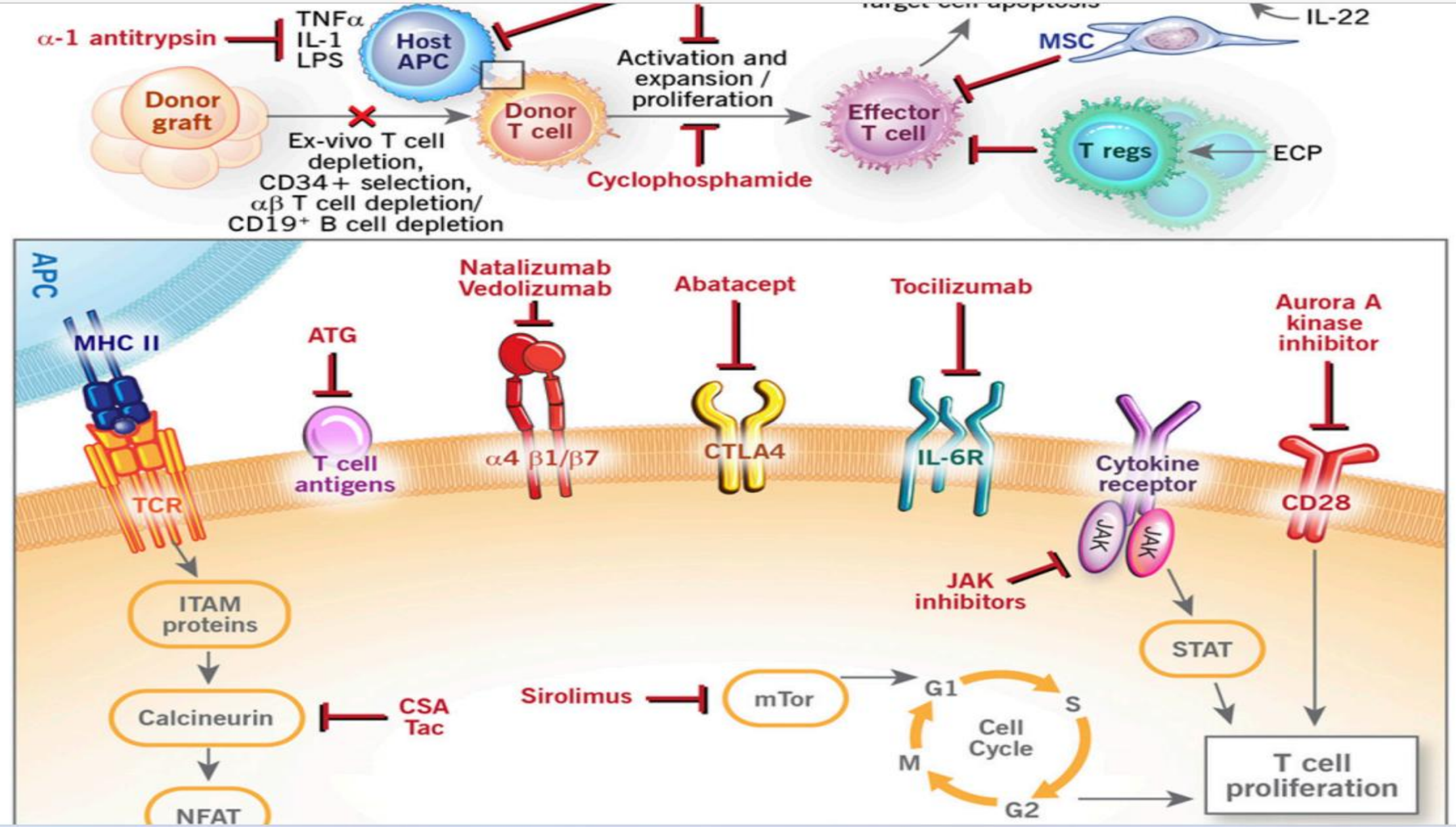


Figure 2. Multivariate risk factor profiles for grades 2-4 acute GVHD and NIH chronic GVHD. Hazard ratio and 95% CI for each risk factor are shown. The analysis included 2355 grades 2-4 acute GVHD events and 1022 NIH chronic GVHD events. Hazard ratios are relative to patients without the risk factor.

Table 3. Summary of factors associated with increased risk of grades 2-4 acute and chronic GVHD

	Acute GVHD		Chronic GVHD	
Factor	Previously reported*	Current study	Previously reported†	Current study‡
HLA mismatch or unrelated donor	yes	yes	yes	yes
Older patient age	yes	no	yes	yes
Older donor age	yes	yes	yes	yes
Female donor for male recipient	yes	yes	yes	yes
Parity of female donor (allosensitization)	yes	§	yes	§
Intensity of conditioning regimen	yes	‖	no	‖
Mobilized blood cell graft	no/yes	no	yes	yes
Donor lymphocyte infusion	yes	¶	yes	¶
Prior acute GVHD	n/a	n/a	yes	yes



- Calcineurin inhibitors (tacrolimus/Tac and cyclosporine/CyA) inhibit the proliferation and activation of Tcells and have been used in combination with either methotrexate (MTX) or mycophenolate mofetil (MMF) as standard prophylaxis in HLA-matched HSCT

- The combination of Tac/MTX was found to be significantly superior to CyA/MTX is the prevention of grade II-IV aGVHD and extensive chronic GVHD in HLA-matched sibling and unrelated donors, although a benefit in overall survival (OS) was not shown

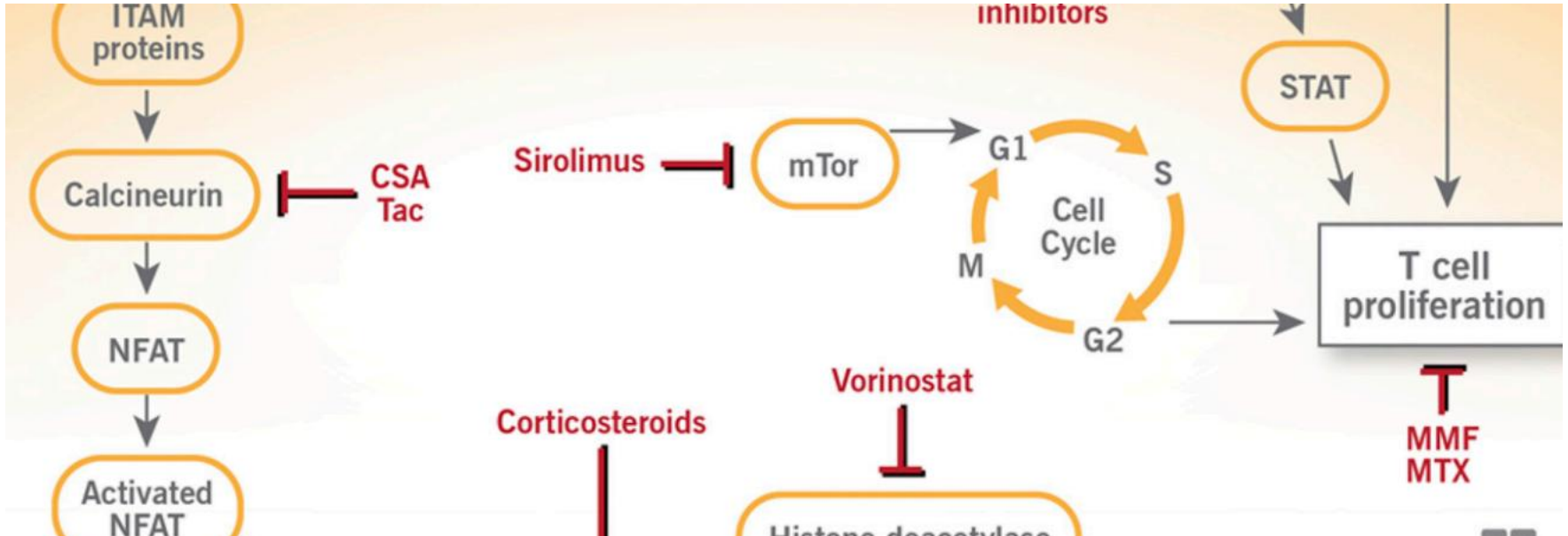
- Therefore, both regimens are considered standard backbones to most GVHD prevention strategies for patients undergoing allogeneic HCT.

