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Delayed Onset of Chronic GVHD in Patients Receiving RGI-2001 Prophylaxis: A Multicenter Phase 2b Study with Comparison to CIBMTR Matched Cohort Data

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INTRODUCTION

Chronic GVHD (cGVHD) remains a major cause of morbidity following allo-HCT.
The donor-derived effector T cells to host can evoke dysregulated reconstitution of T and B cell subsets, leading to the pathogenesis of cGVHD.
RGI-2001, a novel invariant natural killer T (iNKT) cell agonist, induces Tregs which engages CD1d high B cell uptake, promoting immunoregulation through NKT-Treg interactions.
RGI-2001 x 6 weekly doses + TAC/MTX was effective with a very low incidence of aGVHD.[1] We speculated that Treg-mediated immunomodulation may extend beyond the dosing window (day 0-35) post allo-HCT and can prevent cGVHD.

OBJECTIVES & METHODS

Review severity with attention to time of onset of cGVHD in RGI-2001 participants and correlate with Treg and NKT cell kinetics.

- Individual patients in the phase 2b study (RGI-2001-003) who developed moderate to severe cGVHD by NIH criteria were identified.
- Early onset cGVHD was defined as < Day 120.
- Time to onset from allo-HCT to cGVHD was tabulated and incidence was calculated. Data were compared to a concurrent CIBMTR control cohort.
- CIBMTR dataset was procured per study protocol.

RESULTS

aGVHD incidence, GVHD Free Survival (GFS), cGVHD (D180) and Overall Survival (OS) were statistically improved in the RGI-2001 participants compared with the CIBMTR control (Table 2)

cGVHD (mod-severe) incidence at D180 was lower in the RGI-2001-003 cohort (10.4%) vs the CIBMTR cohort (21.1%) (Table 2); suggesting a 50% risk reduction in early cGVHD onset.

This observation prompted a focus on cGVHD onset kinetics. Cumulative incidences curves plotted through 1 yr post-transplant demonstrated patients had markedly low cGVHD through D180. (Figure 2). At D120, cGVHD incidence for RGI-2001 vs CIBMTR control were 2.1% vs 9.1% (p=0.044)(Figure 3).

The delayed occurrence of cGVHD suggests a sustained immunomodulatory effect beyond the dosing window (RGI-2001 last dose on D35).

Correlative analyses of Tregs and NKT cells support this hypothesis. **Patients who did not develop cGVHD had higher levels of both cell populations** by D42 (Figures 4 and 5; Grey lines- No cGVHD, Green- Yes cGVHD). Early and robust reconstitution of donor-derived NK cells after allo-HCT was associated with a lower incidence of cGVHD.

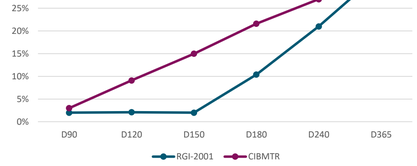
Over time, Tregs can fail to maintain homeostasis due to apoptosis and Treg exhaustion can lead to GVHD emergence. Decrease in Tregs is associated with an increase in GVHD severity[2].
RGI-2001 activates iNKT cells which produce cytokines leading to proliferation and expansion of Tregs. Tregs suppress alloreactive T cells and produce anti-inflammatory cytokines abrogating the onset of aGVHD[3,4]. (Figure 6).

Table 2. GVHD Outcomes and Survival RGI-2001-003 Study

Outcomes	RGI-2001 N=48	CIBMTR N=207	Hazard Ratio* 95% CI	P value
aGVHD (GIII-IV) D180	4.2%	14.0%	0.22 (0.07-0.64)	0.006
GFS (GIII-IV) D180	91.7%	77.3%	0.26 (0.12-0.57)	0.001
Chronic GVHD D180**	**10.4%**	**21.1%**	**0.48 (0.26-0.90)**	**0.023**
Chronic GVHD 1 yr**	33.3%	33.2%	0.88 (0.58-1.34)	0.56
OS 1 yr	91.7%	79.2%	0.32 (0.15-0.68)	0.003

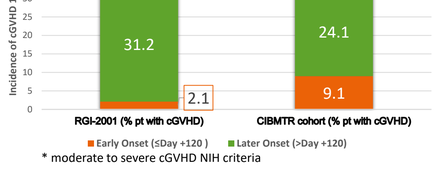
*adjusted IPTW Hazard Ratio, ** moderate to severe cGVHD NIH criteria

