# Benefits of Insulin Therapy Sequence Confirmed

BY KATE JOHNSON

MONTREAL — Insulin added to oral therapy in patients with longstanding type 2 diabetes is best initiated as a basal formulation and then intensified with prandial doses, according to the 3-year results of the Treat to Target in Type 2 Diabetes (4-T) trial.

"The results of our trial support current guidelines, which suggest that basal and prandial insulin regimens should be considered if adequate glycemic control is not achieved with initial regimens," reported lead author Rury Holman, MB, ChB, of the diabetes trials unit at Oxford (England) University.

The findings were announced at the World Diabetes Congress, with simultaneous publication in the New England Journal of Medicine (2009;361:1736-47).

"I think we now have very clear evidence that the sequence of basal with added prandial gives you less weight gain and less hypoglycemia," said Dr. Holman in an interview immediately following his presentation. "It's a no-brainer that that is the way we should now initiate treatment for these patients."

"The 4-T study supports the initiation of treatment with basal insulin, which is consistent with the concept that fasting hyperglycemia contributes more than postprandial hyperglycemia to glycated hemoglobin levels during periods of poor glycemic control," commented Dr. Michael Roden from the German Diabetes Center and the Heinrich Heine University of Düsseldorf, Germany, in an editorial published in the same issue.

However, he suggested "it seems premature to recommend specific insulin regimens for patients with newly diagnosed disease."

The 4-T multicenter, open-label trial included 708 patients who had inadequate glycemic control on dual oral metformin and sulfonylurea therapy. The patients were a mean age of 61.7 years, with a mean disease duration of 9 years.

They were randomized to one of three supplemental insulin regimens in the first year: prandial insulin aspart (NovoRapid) three times daily, biphasic insulin aspart (NovoMix 30) twice daily, or basal detemir (Levemir) once daily, or twice if needed.

In the second year, sulfonylureas were replaced by a second insulin if hyperglycemia became unacceptable, which was the case in almost 90% of the patient population, said Dr. Holman.

For such patients who had started on biphasic insulin, a midday prandial dose was added. For those who had started on either basal or prandial regimens, their treatments converged, so that the basal group added prandial doses (10% of the daily basal dose with a minimum and maximum limit) and the prandial group added a basal dose (10 units at bedtime).

"The importance here is the temporal sequence—they are not identical," said Dr. Holman. "So basal plus prandial was not the same as prandial plus basal. They started at a different place and so the percentages were different. So those who started with prandial had substantially more prandial than basal at the end, and those who started with the basal and then added prandial ended up with about 50/50."

Preliminary results published after the first year of the study did not favor the basal insulin regimen, which was the least successful at bringing hemoglobin $A_{1c}$ levels to 6.5% or less (N. Engl. J. Med. 2007;357:1716-30). "The addition of biphasic or prandial insulin aspart reduced levels more than the addition of basal insulin detemir but was associated with greater risks of hypoglycemia and weight gain," the authors concluded at that time.

However, "the difference in outcomes from the first to the third year is startling," Dr. Roden remarked in his editorial.

Final results showed that fewer than 45% of all patients achieved the $HbA_{1c}$ target of 6.5% or less. In addition, significantly fewer patients on the biphasic regimen (31.9%) compared to the prandial (44.7%) and basal (43.2%) groups, reached the target.

Furthermore, the basal group gained significantly less weight (3.6 kg) than did the biphasic and prandial groups (5.7 and 6.4 kg, respectively), and the median number of hypoglycemic events per patient per year was lowest in the basal group (1.7), compared to the biphasic (3.0) and prandial groups (5.5).

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"Median glycated hemoglobin levels converged after 1 year and remained stable in all groups, for an overall value at 3 years of 6.9%," wrote the authors (7.1% for biphasic, 6.8% for prandial, and 6.9% for basal, with no significant differences). The final mean reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group.

In an interview, Dr. Matthew Riddell commented that the 4-T results confirm the current guidelines from the American Diabetes Association and the European Association for the Study of Diabetes. "It shows that if you use insulin systematically it doesn't really matter which way you start. You can get to the same glucose level, but there are other important differences in treatments. The 4-T gives us a clue that maybe the mealtime insulin treatments shouldn't be the mainstay," said the professor of medicine at Oregon Health and Science University in Portland.

"The overall message of the [final 4-T results] is that you need complex insulin regimens to obtain adequate glycemic control, which is still not reached in a substantial number of subjects," Dr. Roden said in an interview.

The 4-T study was supported by Novo Nordisk A/S and Diabetes UK.

Dr. Holman reported receiving grants and consulting fees from pharmaceutical companies that included Novartis and Novo Nordisk, lecture fees from pharmaceutical companies, and royalties from sale of the Unistik single-use safety lancet. Dr. Roden reported receiving consulting and lecture fees from several drug makers, including Novo Nordisk. Dr. Riddle reported paid lecturing from and advisory board work with several drug companies. ■