Mycophenolate mofetil (MMF)

- a selective inhibitor of inosine monophosphate dehydrogenase that is a key enzyme in the de novo synthesis of guanine nucleotides

- **A recent Center for International Blood and Marrow Transplant** Research study of **3979** matched sibling donors and **4163** unrelated donors showed significantly inferior GVHD and survival outcomes with CSA MMF compared with Tac , MTX, CSA , MTX, and Tac , MMF in **myeloablative transplantation**, suggesting an advantage of MTX over MMF for GVHD prevention.

- Sirolimus is a mTOR inhibitor which inhibits effector Tlymphocytes and in in-vitro studies appeared to spare regulatory T-lymphocytes.
- shown to be associated with better GVHD outcomes and hence sirolimus has an immunologic profile that was thought to be potentially beneficial for GVHD prevention.



- sirolimus in combination with tacrolimus was compared with the standard Tac/MTX platform.
- There was no difference in grades II-IV aGVHD and Cgvhd
- better grade III-IV aGVHD outcomes with sirolimus/Tac were seen

- Tac + sirolimus is thus considered an important alternative for **patients undergoing total body irradiation**-based transplantation, particularly for may be at higher risk for **developing severe mucositis** or **require faster engraftment for risk of infection**.

Translational Advances in GVHD Prophylaxis

- **In-vivo T-Cell Depletion/Modulation**
- Post-transplant Cyclophosphamide
- Anti-thymocyte Globulin

- **Ex-vivo T-Cell Depletion/Modulation**

"ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?"

Prof. Mohamad MOHTY
Clinical Hematology and Cellular Therapy Dpt.
Sorbonne University
Hôpital Saint-Antoine
Paris, France

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

Rationale for the Cyclophosphamide-Based Haplo Approach

- **Properties of post-transplantation Cy:**
  - **Selectively toxic to *proliferating*, alloreactive T cells over non-proliferating, non-alloreactive T cells** (*Fuchs EJ, et al. Bone Marrow Transplant. 2015;50 Suppl 2(0 2):S31-6.*)
  - **Non-toxic to hematopoietic stem cells** (*Ruggeri A, et al. Haematologica. 2017;102(2):401-410.*)
  - **Decreases acute GvHD in animal models** (*Luznik L, et al. Blood. 2001;98(12):3456-64.*)

Signatures of GVHD and relapse after posttransplant cyclophosphamide revealed by immune profiling and machine learning

Shannon R. McCurdy,[1,*] Vedran Radojcic,[2,3,*,†] Hua-Ling Tsai,[4] Ante Vulic,[5] Elizabeth Thompson,[5] Sanja Ivcevic,[2,3] Christopher G. Kanakry,[6] Jonathan D. Powell,[4] Brian Lohman,[3] Djamilatou Adom,[6] Sophie Paczesny,[7,8] Kenneth R. Cooke,[4] Richard J. Jones,[4] Ravi Varadhan,[5] Heather J. Symons,[4] and Leo Luznik[4,†]

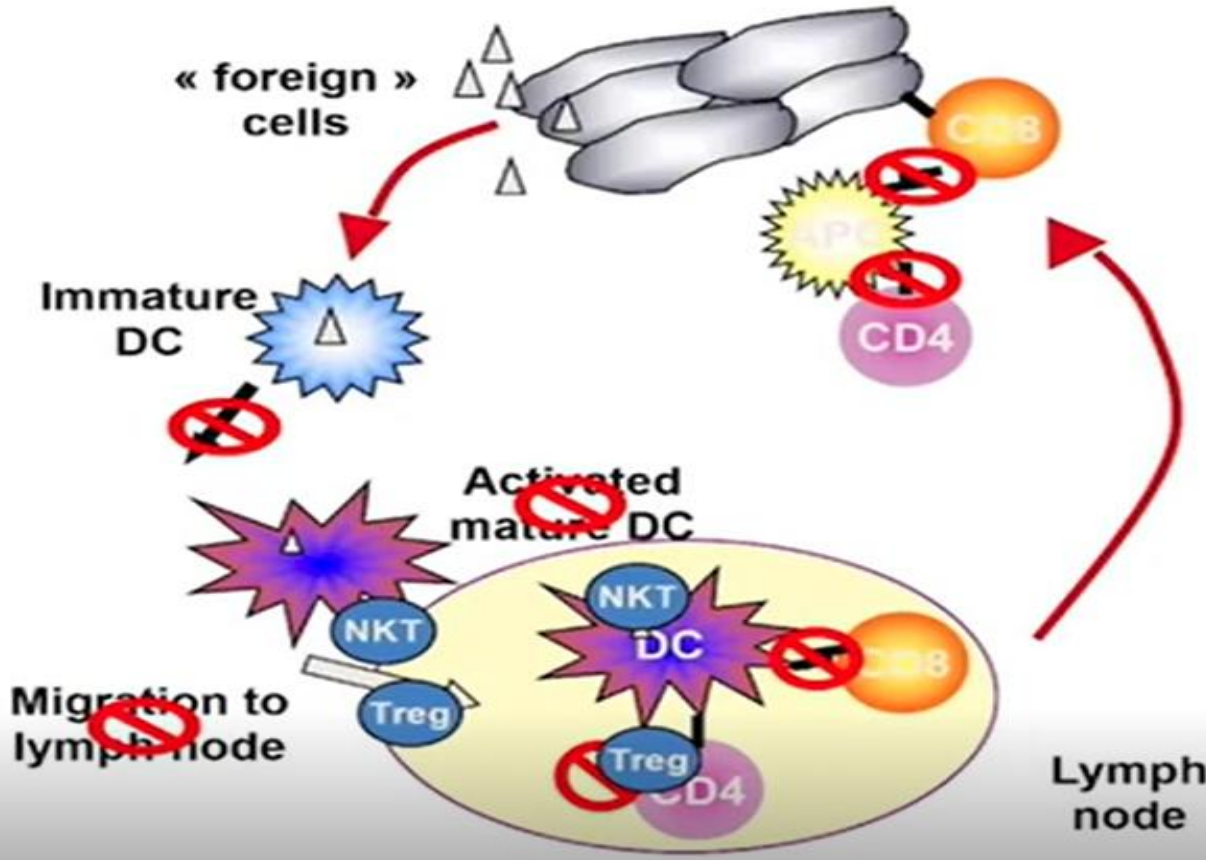
Blood. 2022;139(4):608-623.

Cy: Cyclophosphamide. GvHD: Graft versus Host Disease.

