Type 1 Diabetes

Clinical Findings Show

by Margie Patlak*

Promising news has recently emerged from the front-lines of the war on type 1 diabetes mellitus (T1DM): clinical trials show that various targeted immune therapies can significantly lessen the progression in recently diagnosed children or adults. Because these treatments do not have the debilitating and sometimes dangerous side effects of the more broad-spectrum immunotherapies tried in the past, they also might prove useful for preventing T1DM in those at high risk for developing the condition.

"I'm really very encouraged," said immunologist Lucienne Chatenoud, M.D., Ph.D., of the Université Paris Descartes. She told ***Endocrine News*** that her findings and those of others show it's possible to counter the destructive pathological response that T1DM patients have to their self antigens without disabling their immune reactions to foreign antigens.

These clinical findings build on more than 25 years of painstaking work teasing apart the various immune system components responsible for destroying islet cells in non-obese diabetic mice. This research found the main culprits in this destruction to be T cells, which launch an attack on the antigens of beta pancreas cells.

Researchers first tried to quash T1DM's pathogenic autoimmune reaction with cyclosporine, which is used for organ transplants. Although this non-specific immunosuppressive drug increased the rate and length of remissions in people recently diagnosed with T1DM, the disease resurged once they went off the drug, suggesting the need for indefinite long-term therapy. This treatment was impractical given cyclosporine's serious adverse side effects, which include heightened infection risk and kidney toxicity.

Trying Anti-CD3

A shorter-term and more targeted therapy was developed and tested by Dr. Chatenoud and her international colleagues in a phase 2 trial. When the researchers gave newly diagnosed T1DM adult patients anti-CD3 monoclonal antibodies that targeted mature T cells, they needed significantly less insulin than the controls, especially if they had 50% or more residual beta-cell function at baseline. The very low insulin needs (less than .25 U/kg/day) seen in 75% of this sub-treatment group was compatible with clinical insulin independency. In other words, these patients could conceivably have stopped taking insulin, although none did because it was not part of the protocol. In comparison, the insulin levels of patients in a placebo group doubled within the first 18 months of the trial. Although most patients experienced mild flu-like symptoms after the first infusion, and many developed a transient resurgence in Epstein-Barr syndrome, no one developed serious side effects or infections.

Promise

Based on her studies in animals, Dr. Chatenoud suspects the anti-CD3 treatment doesn't just suppress the T cells that orchestrate the autoimmune attack on islet cells, but in some as yet not-understood way, reprograms the immune system so it is more tolerant of the autoantigens it was previously primed to attack. What's especially amazing about her results is that the treatment was only for 6 days, yet 4 years later, as she recently reported,[1] patients in the treated group still get by with significantly less insulin than those given placebo. Dr. Chatenoud pointed out that such results are likely to be clinically meaningful 15 or so years down the road, because the less insulin T1DM patients need, the less likely they are to develop diabetes complications.

Similar anti-diabetes progression results were seen by immunologist Kevan Herold, M.D., of Yale University, and his colleagues, using a single, 12- to 14-day course of another anti-CD3 antibody.[2] Newly diagnosed children and adults treated with this drug needed significantly less insulin than controls at the end of this 2-year study. Although many patients experienced a mild malaise and rash, none had serious side effects, and measurements taken during the study, as well as additional in vitro findings, suggest the treatment works by stimulating regulatory T cells to suppress the wayward immune response that destroys the pancreas. The insulin usage in the treated group was consistently about half that of the control group, but the need for insulin continued to rise during the study in both groups. According to Dr. Herold, this suggests the treatment needs to be repeated for it to be effective in the long term.

The Earlier the Better

Anti-CD3 treatment might also be more effective if started before the autoimmune reaction has destroyed a significant amount of the pancreas. "The longer you wait [to treat], the less chance you have of a good remission of the disease," said Dr. Chatenoud. She added, "It would be nice to include patients as soon as possible after diagnosis. Even starting at 4 weeks post-diagnosis, like we did, may already be too late, because their beta-cell mass is already too limited" and vulnerable to metabolic stress that can adversely affect insulin production, regardless of whether the autoimmune reaction is successfully staved off.

