Insulin therapy versus oral sitagliptin for treatment of latent autoimmune diabetes in adults

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Insulin therapy versus oral sitagliptin for treatment of latent autoimmune diabetes in adults

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ABSTRACT

A clinical decision report using:


for a patient with an aversion to needles.

Keywords: LADA, latent autoimmune diabetes in adults, sitagliptin, insulin

Clinical-Social Context

Kathleen Jones (pseudonym) is a 34-year-old middle-class Caucasian female with recently confirmed latent autoimmune diabetes in adults (LADA) who presented to the clinic to discuss medication options for her diabetes. Her diagnosis was made after testing positive for GAD antibodies (GADAs) with a fasting C-peptide of 0.8 nmol/L. She also did not require insulin for at least 6 months after diagnosis. Due to her previous misdiagnosis of type 2 diabetes mellitus, she was on Metformin 1000 mg twice a day for the past 2 years. Despite complete adherence, her most recent HbA1c is 9.8%, which has increased from her initial HbA1c of 8.9%. However, her diet consisted of exclusively fast food with a moderate level of activity. Her BMI was 44 kg/m2. During this visit, we needed to reconsider and decide on additional medications to achieve better glycemic control.

First, we discussed the pathophysiology of LADA, in that it is a subtype of type 1 diabetes mellitus, an autoimmune disease, and not due to insulin resistance. We explained the body is attacking the β-cells, which produce the insulin, but at a slower rate than we would see in type 1 diabetes. Therefore, insulin would now be needed, so we discussed the treatment option of replacing the insulin lost with an injection. The pharmacist demonstrated how to give the injection and as Ms. Jones observed, she winced at the site of the needle. She took a minute to think about what we had told her, but then admitted, she was apprehensive of needles. She went on to give the example that she has avoided receiving the influenza vaccine since 2011 because she cannot even handle the thought of it, let alone pricking herself for sugar checks or injecting herself multiple times a day. She additionally expressed that her priority is her son, who is disabled and requires full care from her and explained that she does not have the time to deal with the time-demanding activities of insulin administration and sugar checks. We validated Ms. Jones concerns and expressed our understanding of her situation. Ms. Jones then asked, “Is there anything that I can take by mouth instead that works just as well?”

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Clinical Question
Is there an oral hypoglycemic medication that is an appropriate substitution to insulin that offers the same glycemic control and beta-cell preserving therapy in patients diagnosed with latent autoimmune diabetes in adults?

Research Article

Description of Related Literature
A search for original studies regarding treatment of LADA was conducted on PubMed by searching the terms: (Latent Autoimmune Diabetes in Adults) AND (treatment). This yielded 232 results, in which only randomized control studies and clinical trials that were published within the past 10 years were chosen yielding 11 articles. Of these, only 6 studies were selected because they addressed treatment options and their ability to achieve glycemic control and/or preserve β-cell function.

Pozzilli et al. performed a post-hoc analysis from three randomized studies that was part of the dulaglutide clinical development program in type 2 diabetes but included patients positive for glutamic acid decarboxylase (GAD) antibodies, the most sensitive marker for LADA. By measuring HbA1c, this study evaluated the effect of dulaglutide in GADA-positive LADA versus GAD-negative type 2 diabetes patients. Although, it was concluded that dulaglutide was effective in reducing HbA1c in LADA patients, this study was excluded because dulaglutide is only available in an injectable form.2

In the Johansen study, an exploratory analysis was done from a trial with 1,519 patients diagnosed with type 2 diabetes and HbA1c of 6.5–10.0% on metformin. They were randomized to linagliptin 5 mg daily or glimepiride (sulfonylurea) 1–4 mg for 2 years. By measuring multiple autoantibodies, they classified patients with LADA if positive for one or more autoantibody. The study failed to show a significant decline in C-peptide levels and HbA1c with linagliptin compared to glimepiride. Although this study was randomized with a large sample size, it was excluded due to a lack of placebo, the use of a second line agent as a comparator, and the mean age of the study participants (ages 59-68).3 Furthermore, sulfonylureas have been shown to accelerate β-cell deficiency in type 2 diabetes in the long-term and to exert β-cell toxicity in vitro, so the comparison drug was inferior to the current standard treatment.4,5