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

Summary of rATG Mechanisms of Action

- The polyclonal nature of rATG is reflected in its diverse effects on the immune system :
  - T-cell depletion in blood and peripheral lymphoid tissues
  - Interference with leukocyte/endothelium interactions
  - Apoptosis in all B-cell lineages
  - Induction of Tregs/NKT cells
- ➔ *rATG provides multifaceted immunomodulation*



TG: rabbit Antithymocyte Globulin. T reg: regulatory T cells. NKT: Natural *Killer (NK) T cells.*
PC: Antigen-Presenting Cell. DC: Dendritic Cell.

Adapted from Mohty M. Leukemia. 2007;21(7):1387-94.

Table 3. Randomized studies of rabbit ATG as GvHD prevention in patients given allogeneic hematopoietic cell transplantation.

	N. of patients	ATG brand / total dose (mg/kg)	Acute GvHD II-IV	Chronic GvHD	Non-relapse mortality	Relapse	Overall survival
			% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)	% ATG/ % no ATG (*P*)
Bacigalupo *et al.*[55]	54	T / 7.5	69 / 72 (0.6)	38 / 65 (0.08)	43 / 39 (0.7)[a]	10 / 12 (0.6)[a]	56 / 55 (0.8)[a]
Bacigalupo *et al.*[55]	55	T / 15	37 / 79 (0.001)	41 / 59 (0.3)	47 / 49 (0.9)[b]	36 / 18 (0.8)[b]	43 / 43 (0.8)[b]
Finke & Socie *et al.*[56 60]	201	F / 60	33 / 51 (0.01)	30 / 60 (<0.001)[a]	19 / 34 0.18)[a]	33 / 28 (0.5)[a]	55 / 43 (0.39)[a]
Kroger *et al.*[58]	155	F / 30	11 / 18 (0.13)	32 / 69 (<0.001)[c]	14 / 12 (0.6)[c]	32 / 26 (0.17)[c]	74 / 78 (0.5)[c]
Walker *et al.*[57]	196	T / 4.5	50 / 65 (0.01)[d]	22 / 33 (0.06)[b]	23 / 24 (NS)[b]	11 / 16 (NS)[b]	75 / 65 (0.24)[b]

[a]at 3 years; [b]at 1 year; [c]at 2 years; [d]grade I-IV at day 100. F: ATG-Fresenius; T: ATG-Thymoglobuline.

Table 4. Proposed indications for immunoregulation with ATG in patients given PBSC from allogeneic donors.

	Recommendation for ATG	Dose and timing of ATG
Myeloablative PBSCT from matched sibling donors[53]	standard of care	ATG-F 10 mg/kg/day on days -3, -2 and -1.
Myeloablative PBSCT from HLA-matchedunrelated donors[56,60,57]	standard of care	ATG-F 20 mg/kg/day on days -3, -2 and -1*. ATG-T 0.5 mg/kg on day -2 and 2 mg/kg on days -1 and +1.
RIC-PBSCT fludarabine-busulfan[68]	recommended	ATG-T 2.5 mg/kg/day on days -2 and -1.
Non-myeloablative PBSCT	developmental	/
HLA-haplo-identical stem cell transplantation (Bejing approach)[88]	standard of care	ATG-T 2.5 mg/kg/day from days -5 to -2.

* some centers use smaller doses such as 15 mg/kg total dose.

blood

Regular Article

TRANSPLANTATION

Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation

Giorgia Battipaglia,[1,2] Myriam Labopin,[1,3,4] Nicolaus Kröger,[5] Antonin Vitek,[6] Boris Afanasyev,[7] Inken Hilgendorf,[8] Johannes Schetelig,[9] Arnold Ganser,[10] Didier Blaise,[11] Maija Itälä-Remes,[12] Jakob R. Passweg,[13] Francesca Bonifazi,[14] Jurgen Finke,[15] Annalisa Ruggeri,[16] Arnon Nagler,[3,17] and Mohamad Mohty[1,3,4]

blood® 12 SEPTEMBER 2019 | VOLUME 134, NUMBER 11

Retrospective study using the registry data of the ALWP of the EBMT to perform a matched-pair analysis comparing two strategies, PTCY versus ATG, in a 9/10 MMUD setting; 93 patients receiving PTCY were matched with 179 patients receiving ATG.

ATG: Antithymocyte Globulin. GvHD: Graft versus Host Disease. HLA: Human Leucocyte Antigen. PTCy: Post Transplant Cyclophosphamide. MMUD: Mismatched Unre

KEY POINTS

- **PTCY results in a lower incidence of severe acute GVHD compared with ATG in patients transplanted from 9/10 MMUD for acute myeloid leukemia.**
- **PTCY results in better survival compared with ATG in patients transplanted from 9/10 MMUD for acute myeloid leukemia.**

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

PTCy versus ATG after RIC allogeneic cell transplantation: conclusions

- The use of PTCY for GVHD prophylaxis resulted in similar outcomes compared to ATG in patients who underwent FB2 allogeneic stem cell transplantation with a 10/10 HLA-matched related or unrelated donor.
- Both PTCY or ATG can be used for GVHD prophylaxis in patients receiving FB2 conditioning prior to allogeneic stem cell transplantation with a 10/10 HLA-matched related or unrelated donor.

ATG: Antithymocyte Globulin. PTCy: Posttransplant Cyclophosphamide. RIC: Reduced Intensity Conditioning. FB2: fludarabine +2 days of busulfan at 3.2 mg/kg/d iv. GvHD: Graft versus Host Disease

Brissot E, et al. Presidential Symposium #GS2-2. Van Bekkum Award; EBMT 2021.

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

What's next ?

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

> Leuk Lymphoma. 2021 Dec;62(14):3373-3383. doi: 10.1080/10428194.2021.1966781. Epub 2021 Aug 26.

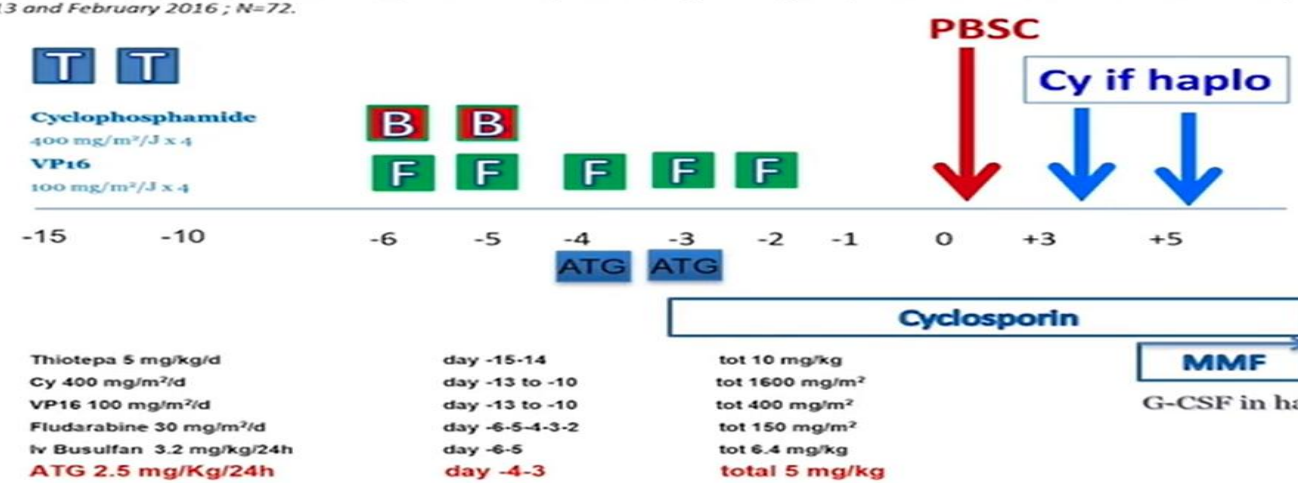
Lower dose of ATG combined with post-transplant cyclophosphamide for HLA matched RIC alloHCT is associated with effective control of GVHD and less viral infections

