Proinsulin peptide immunotherapy in new-onset type 1 diabetes is well-tolerated and associated with reduced daily insulin usage

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Background and aims: In type 1 diabetes (T1D), antigen specific immunotherapy (ASI) strategies have been shown to be effective in disease prevention in pre-clinical settings. Such studies have demonstrated that ASI may be effective when autoantigen is delivered as a short peptide, representing a key target of the pathological T cells response that is characteristic of the disease. To date, however, it has proved challenging to translate these findings into clinical settings. Here, we report safety data on a phase 1b trial of the naturally processed and presented proinsulin peptide C19-A3 (PI C19-A3) in newly diagnosed T1D, as well as, preliminary metabolic and immune results. Aims: We aimed to examine the safety and tolerability of intradermal administration of (PI C19-A3) at a dose of 10μg in new-onset T1D. Secondary endpoints included metabolic and immune effects of (PI C19-A3).
Materials and methods: The trial was a multi-centre, randomized; double-blind, placebo-controlled design, using 10μg of PI C19-A3 administered intradermally at high frequency (HF) every 14 days, or low frequency (LF) every 28 days (a total of 12 doses and 6 doses, respectively) over 24 weeks with a subsequent follow-up phase of 24 weeks. Twenty-seven patients aged 18-45 with new-onset T1D (within a 100 days of diagnosis), HLA-DRB1*0401 genotype, antibody positivity (GAD, IA2 or ZnT8) and a stimulated C-peptide level >0.2 pmol/ml were recruited. To maintain blinding, all patients received 12 injections at fortnightly intervals. The placebo group (n = 8) received normal saline only; the LF group (n = 10) had alternate PI C19-A3 and normal saline administration; and the HF group (n = 9) had PI C19-A3 only.
Results: Administration of PI C19-A3 was safe and well tolerated. The only treatment emergent adverse event noted was transient erythema at the injection site. No systemic type 1 hypersensitivity or treatment related serious adverse events were reported. Within the power of the study, there was no significant change in C-peptide levels between the groups, but there was a trend to greater preservation in the treatment groups. No advantage was seen for 2 weekly over 4 weekly dosing. The mean changes in the daily insulin use were significantly lower in the HF group at 6, 9 and 12 months ($p=0.03$; $p=0.04$; $p=0.01$, respectively) and significantly lower in the LF group at 12 months ($p=0.009$) compared with the placebo group which showed a progressive rise. There was a trend for increased HbA1c levels in the placebo group, whereas change in the treatment groups was minimal or values declined.
Conclusion: PI C19-A3 peptide immunotherapy in the dosing regimen used was safe, well tolerated and free from any systemic hypersensitivity or serious adverse reactions. Treatment with PI C19-A3 was associated with reduced or stable daily insulin use, compared with apparent increase in the placebo group. Furthermore, the stable insulin use in either of the treated groups was not associated with poorer glycaemic control. This phase 1b trial paves the route for future phase 2 trials in new-onset T1D to examine effectiveness of PI C19-A3 on preservation of β cell function and amelioration of T cell autoimmunity.
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