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The efficacy and safety of ustekinumab in adolescents newly diagnosed with type 1 diabetes: the USTEK1D RCT

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Scientific summary

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Scientific summary

Background

Nearly 100 years after the discovery of insulin, over 70% of patients with type 1 diabetes (T1D) continue to have unsatisfactory glycaemic control putting them at risk of long-term complications. Despite major advances in closed-loop insulin pump therapy, much of the morbidity arises from young people failing to engage with complex therapies.

T1D is an autoimmune disease. Immunotherapy has the potential to preserve endogenous beta cell function (insulin-making capacity) and thereby improve metabolic control even in poorly compliant individuals. Novel low-risk targeted biologic therapies are widely used in other autoimmune diseases such as rheumatoid arthritis, psoriasis, inflammatory bowel disease and multiple sclerosis, but no treatment is yet licensed for use in new-onset T1D.

Data from preclinical and observational studies suggest a role for interferon-gamma [IFN-γ; T helper 1 (Th1)] and interleukin 17 (IL-17)-secreting (Th17) T cells in T1D. Ustekinumab (STELARA®, Janssen-Cilag Ltd International NV, Beerse, Belgium) binds and inhibits the p40 molecular subunits of both IL-12 and IL-23, thus blocking their action in inducing pathogenic CD4 Th1 and Th17 T-cell subsets. Ustekinumab is licensed in the UK for the treatment of psoriasis in children and adults, psoriatic arthritis in adults and Crohn's disease in adults and is very well tolerated.

Objectives

The primary objective was to determine the efficacy of ustekinumab for preserving Mixed Meal Tolerance Test (MMTT) stimulated 2-hour insulin C-peptide area under the curve (AUC) at week 52 as compared to control in children and adolescents with new-onset T1D. Secondary objectives included changes in clinical metabolic parameters including glycated haemoglobin (HbA1c), insulin usage, hypoglycaemia and treatment-related harms.

Methods

We conducted a double-blind phase II randomised controlled trial of subcutaneous (SC) ustekinumab in 72 young people aged 12–18 with recent-onset T1D (within 100 days of the first insulin injection) with residual endogenous insulin production (serum C-peptide > 0.2 nmol/l during MMTT) and autoimmune diabetes confirmed by measurement of islet cell autoantibodies. Participants were given ustekinumab or control (saline) SC at weeks 0, 4 and 12 and subsequently every 8 weeks to week 44 (seven doses) with the dose depending on their body weight: 2 mg/kg (if ≤ 40 kg) or 90 mg (if > 40 kg). These equate to the highest doses used previously in trials in other conditions. Participants were followed up 52 weeks after receiving the first dose of ustekinumab/control. The primary end point was assessed at week 52. The final safety data analysis also occurred at week 52. Minimisation by age (12–15 years vs. 16–18 years) and screened peak C-peptide levels (0.2–0.7 vs. > 0.7 nmol/l) was used to ensure balance between treatment groups. The ustekinumab-to-control ratio was 2 : 1 to provide additional data on drug safety (n = 48 : 24).

Results

1. **The recruited sample** was reflective of the national population of teens with T1D in National Paediatric Diabetes Audit (NPDA) 2019–20 (82% vs. 80% Caucasian) with a slightly higher male-to-female ratio (60% vs. 54%). The sample of 16- to 18-year-olds was lower than planned (18% vs. 40%), and lower than the percentage of 16- to 17-year-olds in the 12- to 17-year-old age group of newly diagnosed individuals in the NPDA (30%). This was possibly due to loss of some potential participants to adult care teams but did not appear to be due to a lower consent rate of eligible participants.

