Factors associated with favorable 5 year outcomes in islet transplant alone recipients with type 1 diabetes complicated by severe hypoglycaemia in the Collaborative Islet Transplant Registry
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Factors associated with favourable 5 year outcomes in islet transplant alone recipients with type 1 diabetes complicated by severe hypoglycaemia in the Collaborative Islet Transplant Registry

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What is relevant?

1. **Lack of large pediatric cohorts** in recent publications on islet transplantation

2. Benefits of islet transplantation alone in **adult** patients with type 1 diabetes (complicated by severe hypoglycemia)

3. Identification of **4 factors associated with favourable 5 year outcomes** after islet transplantation

4. 3 out 4 factors **are not directly related to patient age**

5. Lessons learnt from large adult transplant cohort could serve pediatric patients

6. Incl. teenagers in comparable clinical setting
Methods I

1. Based on data from the Collaborative Islet Transplant Registry (CITR), the largest collection of human islet transplant data in the world

2. Retrospective analysis included 398 individuals with type 1 diabetes and at least 1 severe hypoglycaemic events (SHE) who received an allogeneic islet transplant alone (ITA) between 1999 and 2015
### Methods II

3. **Outcomes analyzed:**

| 1. HbA1c <53 mmol/mol (7.0%) and absence of SHEs | 4. Fasting C-peptide ≥0.1 nmol/l |
| 2. HbA1c <53 mmol/mol (7.0%) | 5. Fasting glucose of 3.3–7.8 mmol/l |
| 3. Absence of SHEs | 6. Insulin independence |

4. **Serious adverse events (SAE) related to islet product/infusion procedure or to the immunosuppression regimen**

5. **Univariate analysis and multivariate analysis to identify predictors associated with the highest prevalence of successful study outcomes across all the outcomes investigated**
Baseline characteristics of study cohort

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Immunosuppression</th>
<th>Islet preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age was 46 ± 10 years with 30 ± 11 years of diabetes</td>
<td>54% received induction regimens that included TCD antibodies and/or TNF-α inhibition and</td>
<td>Mean ± SD cold ischemia time was 7.7 ± 4.7 h and culture time was 20.5 ± 16.7 h (which included 19% not cultured)</td>
</tr>
<tr>
<td>0.53 ± 0.18 U/kg daily insulin usage</td>
<td>78% were maintained on regimens of calcineurine and mechanistic target of rapamycin (mTOR) inhibition</td>
<td>Mean ± SD total IEQs infused over one to six infusions was 863,000±395,000</td>
</tr>
<tr>
<td>9.4 ± 4.8 mmol/l fasting glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61.5 ± 13.9 mmol/mol HbA1c (7.8 ± 3.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results: The common favourable factors (CFF)

Four factors were strongly associated with higher prevalence (≥10%) across all the desired outcomes of islet transplantation:

• Recipient age ≥35 years
• Total of ≥325,000 IEQs infused over one to several infusions
• Induction with TCD antibodies and/or TNF-α inhibition
• Maintenance with calcineurine inhibitors (CNI) and mTOR inhibitors (for at least some portion of follow-up)
Results: The common favourable factors (CFF)

Presence of these 4 common favourable factors (4CFF) defines two subgroups:

4CFF (N=126) vs. <4CFF (N=272)
Main study outcomes I

Observed prevalence rates of the study outcomes in the 4CFF subgroup (favorable factors, n=126) vs the <4CFF subgroup (others, n=272).
Main study outcomes II

Observed prevalence rates of the study outcomes in the 4CFF subgroup (favourable factors, n=126) vs the <4CFF subgroup (others, n=272)
Main study outcomes III

Observed prevalence rates of the study outcomes in the 4CFF subgroup (favorable factors, n=126) vs the <4CFF subgroup (others, n=272)
Induction therapy and prevalence of insulin independence

Prevalence of insulin independence 1–5 years post last infusion
## Maintenance immunosuppression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>4CFF Base-line</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>4 Common Favourable Factors Except mTOR+CNI Base-line</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt;53 mmol/mol (7.0%) and Absence of SHEs</td>
<td>0%</td>
<td>83%</td>
<td>78%</td>
<td>77%</td>
<td>73%</td>
<td>73%</td>
<td>0%</td>
<td>63%</td>
<td>62%</td>
<td>59%</td>
<td>67%</td>
<td>57%</td>
</tr>
<tr>
<td>Absence of SHEs</td>
<td>34%</td>
<td>86%</td>
<td>80%</td>
<td>81%</td>
<td>77%</td>
<td>76%</td>
<td>75%</td>
<td>66%</td>
<td>67%</td>
<td>68%</td>
<td>67%</td>
<td>59%</td>
</tr>
<tr>
<td>C-peptide ≥0.1 nmol/l</td>
<td>0%</td>
<td>93%</td>
<td>93%</td>
<td>95%</td>
<td>94%</td>
<td>95%</td>
<td>7%</td>
<td>93%</td>
<td>90%</td>
<td>89%</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Fasting Glucose 3.3–7.8 mmol/l</td>
<td>0%</td>
<td>92%</td>
<td>86%</td>
<td>82%</td>
<td>75%</td>
<td>68%</td>
<td>0%</td>
<td>70%</td>
<td>72%</td>
<td>59%</td>
<td>56%</td>
<td>58%</td>
</tr>
<tr>
<td>Insulin Independence</td>
<td>48%</td>
<td>87%</td>
<td>85%</td>
<td>91%</td>
<td>82%</td>
<td>87%</td>
<td>35%</td>
<td>70%</td>
<td>64%</td>
<td>62%</td>
<td>75%</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>75%</td>
<td>71%</td>
<td>60%</td>
<td>56%</td>
<td>53%</td>
<td>2%</td>
<td>50%</td>
<td>38%</td>
<td>39%</td>
<td>36%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Limitations

• Observational study with its limits (declining completeness of data with increasing length of follow-up)

• Incomplete data could have relevant impact on main findings and conclusions

• The predictors of outcome identified in ITA recipients may not be generalizable to other recipient categories e.g. pediatric patients
Conclusions

• Four factors associated with the highest rates of successful outcomes

• At 5 years after the last islet infusion 95% were
  • protected from severe hypoglycaemia
  • 76% had HbA1c <53 mmol/mol (7.0%)
  • 53% were insulin independent

• Low prevalence of immunosuppression-related serious adverse without complete recovery, disability or death
Conclusions

- Four factors associated with the highest rates of successful outcomes

- At 5 years after the last islet infusion 95% were
  - protected from severe hypoglycaemia
  - 76% had HbA1c <53 mmol/mol (7.0%)
  - 53% were insulin independent

- Low prevalence of immunosuppression-related serious adverse without complete recovery, disability or death

Possible consequences for daily pediatric practice

- Transfer of knowledge about clinical outcomes and benefits of induction therapy and long-term immunosuppressive therapy to pediatric patients
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