# Effects Transient at Best

**Prevention of Type 1** *from page 1*

significant (Lancet 2011 June 27 [doi:10.1016/S0140-6736[11]60895-7]).

Importantly, however, there were no adverse events. "What we've learned is that some of [the agents being tested] don't work in new-onset diabetes, but they are safe. So, they might work earlier in the disease process for prevention. Whether we need a combination of things to really arrest the disease process is another open question," said Dr. Skyler, professor of medicine, pediatrics, and psychology at the University of Miami.

The other TrialNet study involved abatacept (Bristol Myers Squibb's Orencia), which modulates T-cell co-stimulation and prevents full T-cell activation. Orencia is currently on the U.S. market for treating adult rheumatoid arthritis and juvenile idiopathic arthritis. In the study, 112 patients were randomized to treatment with either abatacept (77 patients) or placebo (35 patients) intravenous infusions on days 1, 14, 28, and monthly for a total of 27 infusions over 2 years (Lancet 2011 June 28 [doi:10.1016/S0140-6736[11]60886-6]).

Here, there was a significant difference between groups, with the AUC for C-peptide 59% higher with abatacept than placebo at 2 years, and the estimated delay in C-peptide reduction of 9.6 months. However, despite continued administration of abatacept over 24 months, the decrease in beta-cell function with abatacept paralleled that of placebo after 6 months, suggesting that T-cell activation lessens with time, said Dr. Tihamer Orban of Joslin Diabetes Center, Boston.

Two additional drugs under study, teplizumab and otelixizumab, are both anti-CD3 monoclonal antibodies that bind to the surface of T cells and modulate their action. Two studies of teplizumab were presented. In one phase II study called AbATE (anti-cd3 mAb), 52 type 1 patients aged 8-30 years were given two intravenous courses of the drug 1 year apart, while 25 patients got placebo infusions. There was a significant retention of C-peptide with teplizumab, compared with controls. The teplizumab group had a 45% decrease in beta-cell function over 2 years, compared with a 77% reduction in the untreated group, said Dr. Stephen E. Gitelman, professor of clinical pediatrics at the University of California, San Francisco.

The AbATE trial was sponsored by the Immune Tolerance Network, which is funded by the National Institutes of Health, with funding from the Juvenile Diabetes Research Foundation.

The other teplizumab trial, Protégé, was funded by MacroGenics. It was a 2-year, phase III, double-blind, placebo-controlled, multinational study, with the combined goal of reducing hemoglobin $A_{1c}$ to less than 6.5% for those newly diagnosed with type 1 diabetes and reducing the amount of insulin needed to less than 0.5 units/kg per day. The primary end point did not differ between the two groups, with 19.8% in the teplizumab group and 20.4% of placebo patients achieving the combined end point at 1 year, said Dr. Nicole Sherry, director of the Diabetes Center at Massachusetts General Hospital for Children in Boston (Lancet 2011 June 28 [doi:10.1016/S0140-6736[11]60931-8]).

**These drugs failed in new-onset diabetes, but they are safe, so they might work earlier in the process for prevention.**

DR. SKYLER

However, 5% of the 513 study patients no longer required insulin at 1 year, compared with none of those who received placebo. Moreover, in a post hoc analysis, C-peptide was preserved or increased in 40% of those who received the 14-day regimen of the drug, compared with just 28% of the placebo group. Children were more likely than were adults to retain C-peptide function, as were patients treated within 6 weeks of diagnosis. Adverse events were similar between the two groups.

A phase III study of the anti-CD3 drug oteliximab in 240 newly diagnosed type 1 diabetes patients also produced negative findings. The dose – one-sixteenth of that used in previous trials – had been chosen to reduce adverse events seen previously, particularly Epstein-Barr virus activation. The low dose was not effective in preserving C-peptide. This study, dubbed DEFEND, was funded by Tolerx, with support from the Juvenile Diabetes Research Foundation.

"This is clearly an important pathway. Further studies will try to increase that dosage to duplicate the previous efficacy with fewer side effects," said Dr. Peter Gottlieb, professor of medicine and pediatrics at the University of Colorado, Denver.

Another compound under study, DiaPep277, was developed with the goal of preventing beta-cell destruction. Created by the removal of 24 of 500 amino acids from a "heat shock" protein involved in beta-cell destruction via T-cell activation, DiaPep277 had been shown to change destructive T cells into cytokine-secreting protective T cells in mouse models of type 1 diabetes.

In one phase II study, injections of DiaPep277 in 100 newly diagnosed type 1 patients preserved beta-cell insulin secretion for up to 2 years, said Dr. Itamar Raz, professor of medicine and director of the Hadassah Diabetic Center in Jerusalem, Hadassah Hebrew University Hospital.