Maria Queralt Salas [1 2 3], Eshetu G Atenafu [4], Arjun Datt Law [1 2], Wilson Lam [1 2], Ivan Pasic [1 2], Carol Chen [2], Dennis Dong Hwan Kim [1 2], Fotios V Michelis [1 2], Armin Gerbitz [1 2], Jeffrey Howard Lipton [1 2], Jonas Mattsson [1 2], Rajat Kumar [1 2], Auro Viswabandya [1 2]

ersus post-transplant cyclophosphamide for GvHD prophylaxis

ATG *and* PtCy combination

Retrospective multicenter study including all consecutive patients with R/R hematological malignancy who underwent allo-SCT with TEC-RIC sequential conditioning between April 2013 and February 2016 ; N=72.



Thiotepa 5 mg/kg/d	day -15-14	tot 10 mg/kg
Cy 400 mg/m²/d	day -13 to -10	tot 1600 mg/m²
VP16 100 mg/m²/d	day -13 to -10	tot 400 mg/m²
Fludarabine 30 mg/m²/d	day -6-5-4-3-2	tot 150 mg/m²
iv Busulfan 3.2 mg/kg/24h	day -6-5	tot 6.4 mg/kg
ATG 2.5 mg/Kg/24h	day -4-3	total 5 mg/kg

Cy: Cyclophosphamide, ATG: Anti-Thymocyte Globulin, PBSCs: Peripheral Blood Stem Cells, CsA: Cyclosporine A, MMF: Mycophenolate Mofetil, TEC-RIC: thiotepa, VP16, cyclophosphamide followed by fludarabine, intravenous busulfan and anti-thymocyte globulin.

Dulery R, *et al.* Biol Blood Marrow Transplant. 2018;24(5):1013-102

ATG versus post-transplant cyclophosphamide for GvHD prophylaxis?

ATG *and* PtCy Combination

Outcomes at Year 2	Total (n=72) n (%)	Haplo (n=27) n (%)	MRD (n=16) n (%)	UD (n=29) n (%)	p-value (comparison between Haplo, MRD & UD groups)
Relapse incidence	38.4	35.9	31.2	43.1	*P=0.858*
NRM	23.7	14.8	25	31	*P=0.376*
Acute GVHD II-IV	23.6	11.1	12.5	41.4	*P=0.027*
Chronic GVHD	32.1	30	37.5	31	*P=0.909*

Haplo: Haploidentical. MRD: Matched Related. NRM: Norrelapse Mortality. UD: Unrelated Donor.

Dulery R, *et al.* Biol Blood Marrow Transplant. 2018;24(5):1013-1021.

