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Comparative Evaluation Of Baseline Risk Factors And Acute GVHD Outcomes In Allogeneic Hematopoietic Cell Transplant (ALLO-HCT): RGI-2001 Or Abatacept-based Prophylaxis Studies

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INTRODUCTION

Acute graft-versus-host disease (aGVHD) is a major complication following allo-HCT. RGI-2001, a novel invariant natural killer T (iNKT) cell agonist, is under investigation for aGVHD prophylaxis. Abatacept is FDA-approved for this indication.[1]

Cross-trial comparisons are challenging due to heterogeneous transplant populations and variation of institutional practices such as conditioning regimens, donor, graft sources, and prophylaxis.

OBJECTIVES

We provide a practical evidence-synthesis approach for cross-trial comparisons without meta-analysis by decomposing study populations, design features, statistical methods, and differences between literature-reported and regulatory endpoints, illustrated through comparative evaluation of phase 2 aGVHD prophylaxis studies of RGI-2001 and abatacept.

METHODS

Evidence Identification, Selection, and Review

Published phase 2 clinical studies evaluating RGI-2001 or abatacept for aGVHD prophylaxis were identified through targeted searches of PubMed and Embase:

- Only full-text peer-reviewed publications and publicly available regulatory reviews were included.
- For abatacept, regulatory analyses from the FDA were reviewed in parallel with the primary trial publication to capture differences in analytical intent and endpoint specification.
- Two authors (PY and DL) independently extracted data which were reviewed by the third author (KT).

Population Restriction, Baseline, and Outcomes Characterization

To improve interpretability across heterogeneous transplant populations, analyses were restricted to 8/8 HLA-matched donor cohorts.

- Baseline characteristics and aGVHD-free survival (GFS) outcomes were extracted and tabulated.
- No attempt was made to re-analyze them across trials.
- Outcomes are visualized in a forest plot for the respective studies:
  - ❖ Watkins' analyses on abatacept were based on hazard ratio (HR) with 80% confidence intervals (CI).[2]
  - ❖ Thus, we display FDA analyses based on HR with 95%CI from relevant literature to ensure compatibility.

RESULTS

Population and Baseline Risk[4]

Key differences in the active treatment arms of both studies are shown in Table 1:

- RGI-2001 study enrolled adults (≥18 years) with the median age of 52. In abatacept study, pediatrics patients were included from age 7 with the median age of 44.1.[2]
- More RGI-2001 patients (81.3%) received PBSC than abatacept patients (54.8%).
- A higher proportion of donor-recipient sex mismatch were observed in RGI-2001 study (45.8%) than in the abatacept study (34.3%).
- Conditioning regimens and prophylaxis varied across studies.

Table 1. Baseline Risk Factors in RGI-2001 and Abatacept Studies[2,3]

Parameters	RGI-2001[a] 8/8 MRD and MUD (N=48)	Abatacept 8/8 MUD[b] (N=73)
Median age (yr) (range)	52 (21–65)	44.1 (6.9–71.9)
Graft source (%)		
PBSC	81.3	54.8
BM	18.8	45.2
Donor-recipient sex mismatch (%) Total (F/M+M/F)	45.8 (22.9+22.9)	34.3 (15.1+19.2)
Conditioning regimen (%)		
FluBu	83.3	9.6
TBI-Cy	12.5	27.4
BuCy	2.0	38.4
FluMel	--	24.7
CNI-based prophylaxis (%) Tacrolimus	100	84.9
Cyclosporine	--	15.1

[a]RGI-2001 (8/8): open, label (n=48 vs CIBMTR n=207) (2017–2019) (NCT04014790)
[b]Abatacept (8/8): randomized (n=73 vs. Placebo n=69), including pediatric patients (ages≥1 yr =22%) (NCT01743131)
Bu Cy, busulfan and cyclophosphamide; Bu Flu, busulfan and fludarabine; Mel Flu, melphalan and fludarabine; TBI, total body irradiation; CNI, calcineurin inhibitor; MRD, matched related; MUD, matched unrelated

Analytical Methods and Outcomes: RGI-2001[2]

We constructed Table 2, Figure 1 and 2 to illustrate how inverse-probability-of-treatment weighting (IPTW) was used in the Cox regression to achieve equipoise with CIBMTR control (mimicking randomization) and treatment outcomes:

- By adjusting for age, donor type, stem cell source, donor and recipient CMV status, disease risk index (DRI), and comorbidity burden (HCT-CI).
- Patients with similar clinical profiles therefore had similar estimated probabilities of receiving treatment.

