Comparing diabetes drugs—helping clinical decisions?

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Comparative effectiveness research has become an important line of investigation in many aspects of medicine, but is especially important in diabetes. Many drug classes are available, and to choose which second-line treatment to add to metformin might be challenging. Recommendations from the American Diabetes Association and European Association for the Study of Diabetes suggest at least five different drug classes, with choice dependent on many, and sometimes difficult-to-assess, characteristics when a patient-centred approach is used.[1]

Furthermore, very few studies have assessed differences between drugs within a class, which have similar mechanisms of action and thus probably have very similar overall efficacy. However, the true effectiveness of a drug can be somewhat different from the efficacy reported in clinical trials, and in a large population it could depend on other characteristics, including side-effects and the drug's secondary effects on other factors (eg, the effects of rosiglitazone and pioglitazone on lipids).[2] Differences in dosage (eg, weekly *vs* daily) can also matter to patients and affect compliance (and thereby effectiveness).

In *The Lancet*, John Buse and colleagues[3] compare the efficacy of a once weekly preparation of exenatide with that of a once daily injection of the human glucagon-like peptide 1 (GLP-1) analogue liraglutide in patients with type 2 diabetes. The primary hypothesis was that the HbA_{1c}-lowering capability of weekly exenatide was at least non-inferior to that of liraglutide, but it was prespecified that superiority was not to be assessed if non-inferiority was not achieved, as was the case. Thus, although the results state that the HbA_{1c} change from baseline to endpoint was greater in patients taking liraglutide than in those taking exenatide, the difference was not tested for significance. Nevertheless, the overall difference in HbA_{1c} between the two drugs was small (0·21% [95% CI 0·08–0·33]), which for many patients might not make a difference in achievement of glycaemic goals. Buse and colleagues' hypothesis was based on data from other clinical trials done in different populations. Their trial clearly shows the fallacy of making comparisons on the basis of such data because characteristics of patients, including baseline glycaemia, affect results. Only randomised clinical trials can eliminate such bias. The large number of patients in each group (450 in the liraglutide group and 461 in the exenatide group) is a strength, with both groups including participants who had previously taken various drugs that are frequently used in diabetes.

Unfortunately, the study design was far from what is needed to help with clinical decision making and had flaws that could have affected the results. The dose of liraglutide was up-titrated to 1·8 mg daily during 2 weeks, and patients not tolerating this dose after 4 weeks were discontinued from the trial. This dose might have contributed to the high rate of side-effects noted in the study. In clinical practice, many patients can achieve glycaemic goals with a daily dose of 1·2 mg,[4] and have less severe nausea and vomiting than do those on higher doses. Even if the dose is titrated further to 1·8 mg, the dose can sometimes be reduced to 1·2 mg, alleviating side-effects in some patients (albeit with possibly less efficacy). A true comparison could have been made between the maximum tolerated doses of each drug. Thus, the side-effect profile of liraglutide portrayed by this trial might not be closely similar to that noted in practice. The difference in gastrointestinal effects between liraglutide and exenatide could be attributable to the gradual rise of plasma exenatide concentrations with the extended-release formulation (as has been suggested in studies comparing long-acting with rapid-acting formulations of exenatide).[5,6] The investigators might have missed the opportunity afforded by this trial to assess the effect of differences in pharmacokinetics of the drugs on side-effects. Such an analysis would be very useful if blood samples are available.

Additionally, the study was open label rather than placebo controlled. Patients' preference for a weekly injection might affect their perception of subjective side-effects (eg, nausea). Although the authors raise some discussion about some patients doing better with one drug or the other, they did not seem to do a scientifically robust assessment of the characteristics of patients that might predict response to individual drugs. Although such an analysis was not prespecified in this trial, we believe that the pharmaceutical industry should prespecify if needed and do an analysis

of all drugs to establish the most likely responders. Such a strategy might be especially important in comparative trials. Since a clinically meaningful response to these expensive drugs was noted in only some patients (more than 40% did not meet the HbA_{1c} goal of <7%), identification of factors that could predict efficacy would go a long way towards the goal of optimally tailored therapy.

Unfortunately, the short duration of the trial means that longer-term effects and side-effects could not be compared between treatment groups. Drugs in the GLP-1 agonist class can be associated with the formation of antibodies—neutralising antibodies in the case of exenatide, which are associated with a loss of efficacy with time in 3–9% of patients.[7] In a study of once weekly exenatide, glucose-lowering efficacy seemed decreased in the 24% of patients who developed high-titre antiexenatide antibodies (HbA_{1c} reduction of 1·4%) compared with that in patients without antibodies (1·9%).[7] By contrast, Buse and coworkers have noted that, although a small proportion of patients given liraglutide in six randomised clinical trials developed antibodies, an effect on the glucose-lowering efficacy of liraglutide was not shown.[8] In one of those trials,[9] less glucose lowering was noted in patients in the comparator group (who were given exenatide) who had high exenatide antibody titres. Furthermore, when patients were switched from exenatide to liraglutide, control improved overall,[10] but participants with the highest antibody titres had the greatest falls in glycaemia,[8] suggesting that the antiexenatide antibodies were attenuating the GLP-1-mediated glucose-lowering potential of the drug. In a large analysis of patients given exenatide, Fineman and colleagues[11] reported that low antibody titres generally develop early and decrease with time. High antibody titres developed in 5% of patients given exenatide twice daily and 12% of those given exenatide weekly, and increasing antibody titres were associated with reduced average mean efficacy that was significant for weekly exenatide. Thus, in Buse and colleagues' trial, we question whether patients who did not respond as well as expected had a higher titre of antibodies than those in whom the drugs worked well, and whether a difference in antibodies might have contributed to the noted and perhaps unexpected differences between drugs in the trial.

In summary, the DURATION-6 trial was well done and even though it did not meet its primary endpoint, its results might help some clinicians to make appropriate treatment choices on the basis of relative efficacy and the risk of short-term side-effects. We look forward to more comparative trials that will help to drive clinical decision making in diabetes.

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