2. **Retention of participants and final analysable sample:** Retention of participants over 52 weeks to the primary end point was generally good, especially considering overlap with the COVID-19 pandemic, with four participants (6%) lost to follow-up. However, an additional six participants could not be included in the planned primary outcome intention-to-treat analysis due to missing baseline data, so the final analysed sample was *n* = 62 (86%). The planned sample size in the power calculation was *n* = 66. Missing participants were balanced across the treatment arms considering the 2 : 1 ratio of recruitment (six ustekinumab, four control). Four participants withdrew from treatment (three ustekinumab, one control) but attended for primary end-point collection. Minimisation by age (12–15 years vs. 16–18 years) and initial C-peptide level (< 0.7 vs. > 0.7 nmol/l) ensured balance of these parameters between the groups. Body mass index *z*-score was somewhat higher in the control group, while insulin use per kilogram was higher in the treatment group. Age and entry C-peptide were lower in the treatment group and HbA1c was higher, all of which are factors associated with more rapid C-peptide loss post diagnosis. Adjustment for these baseline factors was pre-planned in the analysis.
3. **Primary end-point analysis:** For the pre-specified primary end-point analysis, ustekinumab was associated with a 49% higher endogenous stimulated insulin production (AUC C-peptide in 2-hour MMTT) than control after adjustments for baseline factors at 52 weeks {geometric ratio of ustekinumab to control was 1.49 [95% confidence interval (CI) 1.08 to 2.06; *p* = 0.02]}.
4. **Additional C-peptide end-point analyses:** Despite treatment, there was still substantial loss of C-peptide in both arms over the 52-week period. At this time point, the mean stimulated AUC C-peptide levels was 65% of baseline in the ustekinumab group (0.45 vs. 0.84 nmol/l) and 45% of baseline in the control group (0.3 vs. 0.87 mmol/l). Secondary analysis of C-peptide levels at week 28 was conducted. However, it should be noted that there was more missing data at this time point (*n* = 55 vs. *n* = 62 at primary end point). At this time point, the geometric mean ratio of ustekinumab to control was not significantly different (1.15, 95% CI 0.81 to 1.63; *p* = 0.45). Hence, it appeared that the benefit of ustekinumab predominantly developed 'late', in the second 6 months of the study, although the missing data at week 28 resulted in a less precise estimated effect value at this time point. 'Late' or 'delayed' effects have not previously been seen in immunotherapy studies.
5. **Secondary end-point analyses – HbA1c:** HbA1c levels rose across both groups from 50 mmol/mol at baseline to around 56 mmol/mol at week 52. No significant difference was seen in HbA1c between the groups, although with insulin use as a covariate (not pre-specified, but found to be relevant), point estimates at weeks 28 and 52 were 2–3 mmol/mol lower in the ustekinumab group. It is noted that sample sizes around two- to threefold larger than in this study would have been required for adequate power to study HbA1c differences.
6. **Secondary end-point analyses – other metabolic parameters:** Exogenous insulin use increased from baseline to week 52 in both groups (0.42–0.63 U/kg in the control group; 0.51–0.63 U/kg in the ustekinumab) with no significant difference after adjustment for baseline factors. Insulin dose-adjusted HbA1c also increased in both groups (8.23–9.46% in the control group and 8.90–9.69% in the ustekinumab group) with no significant difference between the groups.
7. Data from continuous glucose monitoring (CGM) showed decreasing median percentage of time in range of > 70 mg/dl (3.9 mmol/l) to < 180 mg/dl (10 mmol/l) over 52 weeks in both groups (82.40– 61.32% in the control group and 77.30–60.33% in the ustekinumab group). There was no significant difference between the groups in any of the time points of assessment (82.40% in control group vis-à-vis 77.30% in ustekinumab group *p* = 0.61 at baseline; 67.46% vis-à-vis 66.18%, *p* = 0.98 at week 28 and 61.32% vis-à-vis 60.33% at week 52).
8. **Secondary end-point analyses – hypoglycaemic events:** Data from participant diaries identified 68 participants reporting 2946 hypoglycaemic events reviewed and verified by clinicians as either having a blood glucose level that reached the alert value (≤ 3.9 mmol/l) or being a probable symptomatic hypoglycaemic event. Two thousand two hundred and twenty-eight (around 32/person/year) were classed as level 1 (a glucose alert value of > 3.0 but ≤ 3.9 mmol/l) and 615 (around 9/person/year) were classed as level 2 (a glucose level of ≤ 3.0 mmol/l – clinically important hypoglycaemia). Only one person (in the control group) had an event classed as level 3 (severe cognitive impairment requiring external assistance). Participants in the ustekinumab group reported a lower overall incidence per person-year of all types of hypoglycaemia (39.38) than those in the control group (43.80) but the difference did not reach statistical significance [incidence rate ratio (IRR) 1.11, 95% CI 0.69 to 1.79; *p* = 0.66]. Data from CGM showed a lower incidence rate of level 2 hypoglycaemic events in the control group than the ustekinumab group (week 28 IRR 0.49, 95% CI 0.21 to 1.15; *p* = 0.1; week 52 IRR 0.40, 95% CI 0.12 to 1.30; *p* = 0.12), but the difference did not reach statistical significance.

