Immunotherapeutic agents in type 1 diabetes: a systematic review and meta-analysis of randomized trials

CRD summary
This review assessed the efficacy of non antigen-based immunotherapeutic approaches for the preservation of beta-cell function in patients with type-1 diabetes and concluded that long-term immunotherapy may preserve beta-cell function. The possible exclusion of some potentially relevant trials and the poor quality of the included studies mean the authors’ conclusions should be interpreted with some caution.

Authors' objectives
To assess the efficacy of non antigen-based immunotherapeutic approaches for the preservation of beta-cell function in patients with type 1 diabetes.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched from inception to September 2006 with no language or publication status restrictions. Reference lists of included studies were searched and experts consulted for additional studies. SciSearch was searched for additional studies. Broad search terms were reported; a detailed search strategy was available upon request.

Study selection
Eligible studies were randomised controlled trials (RCTs) with a duration of follow-up of six months or over in which non antigen-based immunotherapeutic agents were evaluated in patients newly diagnosed with type 1 diabetes. RCTs with no relevant events in treatment and control groups were excluded.

The most commonly evaluated intervention was cyclosporine with antibody CD3, antibody CD4, methotrexate, azathioprine, BCG, intravenous immunoglobulin, sodium fusidate, photopheresis and linomide; nicotinamide and buffy coat were also evaluated. These were compared against placebo or no intervention.

Outcomes measured related to beta-cell function and arrest in the development of type 1 diabetes. Age of participants in included studies, where specified, ranged from >3 years to 40 years. Duration of treatment ranged from a single dose to 12 months.

Teams of two reviewers independently screened titles and abstracts for selection. Any disagreements were resolved through consensus or arbitration.

Assessment of study quality
Study quality was independently assessed by pairs of reviewers using these criteria: allocation concealment; blinding of patients, health care providers, data collectors and outcome assessors; whether an RCT was stopped early; the extent of loss to follow-up; and funding source.

Data extraction
Mean differences and 95% confidence intervals (CIs) were extracted. Outcomes were extracted in a hierarchical manner with those considered to be of most importance to patients extracted first. Additional or missing data were obtained by contacting study authors when necessary. Data extraction of continuous outcomes was undertaken in duplicate.

Methods of synthesis
Standardised mean differences (SMDs) and their 95% CIs were pooled using a random-effects (DerSimonian and Laird) meta-analysis. Heterogeneity was assessed using the I^2 statistic (low levels of heterogeneity were defined as 25% and under and high heterogeneity defined as 75% and over). Subgroup analyses were undertaken to explore variation...
across studies in relation to study quality, class of agent, monoclonal antibodies, T-cell inhibitors, other agents, control interventions and length of treatment.

**Results of the review**

Twenty RCTs were included (n = 1,187, range 10 to 188). Studies were generally of poor quality: seven undertook allocation concealment; and 11 reported being at least single-blind. Duration of follow-up ranged from six to 36 months.

There was a significant improvement in preservation of beta-cell function in patients with new-onset type 1 diabetes with immunotherapy treatment compared with placebo (SMD 0.37, 95% CI: 0.14 to 0.60). Within this analysis there was moderate heterogeneity across studies, $I^2=65\%$ (95% CI: 39% to 77%). The only group of drugs to produce a significant effect were the monoclonal antibodies (SMD 0.40, 95% CI: 0.05 to 0.74; three studies, n=133).

Subgroup analysis revealed that the preservation of beta-cell function was improved by cyclosporine and antiproliferative agents when used for six months or longer (SMD 0.77, 95% CI: 0.49 to 1.05) compared with treatment for less than six months (SMD -0.11, 95% CI: -0.56 to 0.33) (p=0.002). No other subgroup analyses were significant.

**Authors' conclusions**

In patients newly diagnosed with type 1 diabetes long-term non antigen-based immunotherapy may preserve beta-cell function.

**CRD commentary**

The review question and inclusion criteria were clear. A small number of databases were searched, but no language or publication status restrictions were placed upon the search, which reduced the potential for language or publication bias. All stages of the review process were conducted in duplicate, which reduced the potential for error and bias. Appropriate criteria were used to assess the quality of the included studies. The extraction of outcomes in an hierarchical manner meant that not all outcomes under evaluation were extracted from all studies; it was unclear which outcome was extracted from which study. Appropriate methods were employed for the meta-analysis, with suitable methods undertaken to assess statistical heterogeneity. A moderate amount of between-study heterogeneity was detected and sub-group analyses were used to explore potential sources. The authors' decision to exclude RCTs in which there were no relevant events in both the treatment and control groups from the review, rather than from individual analyses, was questionable as some relevant studies may have been excluded. Although some analytical methods do not estimate effect sizes from such trials, their inclusion in the review would have contributed to the narrative and to the evidence base for the study question. Within the review there was no indication of the number of studies excluded for this reason and no indication of their quality. Given the limitations of the review and the poor quality of the included studies, the authors' conclusions, although cautious, should be interpreted with care.

**Implications of the review for practice and research**

**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that rigorous trials were required that accurately and precisely measured outcomes of importance to patients. Trial participants could enrol in long-term registries to prospectively ascertain the emergence of late-onset complications of immunotherapeutic agents.

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