The Review of DIABETIC STUDIES

CONFERENCE REPORT

Anti-diabetic Agents in Type 2 Diabetes: A Review of New Data Presented and Discussed on the EASD meeting in Rome, 2008

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■ Abstract

The results of a number of large trials and the arrival of new glucose-lowering drugs are changing the scene of diabetes care in patients with type 2 diabetes. The results of the ADVANCE and ACCORD trials have shown that strict glycemic control does not improve macrovascular outcome. Consequently, the importance of duration of disease, presence of cardiovascular disease and risk of hypoglycemia, have been brought again into focus as considerations in designing individual treatment plans. New drugs related to the incretin system have emerged in the past year, and these may decrease certain risks of classic glucose-lowering drugs. However, we have to be aware of the possibility of yet unknown longer-term risks from newly developed drugs. The new insights from the trials presented on the EASD meeting 2008 and the emerging information on the new drugs are used in this paper to start defining the contours of prospective new treatment strategies.

Keywords: type 2 diabetes · glycemic control · sulfonylurea · ADVANCE study · GLP-1 · DPP-4 · gliclazide

Introduction

The year 2008 has been marked by tremendous activity and possibilities for improvement in the treatment of patients with type 2 diabetes. A series of large trials on glycemic control have been presented, and emerging drugs have gained central stage, combined with the promise of further drug development. Both sources add to the arsenal for the design of patient-orientated treatment approaches. However, these developments need broad discussion. The 44th EASD meeting proved to be an excellent opportunity, set appropriately against the background of ancient and modern Rome. This paper highlights the latest results from the ADVANCE and ACCORD trials as well as recent drug developments that could help to optimally design individualized treatment approaches.

Recent large clinical trials with anti-diabetic agents

Two major trials previously presented at the Scientific Sessions of the American Diabetes Association (ADA), were hotly debated during the September annual meeting of the European Association for the Study of Diabetes. All three trials seem to point in the same direction. Firstly, the ADVANCE trial looked at the benefit of strict glycemic control in type 2 diabetes [1]. Patients from Australia, Asia, Europe and the North Americas were randomly assigned to strict gly-

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cemic control. A mandatory part of the regimen in the first (strict) group was the use of gliclazide, a target HbA1c ≤ 6.5% and usual care (based on local guidelines), and an intended contrast in HbA1c between the arms of at least 1.0%. Patients in the second (control) group could use any sulfonylurea except gliclazide. Patients likely to require insulin were excluded.

The study period was extended because achieving the strict target took longer, and achieving acceptable contrast between the groups proved more difficult than expected. After a median of 5 years follow-up, there was a significant decrease in the combined incidence of micro- and macrovascular events, attributable to a difference in microvascular disease. Within microvascular disease, there was a significant reduction in new or worsening of nephropathy, but not in the incidence of need for renal replacement therapy, or doubling of the plasma creatinine level. Nor was any reduction seen in retinopathy. The price to pay was an increase in severe hypoglycemia, which was rather expected. Basically, ADVANCE showed that the first years on intensive glycemic control only affect albumin excretion rate at the expense of hypoglycemia. As expected, there was no effect on macrovascular disease. The results were less dramatic than with the hypertension-arm in ADVANCE [2].

The results of the ACCORD trial extended the ADVANCE data [3]. In this trial, glycemic targets (HbA1c) were ≤6.0% in the intensive group, and between 7.0 and 7.9% in the control group. About one-third had previous cardiovascular disease, similar to ADVANCE. One-third had insulin therapy at baseline in ACCORD. The glycemia-arm was prematurely terminated because of an increase in deaths attributable to different causes, e.g. death due to cardiovascular events, in particular myocardial infarction. No difference was observed in the primary end point (non-fatal myocardial infarction, non-fatal stroke or death from cardiovascular disease). It was suggested that the rapid decrease in HbA1c achieved in the intensive arm may help to explain the result. First statistical impressions presented at the ADA meeting could not identify hypoglycemia as a likely reason, nor for example, the use of rosiglitazone. Based on both studies, the case for improving glycemic control as a means of improving macrovascular disease in type 2 diabetes can be all but discarded. The benefit on microvascular disease is small compared to the risks and costs.

Apart from these ongoing clinical trials there is potential for improved treatment with new anti-diabetic drugs based on incretin analogues and enhancers. First results have also been presented on the meeting.

Drug development

GLP-1 analogues

The incretin system has changed the spectrum of glucose-lowering drugs with the development of advent of oral and parenteral incretin modifiers [4-7]. In short, food intake leads normally to the secretion of glucagons-like polypeptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP). Both substances stimulate the beta-cell function, leading to glucose-dependent insulin secretion, and improved alpha-cell function with lowering of the glucagon levels. Exenatide is the first GLP-1 analogue, and is already on the market. It is associated with a mean decrease in HbA1c of 1% [8]. The question arises, where in the treatment algorithm such a compound would be placed? Heine *et al.* have shown that in patients failing on oral medication, adding exenatide is at least as efficacious as adding insulin glargine [9].