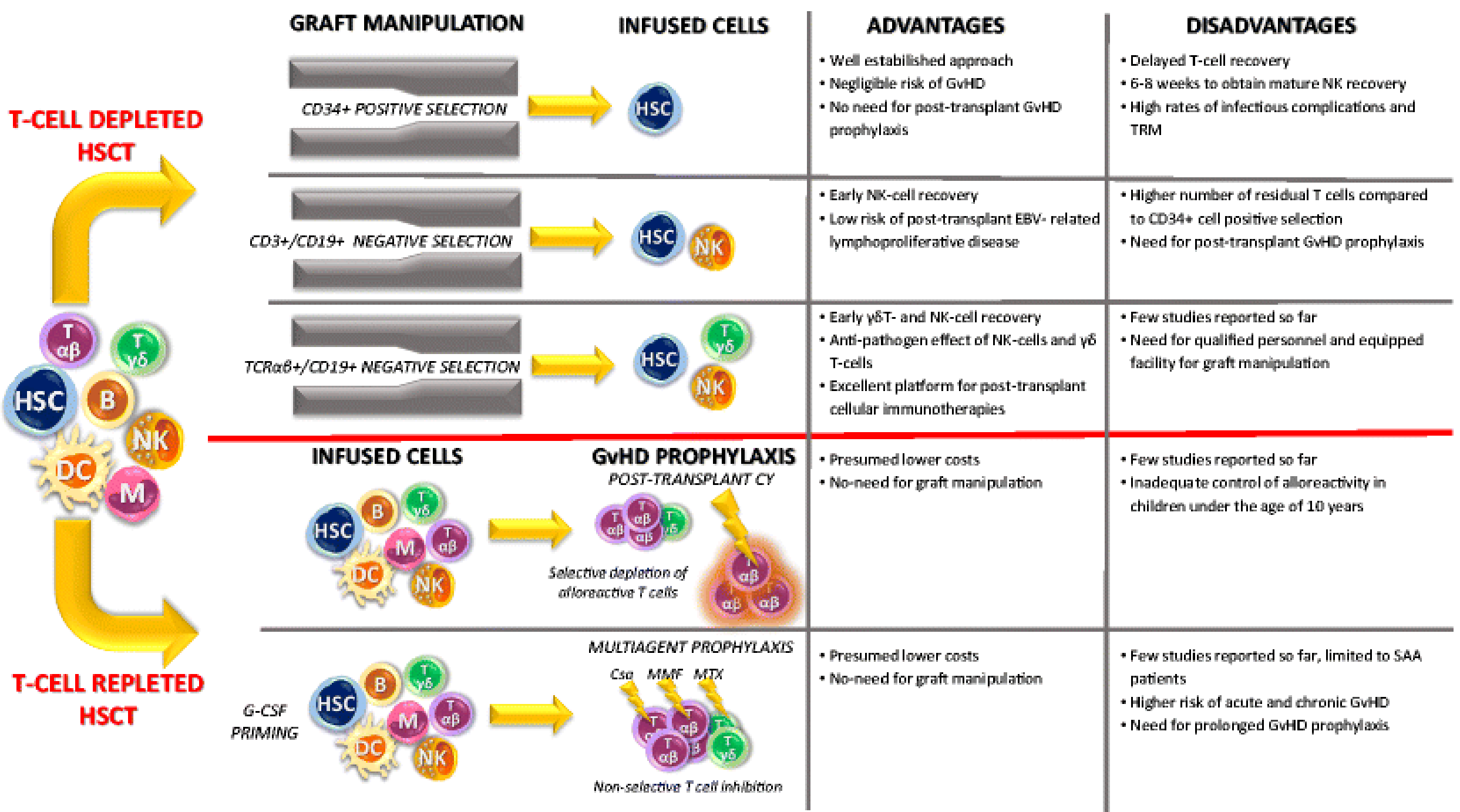

GRAFT MANIPULATION
INFUSED CELLS
ADVANTAGES
DISADVANTAGES
T-CELL DEPLETED HSCT
CD34+ POSITIVE SELECTION
HSC
• Well established approach
• Negligible risk of GvHD
• No need for post-transplant GvHD prophylaxis
• Delayed T-cell recovery
• 6-8 weeks to obtain mature NK recovery
• High rates of infectious complications and TRM
CD3+/CD19+ NEGATIVE SELECTION
HSC
NK
• Early NK-cell recovery
• Low risk of post-transplant EBV- related lymphoproliferative disease
• Higher number of residual T cells compared to CD34+ cell positive selection
• Need for post-transplant GvHD prophylaxis
TCRαβ+/CD19+ NEGATIVE SELECTION
HSC
T γδ
NK
• Early γδT- and NK-cell recovery
• Anti-pathogen effect of NK-cells and γδ T-cells
• Excellent platform for post-transplant cellular immunotherapies
• Few studies reported so far
• Need for qualified personnel and equipped facility for graft manipulation
T αβ
T γδ
HSC
B
NK
DC
M
INFUSED CELLS
GvHD PROPHYLAXIS
POST-TRANSPLANT CY
HSC
B
T γδ
M
T αβ
DC
NK
Selective depletion of alloreactive T cells
• Presumed lower costs
• No-need for graft manipulation
• Few studies reported so far
• Inadequate control of alloreactivity in children under the age of 10 years
T-CELL REPLETED HSCT
G-CSF PRIMING
HSC
B
T γδ
M
T αβ
DC
NK
MULTIAGENT PROPHYLAXIS
Csa
MMF
MTX
Non-selective T cell inhibition
• Presumed lower costs
• No-need for graft manipulation
• Few studies reported so far, limited to SAA patients
• Higher risk of acute and chronic GvHD
• Need for prolonged GvHD prophylaxis

Table 1. Clinical trials with TCR-αβ/CD19-depleted haematopoietic stem cells (HSCs).

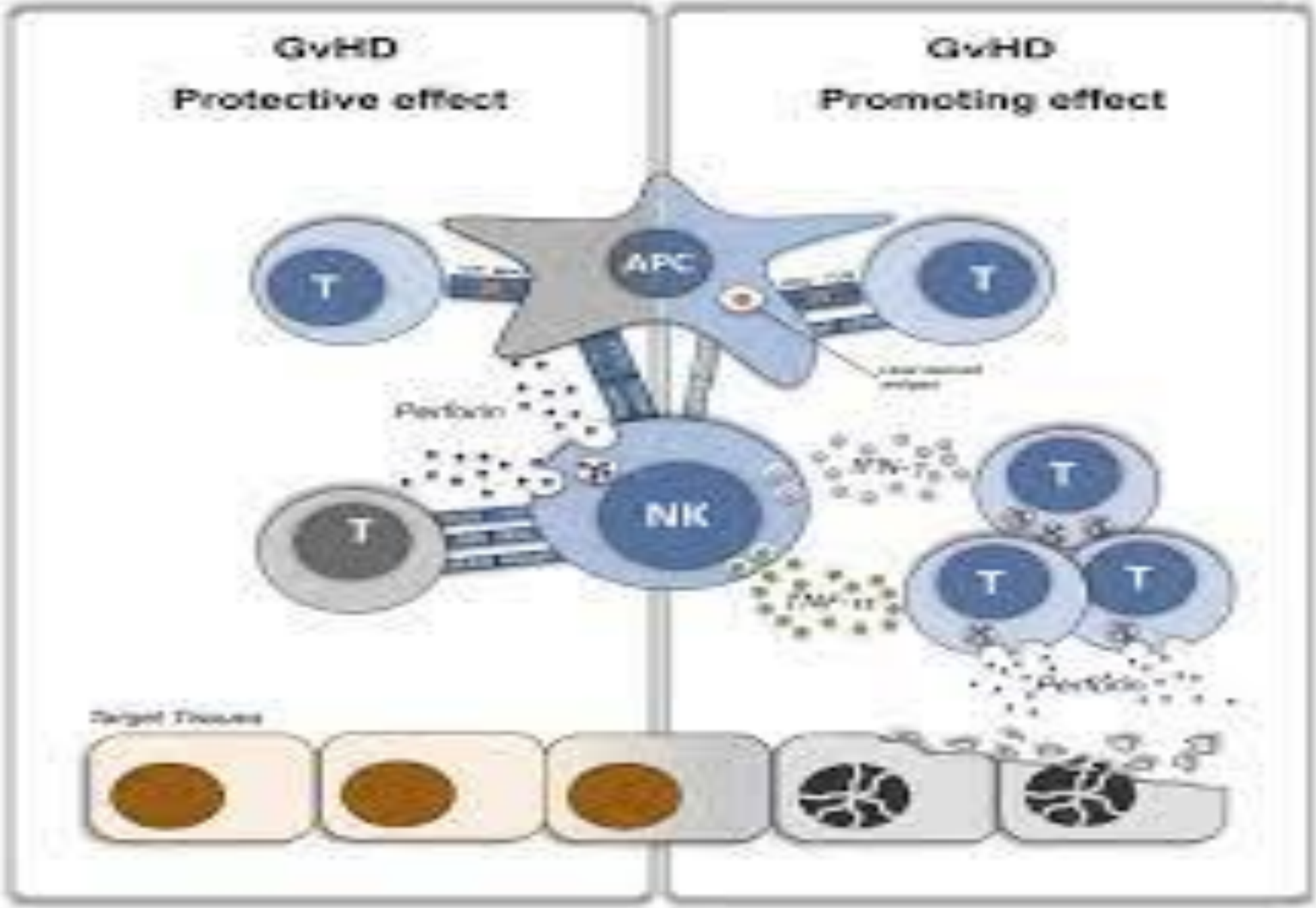
Patients	Disease	Graft-versus-Host Disease (GVHD) Prophylaxis	Acute/Chronic GVHD	TRM	EFS(DFS)/OS	Reference
28	HR-AML	FK506, MTX	39%/30%	10%	60%/67% (2 years)	[19]
37	PID	FK506, MTX; FK506, MMF; CYA, MTX	22%	3.3% (27% GF)	96.7% (15 months)	[20]
41	AL	MMF	10%/9%	N.A.	21/41 patients alive after 1.6 years	[21]
23	Non-malignant	None	13%/0%	9.3%	91% (2 years)	[16,22]
34	HR-AL	N.A.	5.9%/6.1%	14.7%	42%/54% (1 year)	[23]
80	AL	None	30%; no extensive chronic GVHD	5%	71%/72% (5 years)	[24]

Legend: HR-AML = high-risk acute myeloid leukaemia; CYA = cyclosporine-A; MTX = methotrexate; DFS = disease-free survival; EFS = event-free survival; OS = overall survival; GF = graft failure; PID = primary immune deficiencies; AL = acute leukaemia; HR-AL = high-risk acute leukaemia; MMF = mycophenolate mofetil; N.A. = not available; TRM = transplantation-related mortality.

Table 2. Clinical trials with CD45RA T-cell depletion.

