EDITORIAL

Advances in Diabetes Treatment — Once-Weekly Insulin

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The increasing incidence of type 2 diabetes and of health consequences related to complications from inadequate glycemic control is of major concern, even in the midst of a worldwide pandemic. Despite the introduction of new adjunctive medicines, recombinant insulins, and the ability to monitor blood glucose in real time, treatment for diabetes remains less than ideal.[1] Data from the National Health and Nutrition Examination Survey (NHANES) indicate that the mean glycated hemoglobin level for adults with diabetes in the United States dropped to 7.2% in 2016; however, the percentage of patients in whom a target level of less than 7.0% was reached remained a disappointing 55.8%.[2] A number of factors are likely to contribute to these statistics, including socioeconomic status, race, treatment adherence, and adequacy of insurance coverage.[3]

The current treatment algorithms for type 2 diabetes emphasize lifestyle changes and oral therapies as first-line treatment for the disease.[4,5] As the disease progresses over time, additional therapies are often needed to maintain adequate control of blood sugar. As our understanding of pathogenic disease mechanisms has grown, agents such as glucagon-like peptide 1 (GLP-1) receptor agonists and sodium glucose-like transporter 2 (SGLT2) inhibitors have been incorporated earlier in disease-management strategies.[6] These medications can improve control of blood glucose without causing weight gain and are associated with a minimal risk of hypoglycemia. Patients for whom oral agents such as metformin, sulfonylureas, and dipeptidyl peptidase 4 inhibitors have become ineffective may now be offered a choice of one of these newer therapies or once-daily basal insulin treatment. Improvements in drug delivery and pharmacokinetics have resulted in the development of GLP-1 receptor agonists that are now administered once weekly and provide weight loss and reductions in glycated hemoglobin levels that are equivalent to or better than those provided by basal insulin therapy.[7]

In this issue of the *Journal*, Rosenstock and colleagues present an attempt to simplify the delivery of basal insulin therapy for patients with type 2 diabetes with a once-weekly formulation of insulin icodec, an ultra–long-acting basal insulin.[8] The investigators compared weekly insulin icodec with daily insulin glargine U100 in a rigorous double-blind, double-dummy trial in which the effects of these insulins were examined for 26 weeks. The trial population included patients whose diabetes was inadequately controlled with metformin with or without a dipeptidyl peptidase 4 inhibitor and who had not previously received long-term insulin treatment. The authors used treat-to-target algorithms that aggressively increased the dose of each type of insulin to reach fasting blood glucose targets. Icodec was associated with no major adverse events and was shown to be as effective as glargine at lowering glycated hemoglobin levels. The glycated hemoglobin level in the icodec group decreased from 8.1% to 6.7%, and that in the glargine group decreased from 8.0% to 6.9%; icodec achieved these glycemic targets with a lower overall dose of insulin. The incidence of mild hypoglycemia was slightly higher in the icodec group, but the trial was not powered to detect significance. The investigators postulate that less aggressive dose adjustment may lessen this risk of hypoglycemia.

The authors suggest that once-weekly insulin therapy would be easier than daily therapy for patients with type 2 diabetes who are learning to incorporate insulin injections into their treatment regimens. Because there is an expanding number of treatment options for patients with type 2 diabetes, the particular population included in the trial may not represent the typical patient with diabetes. Further studies are therefore warranted to determine how once-weekly insulin can be incorporated into treatment algorithms. Although the simplicity of a once-weekly therapy is an advantage, the inability to vary the dose might make it harder for patients who are trying to incorporate exercise into their care regimens.[9] In addition, patients with type 1 diabetes, the immune-mediated form of diabetes,[10] may benefit from less frequent insulin administration. The pharmacokinetics of icodec are being investigated in patients with type 1 diabetes (ClinicalTrials.gov number, NCT03723772). However, as is the case with patients with type 2 diabetes who are incorporating exercise into their treatment regimens, patients with type 1 diabetes, especially those who are very physically active, need the ability to adjust their doses of short- and long-acting insulin.

Despite these concerns, this trial represents an advance that may eventually add another agent to our armamentarium for the treatment of hyperglycemia. Further studies to determine the patient populations most likely to benefit will aid in personalizing therapies for diabetes.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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1. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes — 2020.* Diabetes Care 2020;43:Suppl 1:S14-S31.
2. Fang M. Trends in diabetes management among US adults: 1999-2016. J Gen Intern Med 2020;35:1427-34.
3. Smalls BL, Ritchwood TD, Bishu KG, Egede LE. Racial/ethnic differences in glycemic control in older adults with type 2 diabetes: United States 2003-2014. Int J Environ Res Public Health 2020;17:950.
4. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes — 2019.* Diabetes Care 2019;42:Suppl 1:S90-S102.
5. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:487-93.
6. Wilding JPH, Rajeev SP, DeFronzo RA. Positioning SGLT2 inhibitors/incretin-based therapies in the treatment algorithm. Diabetes Care 2016;39:Suppl 2:S154-S164.
7. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol 2017;5:355-66.
8. Rosenstock J, Bajaj HS, Janež A, et al. Once-weekly insulin for type 2 diabetes without previous insulin treatment. N Engl J Med 2020;383:2107-16.
9. Reusch JEB, Bridenstine M, Regensteiner JG. Type 2 diabetes mellitus and exercise impairment. Rev Endocr Metab Disord 2013;14:77-86.
10. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383:69-82.

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