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Allogeneic Stem Cell Transplantation Rates and Outcomes in Severe Leukocyte Adhesion Deficiency Type I (LAD-I): A Systematic Literature Review

Joana E Matos, Maria C Chitty-Lopez, Stuart Turner, Miranda Bailey, Jonathan D Schwartz, Gayatri R Rao

Rocket Pharmaceuticals, Inc., Cranbury, NJ, USA

Conclusions

- Severe leukocyte adhesion deficiency type 1 (LAD-I) is a universally fatal disease associated with a significant burden of infection- and hyperinflammation-related morbidity.[1–3] Allogeneic hematopoietic stem cell transplant (Allo-HSCT) is currently the only available definitive treatment option[4]
- Substantial delays in LAD-I diagnosis prevent early access to potentially curative treatment and may indicate a potential gap in disease awareness, highlighting the need to increase LAD-I education amongst healthcare professionals
- Despite indications from expert treating centers that most patients with severe LAD-I should receive allo-HSCT[5], results from this analysis indicate utilization rates are lower than expected, globally and in countries with advanced healthcare systems
- Consistent with the findings of other studies,[2,4] matched sibling donor (preferable donor) availability was limited globally; and among transplant recipients, a substantial risk of poor outcomes (graft-vs-host disease [GVHD], graft failure, and death) continue to be reported even in countries with advanced healthcare systems
- These results support
  - An urgent unmet need for the development of well-tolerated, efficacious, and innovative treatment alternatives for severe LAD-I
  - The need for international consensus guidance to support early identification and diagnosis of patients, taking into account clinical presentation and laboratory findings

Background

- Severe LAD-I is a rare, life-threatening inborn error of immunity caused by mutations in the *ITGB2* gene leading to reduced or defective cluster of differentiation (CD) 18 and/or CD11 a/b neutrophil expression and is characterized by frequent refractory infections and hospitalizations, recurrent skin and periodontal lesions, impaired wound healing, and substantial pediatric mortality[2,3,6,7]
- The prognosis for LAD-I is extremely dire despite supportive care measures such as prophylactic antimicrobials[8]
- Currently, the only definitive option for treating severe LAD-I is allo-HSCT; however, utilization of allo-HSCT is limited by donor availability and recognition of the substantial transplantation-related morbidity and mortality[2,4,9,10]

Objectives

- The main objective of this systematic literature review was to further characterize the natural history of LAD-I in patients with a severe phenotype of LAD-I, with an emphasis on transplantation-related trends and outcomes globally and in a group of countries with more advanced healthcare systems (US, Canada, EU, UK, Japan, and Israel)