9. **Secondary end-point analyses –participant-reported outcome measures (PROMs):** Participant-reported outcomes were collected using the Paediatric Quality of Life Inventory (PedsQL), PedsQL™ (MAPI Research Trust PROVIDE™, Lyon, France) Diabetes Module (PedsQL Diabetes), Diabetes Treatment Satisfaction Questionnaire (DTSQ), Hypoglycaemia Fear Survey-Behaviour (HypoFear-Behaviour, Hypoglycaemia Fear Survey-Worry (HypoFear-Worry) and Hypoglycaemia Fear Survey-Total (HypoFear-Total) at baseline, week 28 and week 52. The DTSQ Change version was used at week 52 to identify changes in level of satisfaction with diabetes treatment. Completion of questionnaires was > 90% at baseline and > 80% during follow-up for almost all questionnaires. There was no significant change in any of the participant PROM scores from baseline to week 52 in either group and no significant differences between the groups.
10. **Secondary end-point analyses – parent/ proxy PROMs:** There were no significant differences in parent/proxy PROMs between the groups.
11. **Secondary end-point analyses – comparison of participant and parent/proxy PROM score:** In ancillary analysis, there was a strong correlation between participant and parent PROM scores for all PROMs with a rho of 0.23–0.68 which was significant at all time points. An exception was the HypoFear (behaviour) scores at week 52. Parents had significantly higher HypoFear (particularly 'Worry') than participants at all time points and lower PedsQL diabetes quality-of-life scores than participants at baseline and week 28.
12. **Sensitivity analyses:** Sensitivity analyses were performed to confirm robustness of the conclusions about the analysis of the primary outcome to protocol deviations. Excluding one participant who accidentally became unblinded, one participant whose primary outcome visit was delayed by 6 months and one participant with a hereditary red cell disorder affecting HbA1c separately had no effect on the primary outcome. Hence the model for analysing the primary outcome was robust to small numbers of people with some protocol deviations and extreme values in key covariates.
13. **Missing data imputation:** According to the pre-specified statistical analysis plan, multiple imputation would be considered if there were > 5% and < 10% (> 3 and < 7 participants) missing. Data were missing for 10 participants (4 withdrawals; 4 with no baseline exogenous insulin use and 2 with missing HbA1c at baseline), affecting > 10% of the participants. A decision was made to perform multiple imputation, purely as a sensitivity check for the primary analysis. Multiple imputation showed that the conclusion about treatment group difference might be sensitive to missing values as the geometric ratio of ustekinumab to control changed to 1.36 (95% CI 0.81 to 1.63; $p = 0.27$) and did not reach statistical significance. The model may therefore be sensitive to missing data.
14. **Ancillary end-point analyses – harms:** Ustekinumab was very well tolerated. No severe adverse events (AEs) were reported and there were no differences between ustekinumab and control in the proportion of participants overall experiencing mild (87% vs. 88%) or moderate (32% vs. 32%) events. When evaluating the AEs deemed by investigators likely to be attributable to study drug, a higher proportion of participants in the ustekinumab group had one AE deemed likely to be related to the study drug in each level of attributability (mild = 32% of participants in ustekinumab group vs. 20% in control; moderate = 11% in ustekinumab group vs. 8% in control). The bulk of the events were mild ($n = 124$) with only 12 events of moderate severity. These moderate AEs attributable to the study drug were experienced by seven participants (control: 2; ustekinumab: 5). In evaluating the evidence of infection, we found 37/117 AEs categorised in the Infection and Infestation class deemed to be possibly related to the study drug. These 37 events were experienced by 17 participants. A higher proportion of participants in the ustekinumab group (30%, $n = 14$) than those in the control group (12%, $n = 3$) experienced one AE deemed to be possibly related to the study drug. Thirty-four of these events were mild. Two moderate AEs were experienced by one ustekinumab participant. They were fever and upper respiratory tract infection. There were six events of injection reaction experienced by five participants (ustekinumab: 9%, $n = 4$, control: 4%, $n = 1$). All six events were mild and resolved with no sequelae. There were no hypersensitivity reactions.
15. **Ancillary end-point analyses – immunology:** We observed significant differences between the ustekinumab and control groups in relevant T-cell populations targeted by the drug. A significant decline in the CD4+ Th17 and Th17.1 populations but not the Th1 population was seen after 6 months of treatment in the ustekinumab group, which became more pronounced by week 52. The most pronounced effect was seen in cells that expressed all four cytokines [IFN-γ, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF+), IL-2+], representing around 0.1% of the CD4 T-cell population, which showed a reduction as early as 3 months after beginning therapy. This was unlikely to be an artefact of multiple testing, as the highly significant changes in T-cell populations ($p \leq 0.001$) all clustered around the Th17 positive subpopulations. We additionally analysed the antigen-specific response by using a cytokine FluoroSpot assay. Overall, 28/64 participants had a positive response after in vitro stimulation