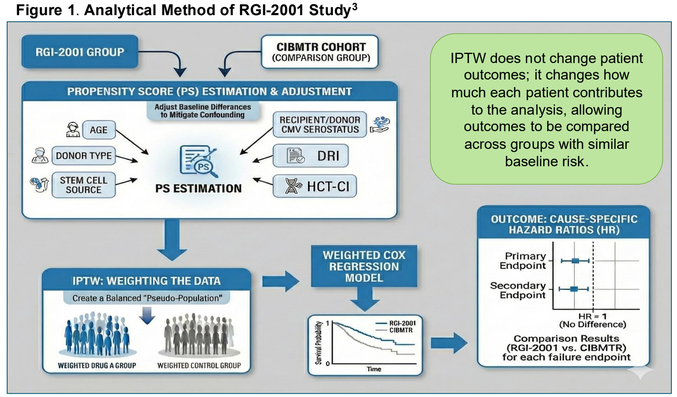
Table 2. Acute GVHD Outcomes: RGI-2001[3]

Parameters	RGI-2001 8/8 MRD and MUD (n=48)	CIBMTR Control (n=207)	IPTW-Adjusted Hazard Ratio (95%CI)	p-value
DeFilipp et al Grades III-IV acute GVHD-free survival by Day 180	91.7%	77.3%	0.26 (0.12-0.57)	0.001
Grades II-IV acute GVHD-free survival by Day 180	70.8%	50.7%	0.45 (0.30-0.68)	<0.001

Clinical Interpretation
After adjustment for baseline transplant risk using IPTW:

- Patients receiving RGI-2001 **experienced substantially lower risk** of developing severe (grade III–IV) aGVHD or death by Day 180 compared with matched CIBMTR controls. **An HR of 0.26 indicates approximately a 74% relative reduction in risk, with the confidence interval excluding 1.0, supporting a statistically significant result.**
- RGI-2001 was also **associated with a significantly lower risk** of developing any clinically relevant (grade II–IV) aGVHD or death by Day 180. **The HR of 0.45 corresponds to an approximate 55% relative risk reduction.**

Figure 1. Analytical Method of RGI-2001 Study[3]



Analytical Methods and Outcomes: Abatacept[1,2,4]
Publication (Watkins B et al)

Phase II screening endpoint is **100-day severe (grade III-IV) aGVHD**; Log-rank test **(one-sided α=0.05) and HR with 80%CI** were presented (Table 3).

FDA Analysis (Norsworthy KJ et al)

Per FDA guidance, the sponsor changed the primary endpoint to **grade III–IV GFS 180 days** with **a two-sided α of 0.05** during the trial (**HR and 95%CI)** (Table 3; Figure 2).

Table 3. Acute GVHD Outcomes: Abatacept[1,2,4]

Parameters	Abatacept 8/8 MUD (n=73)	Placebo (n=69)	Hazard Ratio (95%CI)[a]	p-value
Abatacept Prescribing Information[a] Grades III-IV acute GVHD-free survival by Day 180	87%	75%	0.55 (0.26-1.18)	Not Reported[b]
Grades II-IV acute GVHD-free survival by Day 180	50%	32%	0.54 (0.35-0.83)	Not Reported
Parameters	**Abatacept 8/8 MUD (n=73)**	**Placebo (n=69)**	**Hazard Ratio (80%CI)[c]**	**p-value**
Watkins B et al[c] aGVHD Grade III-IV Day 100	6.8%	14.8%	0.45 (0.22–0.90)	0.14