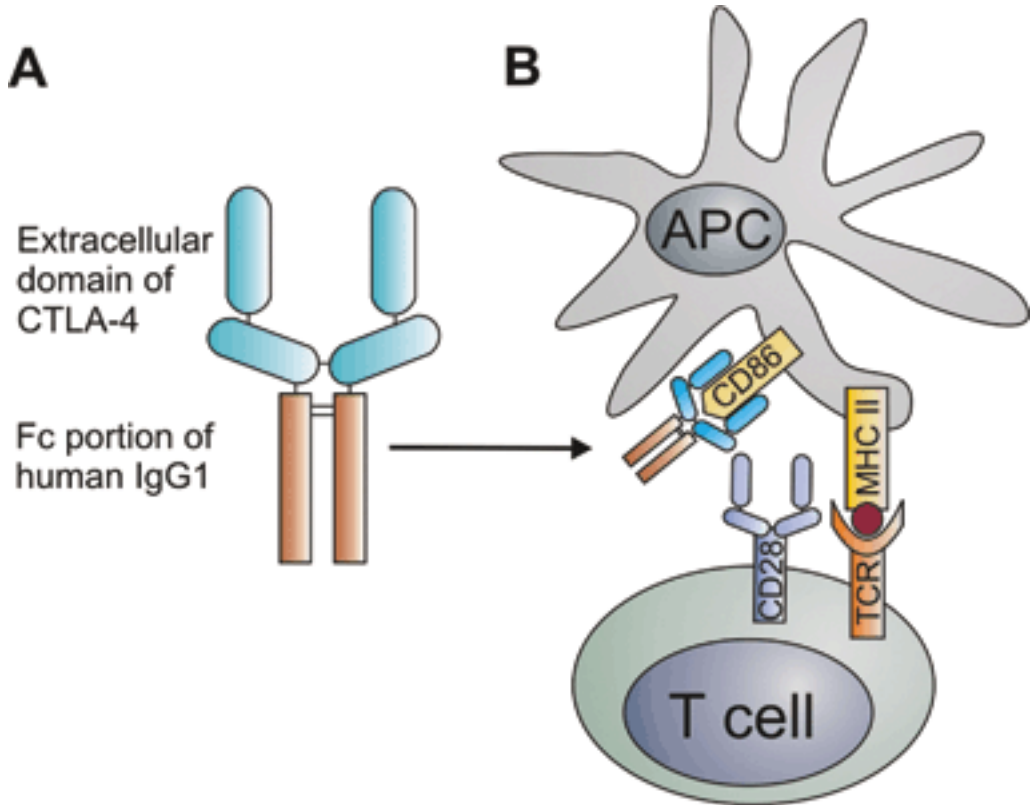
Patients	Disease	Graft-Versus-Host Disease (GVHD) Prophylaxis	Acute/Chronic GVHD	TRM	EFS(DFS)/OS	Reference
35	High-risk leukaemia	Tacrolimus	66%; 9%	9%	70%/78% (2 years)	[29]
8	Solid tumours	Sirolimus	No acute GVHD or GF	1 patient died of sinusoidal obstruction syndrome	N.A. (median follow-up was 184 days)	[34]
17	Haematological malignancies	Sirolimus and MMF	17.6% grades III–IV acute GVHD/6 patients with signs of oral or skin chronic GVHD	11.7%	76.5% of patients alive at a median of 223 days after haematopoietic stem cell transplantation (HSCT)	[35]

DFS = disease-free survival; EFS = event-free survival; OS = overall survival; TRM = transplantation-related mortality; GF = graft failure; MMF = mycophenolate mofetil; N.A. = not available.

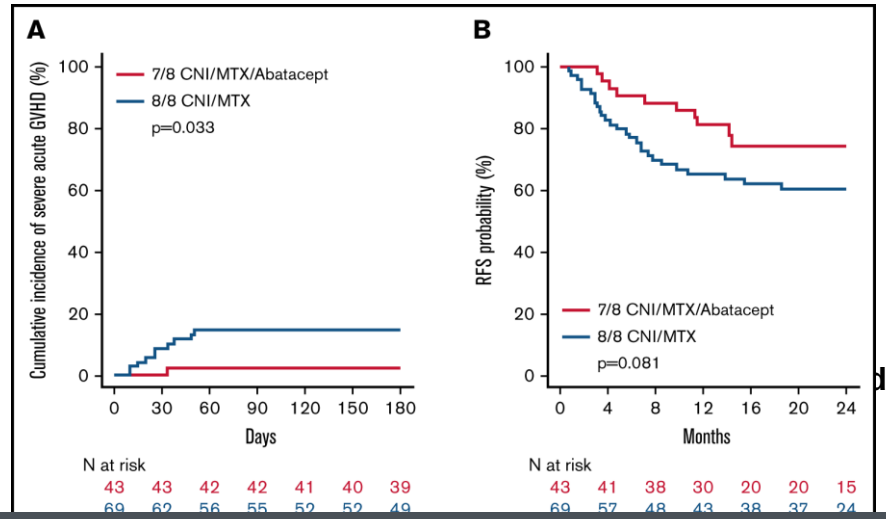

GvHD
Protective effect
GvHD
Promoting effect
APC
T
T
Perforin
NK
T
IFN-γ
T
T
T
TNF-α
Perforin
Target Tissues

Abatacept in HSCT

- **Acute GVHD**
  - FDA approved for prevention
- **Chronic GVHD**
  - Ongoing trials for prevention through extended dosing and treatment of steroid refractory chronic GVHD
- **Host versus Graft**
  - ? induces tolerance thereby preventing graft rejection



Abatacept for GVHD prophylaxis can reduce racial disparities by abrogating the impact of mismatching in unrelated donor stem cell transplantation



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MANAGEMENT OF HIGH-RISK PATIENTS FOLLOWING ALLOGENEIC TRANSPLANT | JANUARY 5, 2023

How I prevent GVHD in high-risk patients: posttransplant cyclophosphamide and beyond

Joseph Rimando, Shannon R. McCurdy, Leo Luznik

Blood (2023) 141 (1): 49–59.

https://doi.org/10.1182/blood.2021015129

Article history

Table 1. Novel approaches to GVHD

Therapies	Mechanisms of action	Data	Ongoing clinical trials
Prevention			
Tocilizumab	Human monoclonal antibody against IL-6R	Phase 2 study of tocilizumab + Tac + MTX: 14% grade 2-4 acute GVHD, 3% grades 3 and 4 acute GVHD at 100 d[39]	NCT03434730
Abatacept	Costimulation blockade of CD28: CD80/86 to inhibit T cells	2 of 10 patients with grade 2-4 acute GVHD, no day 100 TRM[40]	NCT01743131 NCT02867800
Tregs	Regulate self-tolerance, limit GVHD while maintaining GVL effect	Modified expanded umbilical cord blood–derived Tregs: grade 2-4 acute GVHD 9% at 100 d[42]	NCT01660607 NCT00602693 NCT01818479 NCT01795573
T-cell depletion (CD34 selection and selective ex vivo T-cell depletion)	Depletion of alloreactive T cells and selective αβ T-cell depletion, with preservation of γδ T cells and NK cells	CD34+ selection: grade 2-4 acute GVHD 22.7%, chronic GVHD 6.8%[29]	NCT02323867 NCT02600208 NCT03301168 NCT03047746 NCT02345850
Statins	Inhibit proinflammatory Th-1 differentiation, induce Treg expansion, and downregulate APCs	Phase 2 study of statin to both donors and recipients with Tac + MTX—grade 2-4 3.3%; chronic GVHD 52.3%[46]	NCT03066466
Vorinostat	Histone deacetylase inhibitor decreases inflammatory cytokines, enhances Treg function, and reduces GVHD while preserving GVL	Phase 2 study of vorinostat + Tac + MTX: grade 2-4 acute GVHD 22%, grades 3 and 4 acute GVHD 8%; chronic GVHD 29%[51]	NCT01790568
JAK inhibitors (itacitinib, ruxolitinib)	Reduction of proinflammatory cytokines, T-cell activation and function, preserves Tregs, GVL effect	Preclinical studies and use in treatment setting	NCT03320642

Randomized Phase III BMT CTN Trial of Calcineurin Inhibitor–Free Chronic Graft-Versus-Host Disease Interventions in Myeloablative Hematopoietic Cell Transplantation for Hematologic Malignancies