Dr. Skyler is an advisory and/or board member for numerous makers of diabetes-related products. He holds stock in and/or is a shareholder of Amylin, Circulat Biotech, Dexcom, Ideal Life, Inspire Pharmaceuticals, Moerae Matrix, and Tandem Diabetes Care.

Dr. Gitelman and Dr. Sherry stated that they have no disclosures. Dr. Orban is on the data safety monitoring board for Osiris Therapeutics and is a founding member of Orban Biotechs LLC. Dr. Gottlieb receives research funding from Tolerx, GlaxoSmithKline, MacroGenics, and Diamyd.

Dr. Raz is a board member of, adviser for, is on the speakers bureau, or is a consultant for AstraZeneca LP, Bristol-Myers Squibb, Novo-Nordisk Pharma Ltd., Roche Pharmaceuticals, and Andromeda. ■

*To see an interview with Dr. Skyler, scan this QR code using your smartphone.*

# Some DMARDs for RA or Psoriasis Blunt Risk of Diabetes

BY MARY ANN MOON

FROM JAMA

Some disease-modifying antirheumatic drugs that are taken for rheumatoid arthritis or psoriasis appear to reduce the rate of incident diabetes.

In a retrospective cohort study of patients who had RA or psoriasis, the use of a tumor necrosis factor (TNF) inhibitor or hydroxychloroquine to treat the systemic inflammatory disorder was associated with a reduced risk of developing diabetes, compared with the use of methotrexate or nonbiologic DMARDs, said Dr. Daniel H. Solomon of the divisions of phamacoepidemiology and rheumatology at Brigham and Women's Hospital, Boston, and his associates.

"Considering these results, in light of prior findings regarding improved insulin and glucose metabolism and reduced diabetes risk with hydroxychloroquine and TNF inhibitors, there is evidence suggesting a possible role for DMARDs and immunosuppression in diabetes prevention," they noted.

The investigators assessed the relation between DMARDs and the risk of new-onset diabetes because previous studies have shown that inflammatory conditions such as RA and psoriasis predispose patients to insulin resistance, and that some of these anti-inflammatory medications appear to improve insulin resistance and prevent the onset of diabetes. They analyzed information from the databases of a Canadian health care system and a commercial U.S. health plan to identify 13,905 adults with RA or psoriasis who had filled at least one prescription for a DMARD and could be followed for 6 months.

**VITALS**

**Major Finding:** The hazard ratios for diabetes were 0.62 for patients taking TNF inhibitors and 0.54 for patients taking hydroxychloroquine, compared with patients taking nonbiologic DMARDs to treat their rheumatoid arthritis or psoriasis.

**Data Source:** A retrospective observational study involving 13,905 adults who had either RA or psoriasis, received a DMARD, and were followed for approximately 6 months for the development of diabetes. Participants were enrolled in one of two health care systems.

**Disclosures:** This study was supported by Amgen. Dr. Solomon reported ties to Abbott, Amgen, Bristol-Myers Squibb, and Pfizer, and his associates reported ties to numerous industry sources.

The DMARDs were divided into four mutually exclusive groups: TNF inhibitors such as adalimumab, etanercept, or infliximab; methotrexate; hydroxychloroquine; and other nonbiologic DMARDs such as sulfasalazine, leflunomide, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, 6-thioguanine, and the following gold preparations: auranofin, myochrysine, or solganol.

A total of 267 study subjects developed incident diabetes. The incidence was highest among patients who were taking nonbiologic DMARDs.

Patients taking a TNF inhibitor or hydroxychloroquine showed a reduced risk of diabetes, compared with patients taking any other agents. After accounting for the effects of potentially confounding factors such as patient age, sex, and several clinical variables, investigators found that the hazard ratios for diabetes were 0.62 for TNF inhibitors and 0.54 for hydroxychloroquine, compared with the nonbiologic DMARDs, Dr. Solomon and his colleagues said (JAMA 2011;305:2525-31).

"These findings held up across a variety of sensitivity analyses," they added.

"Taken in the context of prior research, [our] study supports the potential role for systemic immunosuppression in prevention and control of diabetes. If future studies show this convincingly, systemic immunosuppression in such situations would be predicated on a favorable risk-benefit profile."

For example, the benefit of immunosuppression may outweigh the risk in a patient with a systemic rheumatic disease for which a DMARD is already indicated. But immunosuppression may not outweigh the risk in a patient who already has diabetes and is prone to infection.

The investigators emphasized that this was an observational epidemiologic study, so causation cannot be inferred. "It is possible that patients receiving a TNF inhibitor or hydroxychloroquine were different from the reference group of other nonbiologic DMARD users in ways that went unmeasured, such as body mass index, exercise participation, family history, or disease severity," they noted.

They added that the findings warrant study in a randomized, controlled trial to test "the ability of these agents to prevent diabetes among participants with systemic inflammatory disorders." ■