Methods

Study Design

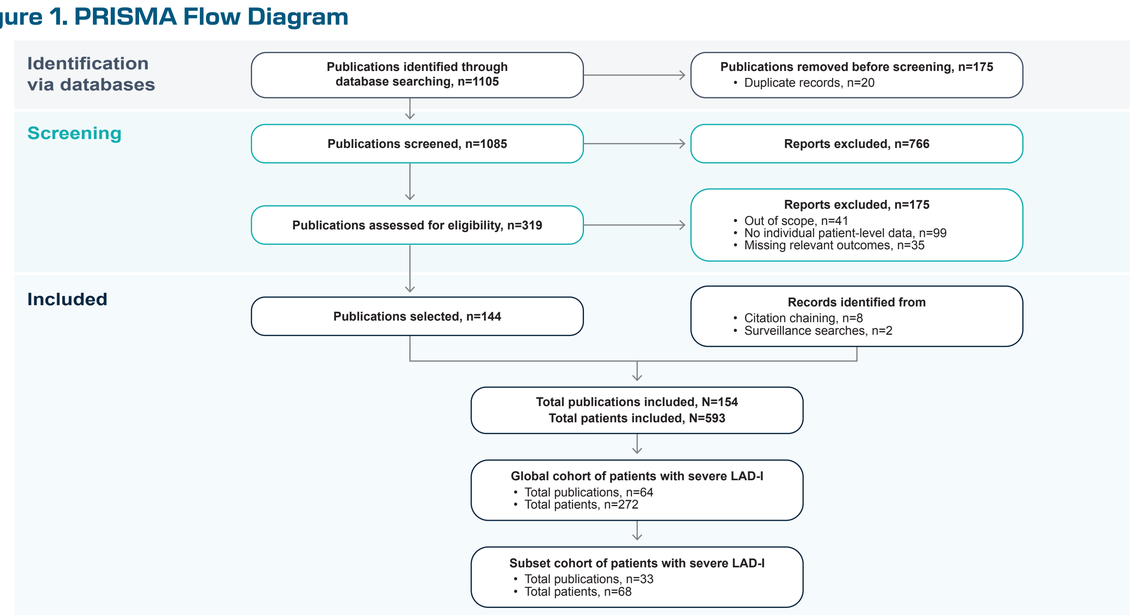
- A systematic literature review was conducted using the following criteria and selection strategy:
  - Peer-reviewed publications published in English with individual LAD-I patient data including percentage of CD18 and/or CD11a/b expression
  - Sources included: MEDLINE, Embase, Cochrane Library, and citation chaining
  - Search terms: (((“Leu?ocyte adhesion deficiency type 1” OR “leu?ocyte adhesion defect type 1” OR “Leu?ocyte adhesion deficiency-I” OR “Leu?ocyte adhesion deficiency-1” OR “type 1 leu?ocyte adhesion deficiency” OR “Leu?ocyte adhesion defect-I” OR “leu?ocyte adhesion deficiency” OR “type i leu?ocyte adhesion deficiency”) OR (“LAD-1” OR “LAD type 1” OR “LAD-I” OR “LAD type I”) OR (“leu?ocyte adhesion” AND (“defect-1” OR “defect type 1”)) OR ((MESH.EXACT(“leukocyte adhesion deficiency syndrome”)) AND (ti,ab(“type 1” OR “type I”)))) NOT (“left anterior descend*” OR “left atrial diameter” OR “anti-LAD-1” OR “light-activated disinfection” OR “distal LAD” OR “LABD” OR “zebrafish” OR “pig*” OR “rat” OR “canine”)) AND (la.exact(“ENG”) NOT rtype.exact(“Conference Abstract” OR “Editorial”))

Results

Study Selection

- Of the 1105 initially identified publications, duplicates were removed, and titles and abstracts were screened for eligibility. The final full-text review included 154 publications published from 1982 through 2022 (**Figure 1**)
- One reviewer extracted data from the included articles into a data extraction template, that was then verified by 2 other reviewers. For patients reported in multiple publications, data were consolidated to ensure that each patient was only counted once
- The analysis of clinical outcomes included only patients with severe disease, defined as patients reported in the publications as having CD18 <2% or CD18 ≥2% with concomitant CD11a/b <2% measured in polymorphonuclear cells, neutrophils, or granulocytes
- A total of 593 patients were identified in the 154 publications. Among those, 272 patients were classified as having severe LAD-I based on the publications reporting the percentage of CD18 and/or CD11 a/b expression
- Most patients with severe LAD-I were documented in publications from India, Pakistan, and Algeria (n=169, 62.1%). Results are presented as a global cohort (all severe LAD-I patients, n=272) and a subset cohort of 33 publications (n=68 patients, 25.0%) from countries with more advanced health care systems (US, Canada, EU, UK, Japan, and Israel; **Figure 1**)

Figure 1. PRISMA Flow Diagram



LAD-I, leukocyte adhesion deficiency type I.