Fortunately, thanks to the discovery of autoantibodies that predict the near onset of T1DM, (see "Antibodies Portend Type 1 Diabetes" in the April 2008 issue of ***Endocrine News*** at *www.endo-society.org/enod_news/index.cfm* and search "Past Issues"), it is now feasible to screen children who have a close relative with T1DM, and then treat them with the anti-CD3 antibodies if diabetes is likely to ensue in the near future, a condition some call "prediabetes." But according to Dr. Chatenoud, this process will not be ethical until the anti-CD3 treatment is definitively shown to be safe and effective in early-onset diabetes, findings that might emerge in the two phase 3 studies of this treatment undertaken by Tolerx in partnership with GlaxoSmithKlein, and by Macrogenics in partnership with Eli Lilly. These trials are currently enrolling early-onset diabetes patients and are not expected to have results for a few years. Clinical trials are also under way to test oral diabetes "vaccines" aimed at inducing tolerance to autoimmune antigens in people diagnosed with prediabetes.

Rituximab Off-Label

In the meantime, another drug showing promise in staving off T1DM progression is rituximab. This drug eliminates B cells, which in the mouse model also play a role in the destructive immune response seen in T1DM. Rituximab is an approved drug, in use for several years to treat lymphoma and rheumatoid arthritis and, off-label, other immune disorders. It appears to have fewer side effects than broad-based immunosuppressants such as cyclosporine. In a phase 2 clinical trial, Mark Pescovitz, M.D., a transplant surgeon and immunologist at Indiana University, along with his colleagues in the international consortium TrialNet, gave children and adults recently diagnosed with T1DM four infusions of rituximab.[3] A year later, those treated had significantly higher levels of the C-peptide marker for insulin production and lower insulin requirements than a control group. Most developed mild reactions such as itching, flushing, or sneezing, with their first infusion. These side effects did not usually reappear with subsequent infusions. Few infections occurred, with more in the control than the treated group.

Because rituximab is not expected to induce tolerance, it will probably have to be given periodically to keep the autoimmune response in check. "We're going to have to knock down the immune system every now and again to get beta cells to continue to function," said Dr. Pescovitz. That stipulation does not diminish his enthusiasm for the treatment. "We're very encouraged by what we've seen so far because it really shows that the idea of diabetes prevention works, and now we need to optimize the treatment plan."

Nonetheless, concern continues that long-term rituximab use in patients with T1DM could cause the deadly side effects that have been linked to its use in lupus and malignancies in a few patients. Dr. Chatenoud also voiced alarm at the possibility of infections occurring in children and young adults regularly depleted of their B cells for years on end.

Frontline Becomes the Field?

The risks and benefits of both rituximab and anti-CD3 therapy won't be fully apparent until the phase 3 results become available, probably in 2–3 years. The data currently look so promising, however, that Dr. Herold gave a provocative title to his recent journal article, which he called "Prevention of type 1 diabetes: the time has come."[4] ■

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References:

1. You S, Candon S, Kuhn C, Bach J, Chatenoud L. CD3 antibodies as unique tools to restore self-tolerance in established autoimmunity: their mode of action and clinical application in type 1 diabetes. *Adv Immunol,* 2008;100:13–37.
2. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes,* 2005;54:1763–1769.
3. Pescovitz MD, Greenbaum CJ, Krause-Steinrauf H, et al., for the Type 1 Diabetes TrialNet Anti-CD20 Study Group. Rituximab, B-lymphocyte depletion, and the preservation of beta-cell function. *N Engl J Med,* 2009;361:2143–2152.
4. Sherr J, Sosenko J, Skyler JS, Herold KC. Prevention of type 1 diabetes: the time has come. *Nat Clin Pract Endocrinol Metab,* 2008;4:334–343.

PATIENT RESOURCES

Insulin and Other Medications

Treatment for type 1 diabetes includes several different types of insulin and delivery, either by injection (needle or pen) or insulin pump infusion. Here are some examples of different insulins and their brand names:

- Regular insulin: Humulin R, Novolin R
- Insulin isophane: Humulin N, Novolin N
- Insulin aspart: NovoLog
- Insulin glulisine: Apidra
- Insulin lispro: Humalog
- Insulin detemir: Levemir
- Insulin glargine: Lantus

Patient Resources

The Endocrine Society's patient affiliate, The Hormone Foundation, has free information about diabetes. Visit *www.hormone.org* and click "Patient Resources" on the left. Among the bilingual fact sheets are:

- Type 1 Diabetes
- Diabetes and New Insulins
- Self Monitoring of Blood Glucose
- Diabetes, High Blood Pressure, and Kidney Protection
- Diabetes and Nutrition: Carbohydrates

The Foundation also has a Patient Guide titled "Patient Guide on the Diagnosis and Management of Hypoglycemic Disorders (Low Blood Sugar) in Adults" to accompany the Society's clinical practice guideline "Evaluation and Management of Adult Hypoglycemic Disorders."