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abstract

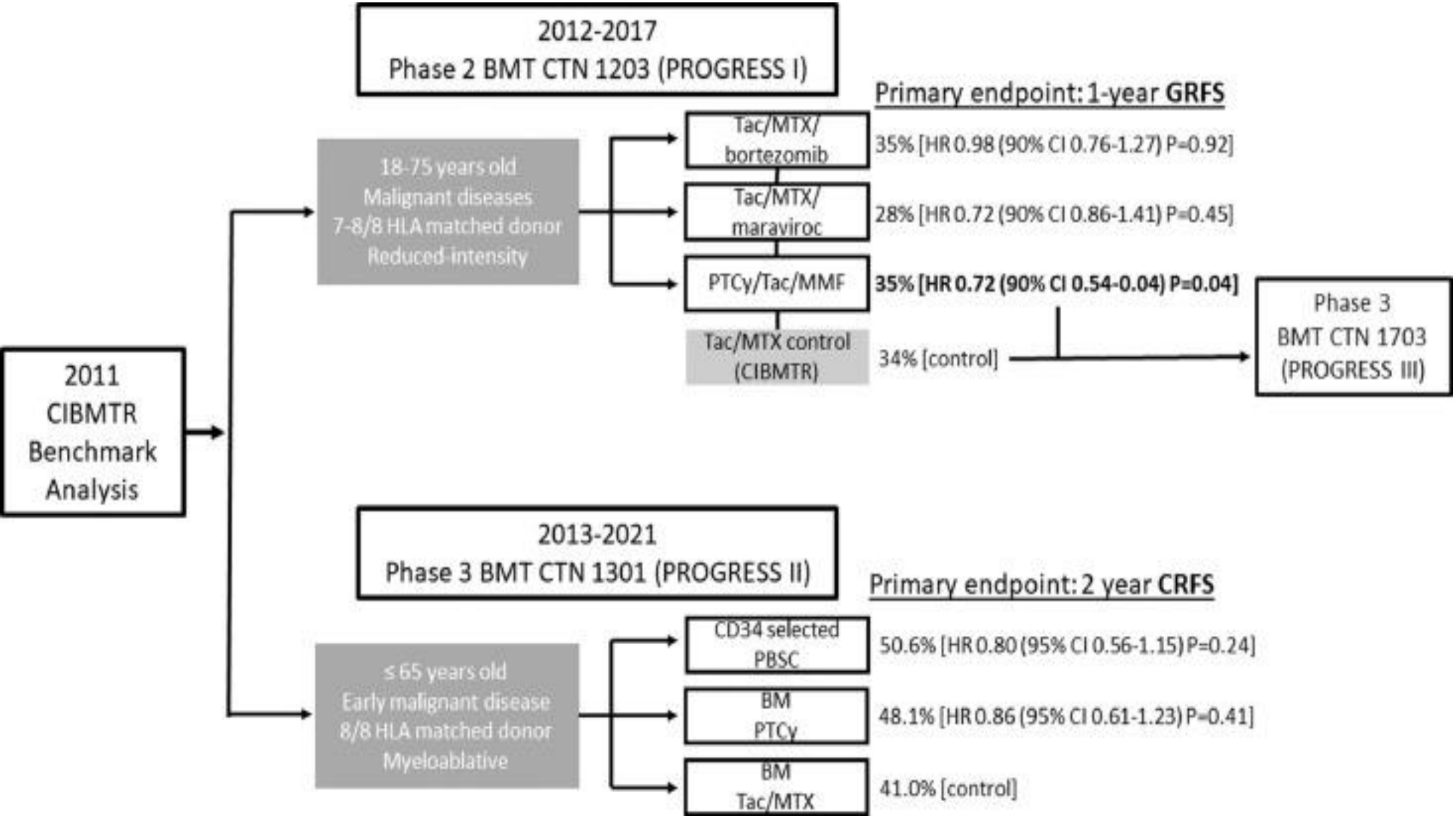
PURPOSE Calcineurin inhibitors (CNI) are standard components of graft-versus-host disease (GVHD) prophylaxis after hematopoietic cell transplantation (HCT). Prior data suggested that CNI-free approaches using donor T-cell depletion, either by ex vivo CD34 selection or in vivo post-transplant cyclophosphamide (PTCy) as a single agent, are associated with lower rates of chronic GVHD (cGVHD).

METHODS This multicenter phase III trial randomly assigned patients with acute leukemia or myelodysplasia and an HLA-matched donor to receive CD34-selected peripheral blood stem cell, PTCy after a bone marrow (BM) graft, or tacrolimus and methotrexate after BM graft (control). The primary end point was cGVHD (moderate or severe) or relapse-free survival (CRFS).

RESULTS Among 346 patients enrolled, 327 received HCT, 300 per protocol. Intent-to-treat rates of 2-year CRFS were 50.6% for CD34 selection (hazard ratio [HR] compared with control, 0.80; 95% CI, 0.56 to 1.15; $P = .24$), 48.1% for PTCy (HR, 0.86; 0.61 to 1.23; $P = .41$), and 41.0% for control. Corresponding rates of overall survival were 60.1% (HR, 1.74; 1.09 to 2.80; $P = .02$), 76.2% (HR, 1.02; 0.60 to 1.72; $P = .95$), and 76.1%. CD34 selection was associated with lower moderate to severe cGVHD (HR, 0.25; 0.12 to 0.52; $P = .02$) but higher transplant-related mortality (HR, 2.76; 1.26 to 6.06; $P = .01$). PTCy was associated with comparable cGVHD and survival outcomes to control, and a trend toward lower disease relapse (HR, 0.52; 0.28 to 0.96; $P = .037$).

CONCLUSION CNI-free interventions as performed herein did not result in superior CRFS compared with tacrolimus and methotrexate with BM. Lower rates of moderate and severe cGVHD did not translate into improved survival.

J Clin Oncol 40:356-368.


2011
CIBMTR
Benchmark
Analysis
2012-2017
Phase 2 BMT CTN 1203 (PROGRESS I)
18-75 years old
Malignant diseases
7-8/8 HLA matched donor
Reduced-intensity
Tac/MTX/
bortezomib
Tac/MTX/
maraviroc
PTCy/Tac/MMF
Tac/MTX control
(CIBMTR)
Primary endpoint: 1-year GRFS
35% [HR 0.98 (90% CI 0.76-1.27) P=0.92]
28% [HR 0.72 (90% CI 0.86-1.41) P=0.45]
35% [HR 0.72 (90% CI 0.54-0.04) P=0.04]
34% [control]
Phase 3
BMT CTN 1703
(PROGRESS III)
2013-2021
Phase 3 BMT CTN 1301 (PROGRESS II)
≤ 65 years old
Early malignant disease
8/8 HLA matched donor
Myeloablative
CD34 selected
PBSC
BM
PTCy
BM
Tac/MTX
Primary endpoint: 2 year CRFS
50.6% [HR 0.80 (95% CI 0.56-1.15) P=0.24]
48.1% [HR 0.86 (95% CI 0.61-1.23) P=0.41]
41.0% [control]

Details

Journal of Clinical Laboratory Analysis
Volume 34, Issue 7
Jul 2020

ARTICLE

The role of serum uric acid in the prediction of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation

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CITE | Check for updates

Received: 7 December 2019 | Revised: 21 January 2020 | Accepted: 12 February 2020
DOI: 10.1002/jcla.23271

RESEARCH ARTICLE

WILEY

The role of serum uric acid in the prediction of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation

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Abstract

Background: Uric acid (UA) level is of the valuable signs of inflammation. However, the role of UA in the outcomes of hematopoietic stem cell transplantation (HSCT) such as GVHD and patients' overall survival is still a matter of debate. In this study, we aimed to evaluate the relationship between UA levels and GVHD incidence and overall survival in allogeneic HSCT patients.