Baseline Characteristics for Patients With Severe LAD-I

- In the global cohort (n=272), 47.4% of patients were female, 48.9% were male, and 3.7% did not have their sex specified; mean (standard deviation [SD]) age at first symptom was 2.2 (10.2) months and mean (SD) age at diagnosis was 13.5 (29.2) months (**Table 1**)
  - The sex distribution, age at first symptom, and age at diagnosis was not dissimilar between the global and subset cohort. However, the age at last follow-up was substantially larger in the subset cohort (mean, 65.2 mo; median, 30.6 mo) vs the global cohort (mean, 32.4 mo; median, 6.0 mo)

Table 1. Baseline Characteristics for Patients With Severe LAD-I

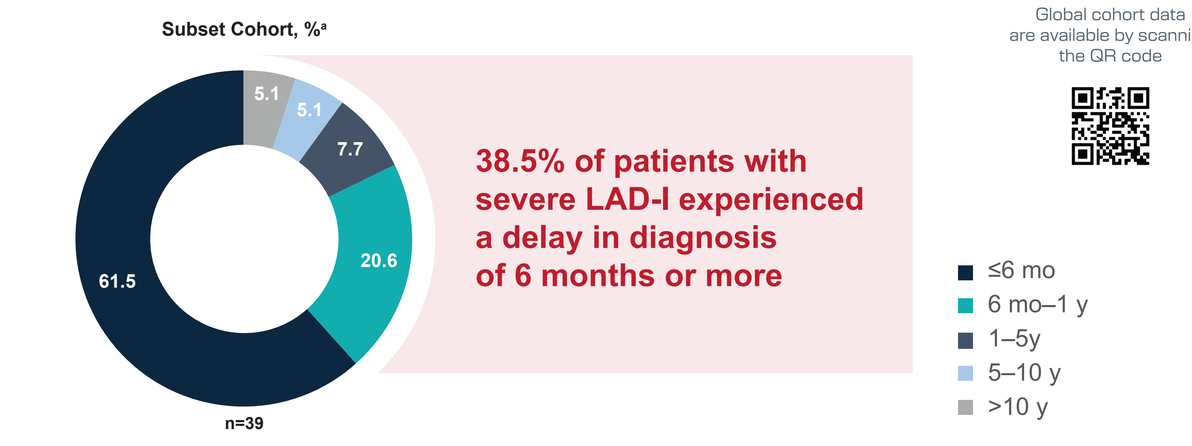
	Global cohort (n=272)	Subset cohort (n=68)
Sex, n (%)		
Female	129 (47.4)	33 (48.5)
Male	133 (48.9)	35 (51.5)
Not stated	10 (3.7)	0
Age at presentation, mo		
n	236	46
Mean (SD)	2.2 (10.2)	1.6 (5.2)
Median (IQR)	0.7 (0.2–1.0)	1.0 (0.3–1.0)
Age at diagnosis, mo		
n	214	49
Mean (SD)	13.5 (29.2)	16.3 (33.9)
Median (IQR)	3.0 (1.0–9.0)	3.0 (1.0–11.0)
Age at last follow-up, mo		
n	261	67
Mean (SD)	32.4 (53.4)	65.2 (70.3)
Median (IQR)	6.0 (2.0–39.0)	36.0 (7.0–110.0)

IQR, interquartile range; LAD-I, leukocyte adhesion deficiency type I; SD, standard deviation.

Time From First Symptom Onset to Diagnosis in Patients With Severe LAD-I

- The results demonstrated substantial delays (>6months) from first symptom onset to diagnosis in both cohorts (global vs subset; supplementary material)
- Interestingly, over 10% of patients in the subset cohort faced a delay to diagnosis of 5 years of more after initial symptom onset (**Figure 2**)

Figure 2. Time From First Symptom Onset to Diagnosis in Patients With Severe LAD-I in the Subset Cohort