Figure 2. cGVHD incidence by Days Post Allo-HCT in RGI-2001 and CIBMTR cohorts



RGI-2001 cGVHD onset is later (delayed) with the incidence remaining significantly lower through D180

Figure 3. cGVHD incidence at Day 120



Early onset cGVHD was lower in RGI-2001 cohort vs. CIBMTR cohort (2.1% vs 9.1%) p=0.044, Fisher's exact test)

Figure 4. Tregs in patients with or without chronic GVHD who received RGI-2001

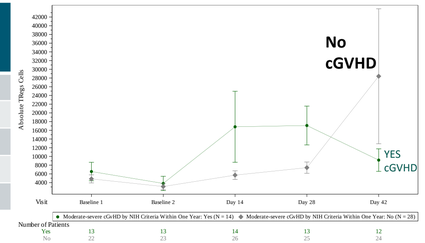
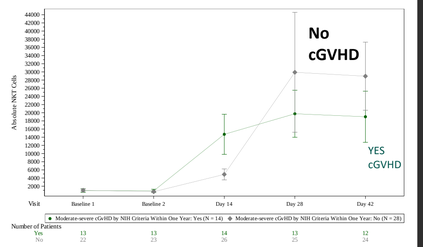
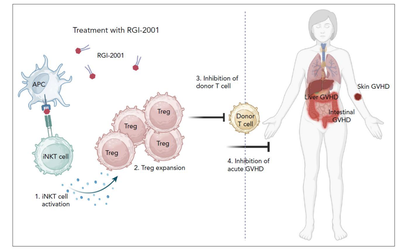


Figure 5. NKT cells in patients with or without chronic GVHD who received RGI-2001



By Day 42 after allo-HCT, Abs Tregs and NKT cells were higher in subjects without cGVHD

Figure 6. RGI-2001 Mechanism of Action



Mechanism of action of RGI-2001. RGI-2001 is a glycolipid presented through the CD1d molecule of APCs and thereby selectively activates iNKT cells. The iNKT cells produce cytokines resulting in proliferation and expansion of Tregs. Tregs suppress alloreactive T cells and produce anti-inflammatory cytokines abrogating the onset of aGVHD.

DEMOGRAPHICS

Forty-eight-8/8 HLA-matched participants received RGI-2001+ Tac/MTX for GVHD prophylaxis during allo-HCT. CIBMTR control cohort included 207 patients Demographics and risk factors were comparable (Table 1).

Table 1. Demographics and Risk Factors

	RGI-2001 N=48	CIBMTR matched cohort N=207
Age: median (range)	52 (21-65)	50.4 (18-66)
Female (%)	43.8	45.9
PBSC Graft source (%)	81.3	82.6
MAC Conditioning (%)		
Fludarabine/Busulfan	83.3	69.1
TBI/Cyclophosphamide	12.5	15.0
aGVHD prophylaxis		
Tac/MTX (%)	100	99
HLA Matched Unrelated 8/8 (%)	66.7	61.4
CMV Serostatus (%)		
Recipient+/Donor + or -	66.7	69.1
Recipient-/Donor +	10.4	10.6

CONCLUSIONS

1. RGI-2001 shifted the temporal onset of cGVHD, significantly reducing early cases and delaying onset beyond day 120 post-transplant.
2. **The delayed onset of cGVHD** suggests RGI-2001 may have **disease modifying potential.**
3. RGI-2001 induces Tregs expansion promoting immunoregulation through NKT-Treg interactions[5]. The effect may be driven by Treg-mediated immunomodulation that persist beyond the acute phase**; further Treg-mediated restraint may allow effector T cells to persist longer, potentially benefiting the graft-versus-leukemia effect and altering the pathogenesis of cGVHD**
4. The current RGI-2001 dosing regimen was designed for aGVHD prevention and demonstrated clinical efficacy in this setting. **These analyses indicate a potential benefit of RGI-2001 for prevention of cGVHD. Ongoing Treg expansion is likely required for long term cGVHD control.**
5. These findings support further investigation by **extending RGI-2001 dosing** beyond the first 6 weeks after allo-HCT to **maintain long-term immune tolerance** and reduce overall cGVHD incidence.

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NOTE: Authors acknowledge the limitation of a registry (CIBMTR) comparison. CIBMTR data was limited to RGI-2001 study centers only. Robust statistical methods (IPTW) utilized to maintain equipoise.

FINANCIAL DISCLOSURES

Investigators (ZD,HC,YE,AS,SF,LL,JY,GS,MM,AA,YC) participated in RGI-2001-003 (**NCT04014790**) received research funding.

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