[a]Orencia (abatacept) prescribing information, Bristol-Myers Squibb, May 2024. **Outcome analyses were based on 95%CI.**
[b]Per Orencia prescribing information 5/2024: ORENCIA + CNI and MTX did not significantly improve grade III-IV GFS versus placebo + CNI and MTX at Day 180 post-transplantation.
[c]Watkins B et al. J Clin Oncol. 2021;39(17):1865-1877. **Outcome analyses were based on 80%CI.**

FDA Interpretation (Norsworthy KJ et al)

- **The primary endpoint grade III–IV GFS D180 was not significant** for the abatacept arm (HR 0.55; 95%CI, 0.26–1.18; p-values not reported) (Note: 95%CI **includes** 1, indicating statistically insignificant result).
- The secondary endpoints of grade II–IV GFS (HR 0.54; 95%CI, 0.35–0.83; p-value not reported) at D180 demonstrated evidence of efficacy. (Note: 95%CI **excludes** 1, indicating statistically significant result).*

Publication Interpretation (Watkins B et al)

- aGVHD GIII-IV D100 incidence was 6.8% (abatacept) versus 14.8% (placebo) (HR 0.45; 80%CI, 0.22–0.90; P=0.14). (Note: **80%CI excludes** 1, indicating statistically significant result).*

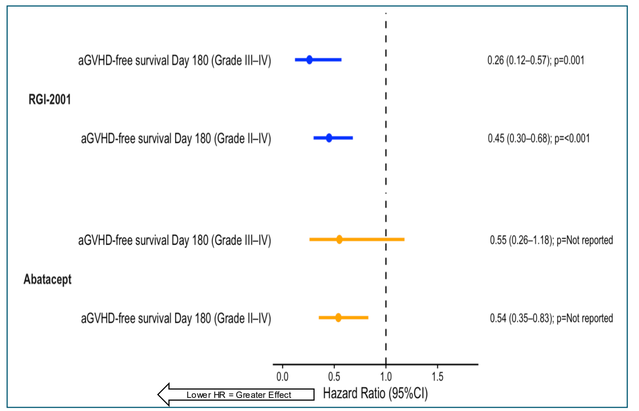
***Statistical Pearl for Clinicians**

- The **80%CI** is narrower and less stringent, easier to exclude HR=1.0.
- The **95%CI** is wider and more stringent, harder to exclude HR=1.0.[6]
- **FDA typically utilizes 95% CI and a significant p value to ascertain substantial evidence for drug approval.**[7]

Figure 2. Forest Plot of RGI-2001 vs CIBMTR Controls and Abatacept vs Placebo[1,3,4,6]

RGI-2001
- Both 95%CIs excludes 1, indicating statistically significant results
- Both 95%CIs are relatively narrow, reflecting good precision and stability of the estimated treatment effects.
- Both HR point estimates and 95% CIs align on the left side, suggesting a coherent and robust protective effect across endpoints

Abatacept
- Grade III–IV: 95% CI crosses 1.0, indicating statistically non-significant results
- Grade II–IV: 95% CI excludes 1.0, showing significant result
- Although both point estimates lie to the left of HR = 1, 95%CIs show inconsistent effects across GVHD severity endpoints.



Forest plot showing hazard ratios (HR) with 95% CI for RGI-2001 and Abatacept prophylaxis versus respective controls. Outcomes are illustrated for survival endpoints (Tables 2–3). All analyses are based on 95% CI for comparability.

CONCLUSIONS

We demonstrated a pragmatic approach to cross-trial evidence synthesis without conducting a formal meta-analysis. Our findings showed that the observed differences between the RGI-2001 and abatacept studies reflected not only differences in outcomes, but also the impact of statistical methods and differences between regulatory and literature-based perspectives. The use of IPTW statistical analysis in the RGI-2001 study provides a robust and clinically relevant comparison with real-world registry data. Greater adoption of such methods would facilitate the meaningful integration of real-world data into clinical trials.

Cross-trial comparisons are most informative when used to contextualize and elucidate differences rather than infer relative efficacy. Adoption of structured evidence-synthesis approaches may improve clinical interpretation and support rigorous evaluation of future aGVHD prophylaxis strategies.

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