Report on EudraCT trial 2010-022677-34

Influence of high dose vitamin D substitution on humoral immunity and lymphocyte function in patients with type 1 diabetes mellitus or Addison´s disease (ViDDA1)

Sponsor

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Investigators

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Publications (references):

High-dose vitamin D in Addison's disease regulates T-cells and monocytes: A pilot trial.
Penna-Martinez M, Filmann N, Bogdanou D, Shoghi F, Huenecke S, Schubert R, Herrmann E, Koehl U, Husebye ES, Badenhoop K. Nutrition. 2018 49:66-73. doi: 10.1016/j.nut.2017.10.021.

T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: A randomized controlled trial with sequential crossover.
Bogdanou D, Penna-Martinez M, Filmann N, Chung TL, Moran-Auth Y, Wehrle J, Cappel C, Huenecke S, Herrmann E, Koehl U, Badenhoop K. Diabetes Metab Res Rev. 2017 Mar;33(3).
doi: 10.1002/dmrr.2865.

Date of first enrolment:

11th September 2012

Date of last participant visit:

13th December 2013

Phase of development

Phase 3

Objectives

Primary objectives:
Difference in vitamin D levels, T lymphocyte subsets, T regulatory lymphocytes, dendritic cells and NK lymphocytes after 3 months of treatment between Vigantol Oil and Placebo Oil.
Secondary objectives:
Difference in lymphocyte cytokine status (IL-1, IL-4, IL-10, TNFα), pharmacogenomics of vitamin D variables and vitamin D-dependent immune signatures as well as glucometabolic parameters in type 1 diabetes after 3 months of treatment between Vigantol Oil and Placebo Oil.

Methods

Randomised controlled trial with sequential cross-over

Study population

Patients with type 1 diabetes mellitus or Addison´s disease

Oral vitamin D3 (Colecalciferol) 4000U/d for three months or placebo with sequential crossover to the alternative

Number of patients planned

N=180

Number of patients analysed

N=52

Test product dose

Vigantol oil (Merck KGaA, Merck Serono, Darmstadt, Germany) 4000U daily

Duration of treatment

3 months

Reference therapy

Placebo oil

Criteria for evaluation

Primary endpoints

Immunologic effects of study treatment. The sample size calculation is based on the assumption that a variance of 4 and a difference of 0,5 for the quantification of the T lymphocyte subsets and dendritic cells and/or c) on the genes´ mRNA expression can be detected with a power of 80% and an alpha of 0.05.

Secondary endpoints

Pharmacogenomic influence on vitamin D metabolism and immune markers, HbA1C and insulin demand in type 1 diabetes

Time points of evaluation

After 3 months of study or placebo treatment in each arm followed after another 3 months with the alternative (Vigantol/placebo)

Statistical methods

Intention to treat analysis was used for the major outcomes. A 2 sided p value of <0.05 was taken as significant for all analyses.

For each outcome, the difference between groups at each timepoint was compared adjusting for baseline. In addition, repeated measures ANOVA was undertaken to give an estimate of overall treatment effect across time.

Preplanned adjustment for covariates (ANCOVA) was undertaken for all outcomes.

Adjustment was made for baseline values of the outcome under study, along with baseline vitamin D as well as pharmacogenomic stratification. P-values were corrected for the number of comparisons made.

Summary results and conclusions

Results

Median 25-hydroxyvitamin D3 levels rose both in type 1 diabetes and in Addison´s disease patients (38,8ngml and 41,5ng/ml p=0.0005). T lymphocyte profiles did not change significantly in type 1 diabetes but in males Tregs were enhanced. In Addison´s disease late activated T helper cells and late activated T cytotoxic cells decreased (p=0.02 and p=0.03), whereas monocytes increased after vitamin D3 treatment (p=0.008). T-cell changes were associated with two polymorphisms (CYP27 B1-rs108770012 and VDR-rs10735810). Cytokine levels did not change significantly. In type 1 diabetes insulin dose requirements declined significantly (p = .003–.039) and HbA1C improved (p < .001) after vitamin D3 treatment.

Conclusions

A daily vitamin D dose of 4000 IU for 3 months was well tolerated in both type 1 diabetes and in Addison´s disease. Treatment enhanced Tregs in males with type 1 diabetes and improved glucometabolic control in all patients. Vitamin D3 treatment can regulate late-activated T-cells and monocytes in patients with Addison´s disease. Explorative analysis revealed potential genetic contributions. This trial provides novel insights about immunomodulation by vitamin D3 treatment in type 1 diabetes and Addison´s disease.

Subsequent larger trials need to address gender specific vitamin D3 effects on immune function, glucometabolism and genotyping for individualized vitamin D doses.

Date of report upload to EUDRACT system:

27th June 2022