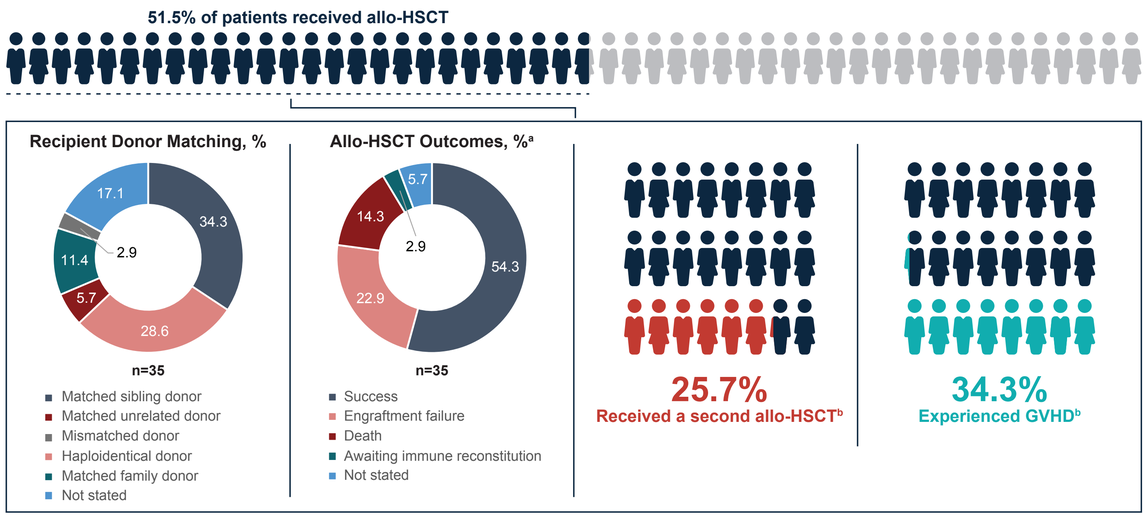
Global cohort data are available by scanning the QR code

LAD-I, leukocyte adhesion deficiency type I.
[a]Patients for whom an age at first symptom and/or at diagnosis were not available were excluded from the analysis.

Allo-HSCT Rates and Outcomes in Patients With Severe LAD-I

- Despite being the only available definitive treatment for severe LAD-I,4 results demonstrated relatively low reported utilization of allo-HSCT in the global and subset cohorts (24.3% and 51.5% respectively)
- Reported transplant outcomes in the subset cohort were not dissimilar from other published reports[2,4] (**Figure 3**)
  - Matched sibling donor transplants, which are regarded as having the highest success rates, were available and used in only about one-third of transplantations
  - Allo-HSCT was successful with the first transplant in approximately half of cases; the main complications associated with allo-HSCT included GVHD in 34.2% of patients, engraftment failure in 22.9%, and death in 14.3%
  - Approximately one-fourth of patients required a second transplant

Figure 3. Allo-HSCT Rates and Outcomes of Patients With Severe LAD-I in the Subset Cohort



GVHD, graft-vs-host disease; allo-HSCT, allogenic hematopoietic stem cell transplantation.
[a]Percentages may not add up to 100 because of rounding.
[b]Of patients who received a first allo-HSCT (n=35).

Full global and subset cohort data are available by scanning the QR code

Limitations

- Limitations to this analysis include potential publication biases that may reflect a preference for reporting more severe cases, favorable outcomes, or unique presentations of severe LAD-I
- Many of the included publications (especially those from low- or middle-income countries) did not contain detailed data, often excluding age at transplantation or death, or were missing data on outcomes
- The rarity of LAD-I is reflected in the relatively low number of publications for analysis, resulting in the need for a relatively long range of publication dates to ensure adequate patient sample size and data for analysis

References 1. Kambli PM, et al. *Front Immunol.* 2020;11:612703; **2.** Almarza Novoa E, et al. *J Allergy Clin Immunol Pract.* 2018;6(4):1418-1420 e1410; **3.** Fischer A, et al. *Immunodefic Rev.* 1988;1(1):39-54; **4.** Qasim W, et al. *Pediatrics.* 2009;123(3):836-840; **5.** Data on file. Rocket Pharmaceuticals. Delphi Panel Report. 2024; **6.** Levy-Mendelovich S, et al. *Immunol Res.* 2016;64(2):476-482; **7.** Deshpande P, et al. *Indian J Pediatr.* 2016;83(8):799-804; **8.** Madkaikar M, et al. *Indian Pediatr.* 2012;49(1):43-45; **9.** Bakhtiar S, et al. *Blood Adv.* 2021;5(1):262-273; **10.** Kanate AS, et al. *J Natl Compr Canc Netw.* 2020;18(5):635-643.

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