with proinsulin at baseline. A highly significant fall in beta cell targeted (proinsulin specific) IL-17A-secreting T cells was also seen (p = 0.0003) in comparison to baseline from 3 months in ustekinumab group only. There was no significant change in the IFN-γ FluoroSpot response. Preservation of C-peptide from 28 to 52 weeks after baseline correlated with the reduction in T cells co-secreting IL-17 and IFN-γ (Th17.1 cells, p = 0.04), and in particular with the change in a subset also co-expressing IL-2 and GM-CSF (p = 0.04) representing < 0.1% of circulating CD4 cells.

Conclusions

1. Ustekinumab was very well tolerated with no treatment-related withdrawals.
2. Participants treated with ustekinumab had 49% higher levels of MMTT stimulated C-peptide at week 52 (primary end point) than those treated with the control.
3. Stabilisation of C-peptide loss appeared to occur late (between weeks 28 and 52).
4. C-peptide preservation from week 28 to week 52 was correlated with reduction in a highly specific subset of T cells expressing the cytokines IL-17, IFN-γ, IL-2 and GM-CSF, representing as few as 0.1% of circulating CD4 T cells.
5. No significant differences in metabolic end points or PROMs were seen between the groups, although the study was not powered for these end points.
6. Ustekinumab appears to slow down the autoimmune process providing the first clinical trial evidence that IL-17-secreting T cells play a pathogenic role in T1D. Alone, it is insufficient to halt the autoimmune process. Consideration may be given to testing other drugs targeting the IL-17 pathway, using ustekinumab in combination with other agents or using it earlier in the disease pathway (preclinical disease) since it is so well tolerated and simple to use.

Study registration

Current Controlled Trials ISRCTN14274380.

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