Other patient resources include the Juvenile Diabetes Research Foundation (*www.jdrf.org*) and the American Diabetes Association (*www.diabetes.org/diabetes-basics/type-1*).

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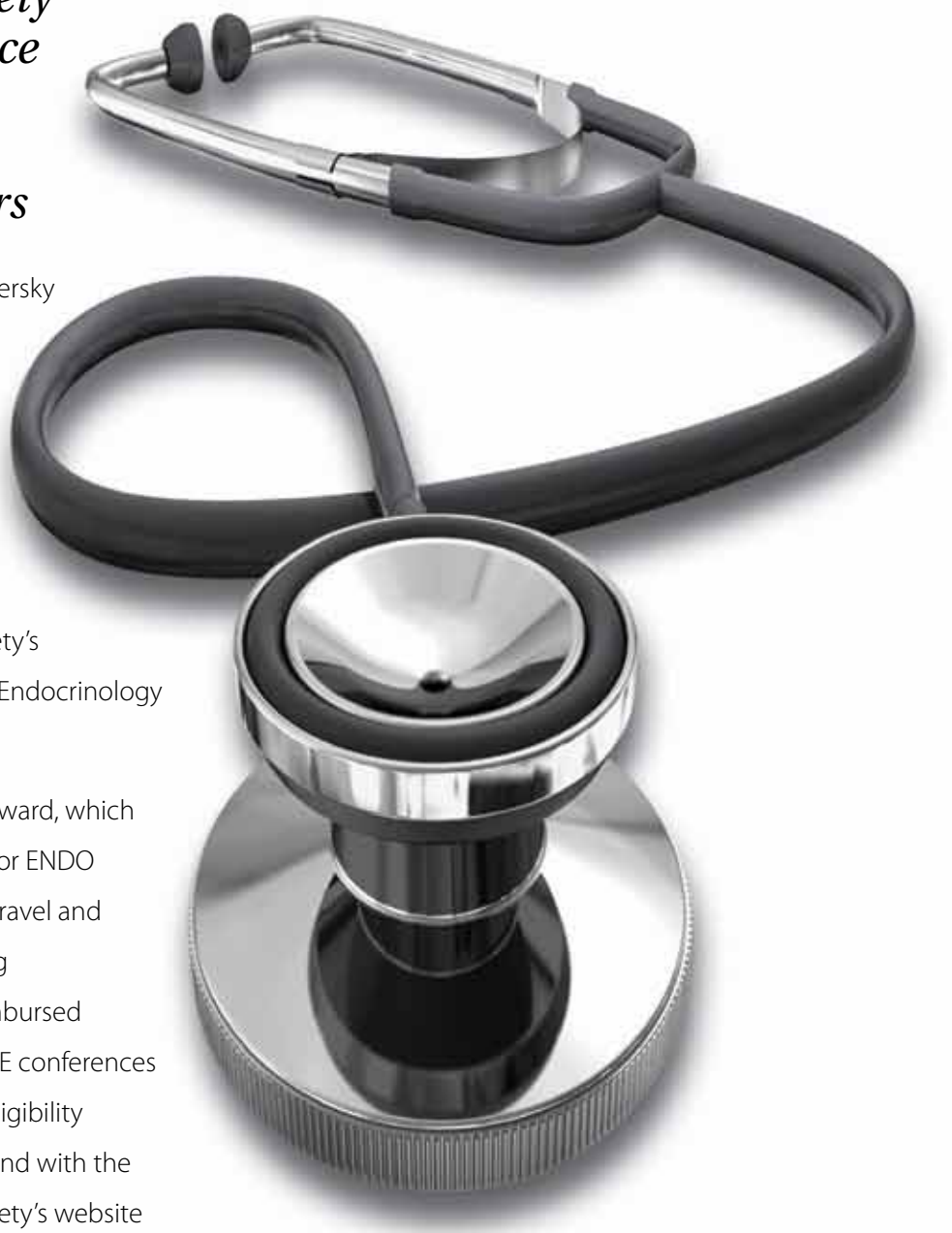

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