LAD-I is a rare disorder of leukocyte adhesion, characterized by infections, granulocytosis, and absence of pus. It results from mutations in the ITGB2 gene, which encodes integrin β2 (CD18). Reduced CD18 expression (<2%) is associated with a poor prognosis in the absence of HSCT. The purpose of this study was to update the natural history of severe LAD-I and assess the role of CD18 expression as a predictor of prognosis.

Methods:
- A descriptive analysis of published cases of severe LAD-I with CD18 expression <2%.
- Kaplan-Meier survival analysis with log-rank test for comparison of survival outcomes.
- Multivariate Cox proportional hazards regression for assessment of prognostic factors.

Results:
- Survival to age 2 years was reported for 265 patients with severe LAD-I and CD18 expression <2%.
- Survival was 17% at age 2 years, with 61% mortality at age 20 years.
- The median age at presentation was 6 months, with a range of 0-24 months.
- Infection details and CD18% were available for 154 (48%) cases.
- The most frequent infections in pts with CD18 <2% were skin ulcers (8%, umbilical complications (92% of pts), and respiratory infections (33%).
- Mutation type provided: n=100.
- ITGB2 mutations on Exons 5, 6 and 7 accounting for 44% of specified cases. In 18 cases, CD18 expression was available; <2% for 17 cases, >4% for 1 case.
- ITGB2 -4% (CD18 <2%): Survival to age 2 years was 17%.
- ITGB2 >4% (CD18 >2%): Survival to age 2 years was 77%.
- Kaplan-Meier survival estimates for patients with moderate LAD-I not receiving allogeneic HSCT, by neutrophil CD18 expression.

Conclusions:
- Prognosis for severe LAD-I in the absence of HSCT is poor, with a median survival to age 2 years of 17%.
- CD18 expression <2% is associated with a poor prognosis.
- HSCT is curative in approximately 75% of cases, however engraftment failure, HSCT-related mortality are frequent.
- Multivariate Cox proportional hazards regression for assessment of prognostic factors.
- These observations provide additional rationale for the initiation of an LAD-I clinical trial evaluating LV-based gene therapy of autologous CD34+ cells.

References:

Figure 1. Overview of cases: Table 1. Patient numbers by country:

Figure 2. LAD-I cases by transplant status, severity & duration of follow-up:

Figure 3. Survival to age 2 in absence of HSCT based on CD18 expression:

Figure 4. Gene and protein map of reported ITGB2 mutations:

Figure 5. Neutrophil CD18 expression:

Figure 6. Neutrophil CD18 expression:

Table 1. Patient numbers by country:

Table 2. Survival to age 2 in absence of HSCT based on parameters of severity:

Table 3. Infections & umbilical complications based on severity:

Table 4. Allogeneic stem cell transplant (HSCT) outcomes (n=101):

Table 5. Risk of infection after HSCT:

Table 6. HSCT outcomes:

Figure 7. Kaplan-Meier survival analysis with log-rank test for comparison of survival outcomes:

Figure 8. Multivariate Cox proportional hazards regression for assessment of prognostic factors:

Figure 9. These observations provide additional rationale for the initiation of an LAD-I clinical trial evaluating LV-based gene therapy of autologous CD34+ cells: