Seasonal changes may influence the efficacy of vaccination against diabetes

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The development of a medicine for patients with type 1 diabetes mellitus, based on autoantigen GAD65, received a setback following crucial clinical phase 3 trials that failed to show significant effects. One possible explanation may be seasonal variations in the immune system, claim those responsible for the study that was published in the *New England Journal of Medicine* (*NEJM*).

At the onset of type 1 diabetes mellitus, the immune system attacks the insulin-producing pancreatic beta-cells. In conjunction with this development antibodies are often directed against different proteins/antigens in the beta-cells. The GAD65 is such an antigen, an enzyme typically present in the brain, however its function in the beta-cells is as yet unknown.

Led by Johnny Ludvigsson, Professor Emeritus of Paediatrics at Linköping University, clinical trials were conducted on the treatment with alum-formulated GAD65 (GAD-alum) for patients with recent-onset type 1 diabetes mellitus. Three years ago, researchers showed in a phase 2 trial that this type of vaccination could retard the degradation of beta-cells. At a four-year follow-up it was established that C-peptide (a measure of endogenous insulin production) was significantly higher in patients who had fallen ill less than six months before the start of the study, compared to that of a control group.

For the phase 3 trial, 334 patients 10 to 20 of age, with type 1 diabetes were recruited. Within three months after diagnosis, patients were

randomly assigned to receive one of three study treatments:

- Four doses of GAD-alum
- Two doses of GAD-alum followed by two doses of placebo
- Four doses of placebo

The primary outcome was the change in C-peptide levels 15 months after beginning the treatment. The results showed a positive trend but no significant effect.

The authors of the article in this week's edition of *NEJM* ask the question: "Why did this phase 3 study show a lack of efficacy, in contrast to our earlier phase 2 study?"

Seasonal variations in the immune system may play a role and have been proposed as one possible explanation. When the material is broken down into subgroups, it appears that the treatment had significant effect among those patients who received their first GAD-alum dose during March or April, which was the period when all patients in the phase 2 trial were vaccinated.

Another discrepancy that may have been significant for the results was that the phase 3 study coincided with the outbreak of the swine influenza epidemic, which led to widespread vaccination. The diabetic patients who were not vaccinated against influenza within 150 days responded better to the GAD-alum treatment than the others in the study. Additional factors affecting the results can be related to age and gender. The effects were significant for boys in the large European phase 3 trial.

The authors write that treatment for type 1 diabetes will probably be based on knowledge gained from this and other studies of single agents or combination therapies. Further analyses are under way addressing,

partly the results following a longer follow-up than 15 months, and partly how the immune system responds.

"We have not given up, rather we still believe that the GAD-alum may prove to be an important part of both future prevention and treatment of type 1 diabetes," says Johnny Ludvigsson.

More information: GAD 65 antigen therapy in recently diagnosed type 1 diabetes mellitus by Ludvigsson et al. *New England Journal of Medicine* 366:5, 2 February 2012.

Provided by Linköping University