In the Buzzetti study, a post hoc analysis was conducted from five trials, with 2709 participants from two studies of saxagliptin as monotherapy, one study of saxagliptin as add-on therapy to metformin, glyburide, or a thiazolidinedione. It also evaluated different dosages of saxagliptin. Although it concluded that saxagliptin improves glycemic control, this study was excluded because it used p < 0.1 as statistically significant and missing data were imputed using the last observation carried forward, decreasing the strength of the evidence and validity of the study.6

Three of the studies selected focused their research on the dipeptidyl peptidase 4 inhibitor (DPP-4), sitagliptin with insulin as the compared conventional treatment. The Zhao et al. study is an open-label, randomized-controlled study with 15 participants receiving insulin therapy and sitagliptin and the other 15 participants receiving insulin without sitagliptin for 12 months. The study found that β-cell function was better maintained using sitagliptin compared to insulin alone. However, the study was limited because it was only in Chinese populations; therefore, the treatment may not apply as well in individuals of non-Asian backgrounds. Also, it was excluded because it had a very low power with only 15 patients in each of the treatment arms, the study was open label, decreasing the validity of the study, and that both treatment arms included injectables.2 The Wang et al. study was also a one year open-label randomized controlled trial, but the primary emphasis was on the mechanism of how sitagliptin improves glycemic control and β-cell function by studying T-lymphocytes and relevant transcription factors. Although this study concluded that sitagliptin altered the phenotype of T cells and improved glycemic control in LADA patients, it was excluded because the study was open label, both treatment arms included an injectable, and it was done in an exclusively Chinese population.6

Ultimately, the Hals et al. study was the most ideal choice for the critical review in the context of Ms. Jones. This randomized controlled trial recruited GAD antibody-positive individuals. Glucagon-stimulated C-peptide tests (GSCTs), which evaluate β-cell
function, were performed at baseline, 3, 9, and 21 months. This study revealed that β-cell preserving function was similar in insulin and sitagliptin participants with LADA. Also, the results of this trial agree with the findings of the two other articles reviewed in this process. The study has an appropriate sample size, randomized set-up, and focus on β-cell preserving function using only an oral medication, which made it relevant to Ms. Jones, therefore, this study was used to answer my clinical question. Given the above literature, this body of evidence would be a Grade B strength of recommendation based on the SORT criteria.  

Critical Appraisal

A non-blinded randomized control study was done to assess and compare the β-cell preserving function of sitagliptin, a DPP-4 inhibitor, to insulin, the treatment of choice in patients with LADA. According to the SORT criteria, it meets Level 2 evidence. Participants were recruited after testing positive for GAD antibody by their primary care physicians (PCP), health center screening done by the investigators of this study, or through referral from PCPs. However, it is important to recognize that there are many GAD antibody negative patients with LADA. Other antibodies that could be tested for are islet cell autoantibodies (ICA), tyrosine phosphatase–related islet antigen 2 (IA-2), and insulin autoantibodies (IAA), however, these were not part of the studies recruitment method, therefore, many GAD antibody negative LADA patients were not included in the study, which would have increased the sample size. Participants that qualified for partaking in this trial had to meet several criteria: (1) ages 30 to 75 years, (2) positive for GAD antibodies with <3 years of diagnosed diabetes, (3) no pharmacological treatment for diabetes except metformin, (4) no clinical need for insulin, (5) HbA1c had to be at least 10% above the upper limit of normal (ULN) before treatment, or 5% above the ULN when on treatment with metformin, but not exceeding 60% above the ULN at the time of randomization, and (6) fasting C-peptide ≥0.3 nmol/L. Patients were excluded from the study if they had the following: (1) kidney failure (creatinine >150 μmol/L), (2) proliferative retinopathy with or without sequelae, (3) myocardial infarction within the last 6 months, (4) unstable angina pectoris, (5) serious chronic diseases, and (6) fertile women who planned to become pregnant during the study period. Participants were started on metformin, if they were not already receiving it, with the dosage gradually being increased to 2 grams/day during the 3-month run-in period. Anthropometric measurements, blood pressure, relevant blood samples were taken and measured at baseline. The primary outcome of the study, β-cell function, was evaluated using glucagon-stimulated C-peptide tests (GSCTs). Using a centralized randomization database, a total of 64 participants were randomized, non-blinded, with 32 individuals in the insulin arm and 32 individuals in the sitagliptin arm. The participants were also divided by age (≤53 years or >53 years) and body mass index (BMI; ≤26 kg/m2 or >26 kg/m2). Also, similar metabolic control in the two arms of the study was attained because a large difference could potentially influence measures of β-cell function. While there was no explanation for why the study was not blinded, a potential explanation could be because the two treatments are delivered via different routes and therefore, would be difficult to blind both treatment arms and the study’s staff. It is notable that this could potentially introduce detection and performance bias through the study participants, data collectors, and data analysts. This could be minimized by administering a placebo injection to the oral medication arm and placebo oral medication to the insulin arm. Patients followed up with the research group after 3, 9, and 21 months. In Norway, 25 were followed up in Trondheim, one in Namsos and five in Bergen. In Sweden, 32 were followed up in Stockholm and one in Malmö. The difference in follow up location could potentially produce variability due to different equipment being used and those operating the equipment in each location. After 21 months of intervention, it was ultimately revealed that there was no difference in fasting C-peptide concentrations and stimulated C-peptide levels compared to baseline in both treatment arms. Also, the change of HbA1c levels was similar between treatment arms. Therefore, it was concluded that β-cell function was similarly affected in insulin and sitagliptin treated participants with LADA. Additionally, the sitagliptin treatment group experienced greater weight loss with an average of 3.4 kg. While the insulin arm had three participants that experienced hypoglycemia, there were no hypoglycemic events in the sitagliptin arm. The mean age and BMI of the participants in the study was 53 years old and 27 kg/m2 in both treatment arms, respectively. Although Ms. Jones was younger than the mean age (34 years old) and her BMI was over the mean BMI (44 kg/m2), she is still an appropriate patient to apply this trial to as she meets all the inclusion criteria and does not meet the exclusion criteria. A limitation
of the study is the lack of a control group. It would be beneficial to include another arm with participants treated with metformin alone to assess the β-cell preserving function to both treatment arms. Other limitations include the lack of uniformity in follow up measurements due to different locations and lack of a blinded approach. Additionally, another limiting factor is that the study was done in another country, where ethnicity and diet of participants differs from Ms. Jones.