Methods: A total of 201 patients who were admitted for allogeneic transplantation at Taleghani hospital, Tehran, Iran, were considered for retrospective analysis. Serum UA levels from 1 week before transplantation until 2 weeks after transplantation were used to determine thresholds and find out the association of serum UA levels with GVHD and overall survival.

Results: We showed that the determined thresholds using receiver operating characteristic curves have poor predictive value for GVHD and overall survival. The patients with serum UA higher than 3.4 mg/dL had 37% lower odds of GVHD incidence and 35% lower hazard of death than patients with UA lower than 3.4 mg/dL.

Conclusion: Our results indicated that serum UA levels lower than 3.4 mg/dL could significantly increase the incidence of GVHD and hazard of death. The antioxidant functions of UA could explain the lower incidence of GVHD in hyperuricemic patients. However, the inconsistencies of the previous studies require further investigation to elucidate the role of UA in the prediction of GVHD.

KEYWORDS
Allo-HSCT, GVHD prediction, uric acid

1 | INTRODUCTION

Today, the rate of allogeneic hematopoietic stem cell transplantations are performed annually, worldwide.[1] Graft-versus-host disease (GVHD) is a major complication and therapeutic challenge of allo-HSCT with the prevalence of 20%-60%.[2,3] During the

Int J Cancer Manag. 2022 April; 15(4):e120888. doi: 10.5812/ijcm-120888.

Published online 2022 May 14. **Research Article**

Soluble T Cell Immunoglobulin and Mucin Domain-3 (sTIM-3) Predicts Graft-Versus-Host Disease (GVHD) in Iranian Allogeneic Hematopoietic Stem Cell Transplantation

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Received 2021 November 09; **Revised** 2022 April 26; **Accepted** 2022 April 30.

Transfusion and Apheresis Science
Volume 60, Issue 2, April 2021, 103009

The apheresis content analysis in Allo-HSCT represents reliable influential factors on graft-versus-host disease and overall survival

Atefeh Rauofi, Abbas Hajifathali, Samira Karami, Farzaneh Tavakoli, Elham Roshandel, Hossein Bonakchi, Sayeh Parkhideh

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Material and methods

We analyzed 87 patients with hematological malignancies who underwent allogeneic hematopoietic stem cell transplantation at the Taleghani Stem Cell Transplantation and Cell therapy center, Tehran, Iran from January 2016 to December 2018. Patients were conditioned with either myeloablative conditioning regimen or reduced-intensity regimen.

Result

A $CD34^+$ cell dose < 4.35×10^6/kg and $CD3^+$ cell dose < 365×10^6/kg was associated with higher survival and lower acute and chronic GVHD incidence, although their association was not statistically significant. Moreover, there was a significant association between MNC count < 6.15×10^8/kg and acute GVHD incidence.

مرکز آموزش و پژوهش در بیماری های پوست و جذام

پروپوزال طرح پژوهشی

با عنوان:

بررسی ریسک فاکتور های GVHD مزمن پوستی به دنبال انجام پیوند سلول های بنیادی خون ساز غیر همنوع در جمعیت بیماران ایرانی

استاد راهنما :

دکتر علیرضا فیروز

اساتید مشاور :

دکتر مهشید مهدیزاده

دکتر مریم دانش پژوه

نگارش: دکتر شایان زمانی

عنوان طرح تحقیقاتی : بررسی اثربخشی داروی Baricitinib در درمان GVHD مزمن به همراه درگیری پوستی در بیماران پیوند مغز استخوان آلوژنیک

Title : Evauation of Baricitinib as a possible treatment for chronic GVHD with cutaneous involvement among allogeic HCT patients

کد رهگیری: ۶۳۵۲۸
پژوهشگر: شایان زمانی
تخصص:
مرکز هدف اول: مرکز آموزش و پژوهش بیماریهای پوست و جذام
مرکز هدف دوم: خارج از دانشگاه علوم پزشکی تهران
مرکز هدف سوم:

کد طرح: ۱۴۰۱-۴-۱۰۵-۶۳۵۲۸
کد اخلاق:

تاریخ ثبت اولیه: ۱۴۰۱/۰۹/۰۸ ۰۱:۴۰:۳۶
تاریخ ارسال: ۱۴۰۱/۱۲/۰۳ ۱۳:۵۸:۴۳
تاریخ این ویراست:

مشخصات کلی و چکیده طرح

عنوان فارسی طرح

بررسی اثربخشی داروی Baricitinib در درمان GVHD مزمن به همراه درگیری پوستی در بیماران پیوند مغز استخوان آلوژنیک

عنوان انگلیسی طرح

Evauation of Baricitinib as a possible treatment for chronic GVHD with cutaneous involvement among allogeic HCT patients

Patient No.	Diagnosis	Age	Donor	Type of Graft manipulation	Gvhd
1 (SF)	SAA	34	Unrelated (9/10)	CD34 Selection	NO
2 (ST)	AML	38	Related (FM)	CD3/CD19 depletion	NO
3 (KR)	SAA	29	Related (FM)	CD34 Selection	NO
4 (NF)	SAA	30	Related (FM)	CD34 Selection	NO
5 (RR)	MD	7	Haplo-father	CD3/CD19 depletion	NO
6 (ANA)	SAA	29	Related (FM)	CD34 Selection	NO
7 (MA)	SAA	26	Unrelated (9/10)	CD34 Selection	NO
8 (ZG)	AML	27	Unrelated (FM)	CD3/CD19 depletion+T cell Add-back	NO
9 (HR)	HD	17	Haplo-brother	CD3/CD19 depletion+T cell Add-back	Grade I
10 (MJ)	NHL	37	Related (FM)	CD34 selection +T cell Add-back	NO
11 (FY)	AML	19	Haplo-Sister	CD34 Selection + T cell Add-back	NO
12 (AZ)	AML	16	Haplo-mother	CD34 Selection + T cell Add-back	NO
13 (FF)	AA	22	Haplo-sister	CD3/CD19 depletion	NO
14 (EA)	AML	18	Unrelated (9/10)	CD3 Selection	NO
15 (HF)	ALL	42	Related (FM)	CD3/CD19 depletion	Grade III
16 (MM)	AML	52	Haplo-brother	CD3/CD19 depletion	HC
17 (AS)	SAA	40	Haplo-sister	CD3/CD19 depletion	Grade IV
18 (MF)	SAA	35	Unrelateed (FM)	CD3 Selection	NO
19 (MA)	AML	55	Related (9/10)	CD3/CD19 depletion	Grade II
20 (SF)	MD	7	Related (FM)	TCRαβ/CD19 Depletion	NO

Take home

- Choose an appropriate combination of immunosuppressants with respect to the pharmacokinetics and pharmacodynamics in the target species
- Single-drug protocols should be limited to verified exemptions

- Along with the changing transplant population, the field of HCT has dramatically shifted in the past decade because of the widespread adoption of posttransplantation cyclophosphamide (PTCy), which has increased the use of HLA-mismatched related donors to levels comparable to HLA-matched related donors.

- Role of biomarkers
- Preventive algorithm based on biology
- Graft manipulation accessible for bmt ward


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