One strength of the study is the appropriate sample size. A power calculation determined that 52 participants would be needed to detect a 20% difference between treatments with a certainty of 80% at a P value of < 0.05. This study used 64 participants. Additionally, the accumulated dropout was 9.4%, and while results of GSCTs from the dropouts at 3 to 9 months were carried forward using the intention-to-treat principle, significance testing without these data did not change the study results. Other strengths are the extended duration of the study and the randomized approach.²

Clinical Application

Ms. Jones presented to the clinic to discuss treatment options for her recent diagnosis of LADA, but expressed multiple concerns regarding the use of insulin injectables, the typical treatment. After extensive research, we found our answer based on the article presented. This study concluded that β-cell function was similarly affected in insulin and sitagliptin treated participants with LADA. The clinical background of the participants in this study closely match that of Ms. Jones, therefore, the study’s conclusions should also apply to Ms. Jones.

We spoke with Ms. Jones over the phone and explained to her that there is an oral hypoglycemic medication, sitagliptin, that could work just as well as insulin in preserving her insulin producing cells. This would be added on to her metformin, corresponding to the study. Furthermore, the importance of following up was explained to assess how the medication is working for her and any side effects experienced, such as headache, throat irritation, and upper respiratory tract infections. We came to an understanding that if proper glycemic control is not achieved, then we will have to resort back to insulin injectables. She expressed understanding and was agreeable with this plan. In addition to this, Ms. Jones was reminded of our extensive conversation regarding diet modification and exercise. She was re-encouraged to commit to changes and explained that this will give her a better chance at achieving glycemic control with her new treatment plan.

New Knowledge Related to Clinical Decision Science

Formulating a management and treatment plan for a patient should be collaborative and should take into account the medical and social issues at hand. After witnessing Ms. Jones’s distress with insulin injections and listening to how she takes care of her disabled son full-time, it became clear that imposing the injections would not be the best solution. This then led to the search for a hypoglycemic medication that would serve as an appropriate substitute to insulin.

When calling the patient with the results of the literature review during clinic hours, it was apparent how grateful she was at both her new treatment regimen and to hear from a provider. She discussed how clinic visits are time consuming, and this one phone call trip saved her hours. Delivering follow up clinical care over the phone is a clinical practice that other doctors should emulate as it is convenient, quick, and provides better access to patients.

Conflict Of Interest Statement

The author declares no conflicts of interest.

References