A new GLP-1 analogue has emerged now, liraglutide, which is to be administered once daily. A number of presentations were dedicated to liraglutide, detailing aspects of the clinical development program. These showed that liraglutide is a potent once-daily GLP-1 analogue in various combinations with other drugs, resulting in decreased HbA1c levels, low hypoglycemia rates and weight loss [10-15].

An intriguing new development is to extend the duration of action of the GLP-1 analogues to a week, as reported on exenatide [16]. It may be that even longer intervals are possible, enabling weekly or even monthly use of these drugs. However, everything comes at a price. It has recently been reported by the FDA that exenatide may be associated with the possibility of developing pancreatitis. Whilst it remains to be established whether such an association exists and how strong it is, it serves as an outright reminder of the potential long-term risks of new drugs. It seems that there is some risk that was not revealed during the clinical development program.

DPP-4 inhibitors

Oral modifiers of the incretin system are the focus of a large body of research, and hold a great promise for the future. The oral inhibitors of DPP-4 increase circulating GLP-1 levels by decreasing its breakdown. Currently, vildagliptine and sitagliptin are approved in Europe. For both compounds, efficacy and safety have been shown both as monotherapy and in combination therapy. The durability of the glucose-lowering effect is a critical issue. Qi *et al.* reported on the effect of

combining sitagliptin with various doses of metformin, in a study over a duration of 104 weeks [17]. In this study, 587 of 915 patients participating in the original 54-week study, consented to a 50-week extension using the same treatment. After 104 weeks, sitagliptin 100 mg and metformin 2000 mg resulted in a reduction of HbA1c of 1.7%. Sitagliptin (100 mg) plus metformin (1000 mg) caused a reduction of 1.4%. Metformin only (2000 mg or 1000 mg), or sitagliptin only, resulted in decreases of 1.2%, 1.1% and 1.2%, respectively. The percentages of patients achieving an HbA1c < 7% at the end of the trial were 60% (100 mg sitagliptin plus 2000 mg metformin), 45% (100 mg sitagliptin plus 1000 mg metformin), 45% (2000 mg metformin only), 28% (1000 mg metformin only) and 32% (100 mg sitagliptin only). The highest dosed combination seems to have the best and most durable effect on glycemic control, although statistical significance was not given. Nor was the effect on weight and hypoglycemia given.

Regarding combination therapy, DPP-4 inhibition with insulin is an interesting combination Coupling exogenous insulin with a drug that stimulates endogenous glucose-dependent insulin secretion (depending on residual beta-cell function) inhibits glucagon secretion, and thus endogenous glucose production. The study by Fonseca *et al.* in 2007 already showed that adding vildagliptin to existing insulin therapy resulted in a significant decrease in mean HbA1c without an increase in hypoglycemia [18]. Even stronger, the risk of severe hypoglycemia may be less with vildagliptin as an add-on drug, since vildagliptine improves alpha-cell function with restoration of glucagon secretion in the low glucose range [19]. Unfortunately, a more detailed analysis is lacking, as the Fonseca study encompassed a large patient group seen in many centers. One major issue is that in the study the insulin dose was largely fixed, whereas in normal circumstances, insulin treatment is adjusted according to glucose levels. Also, the regimen was mostly a mixed insulin twice daily, whereas now, more intensive insulin regimens are commonly used.

A host of new DPP-4 inhibitors are emerging. Data on alogliptin and saxogliptin were presented at the EASD meeting. An interesting study was performed with alogliptin by Rendell *et al.* [20]. Insulin-treated patients with type 2 diabetes were randomized between, adding a lower dose of alogliptin, a higher dose of alogliptin, or placebo. No change was allowed in the insulin dose during the 26-week trial. In common with the Fonseca trial, HbA1c decreased significantly and similarly for both doses of alogliptin compared with placebo (lower dose -0.63%, higher dose -0.73%, placebo -0.13%).

The logical question is, why does DPP-4 inhibition results in such an improvement? The effect occurs within a few weeks and would logically be ascribed to the improved beta- and alpha-cell function. Residual beta-cell function is rather limited in insulin-requiring patients with type 2 diabetes [21], and one would suspect that the DPP-4 effect may be influenced by a significant decrease in glucagon levels. It should be noted that uncontrolled hyperglucagonemia is a natural phenomenon in type 2 diabetes resulting in stimulation of endogenous glucose production in both the fasting and the post-prandial state. If anything, the incretin system has placed glucagon back on center stage.

Recently, a new algorithm on the treatment of patients with type 2 diabetes has been published [22]. This algorithm is presented as a consensus statement from the ADA and the EASD. As the authors state, the algorithm is based on medication trials and on clinical judgment, tinged with personal subjectivity. This aspect needs to be borne in mind, although it should not detract greatly form the general meaning and value of the algorithm. Efficacy and safety, ease of use and costs, are integrated in the judgments. The algorithm is divided in two parts, the well-validated tier, and the less well-validated tier. The well-validated (classic) tier is that metformin is the drug of first choice in combination with lifestyle interventions. This conforms to guidelines in many countries. The next step is adding a sulfonylurea, or adding basal insulin with more intensive schemes, if basal insulin alone is not enough. The second tier is metformin with either a GLP-1 analogue or a thiazolidinedione derivative (in this case pioglitazone). If these combinations fail, triple therapy (metformin, pioglitazione and sulfonylurea) is advised, or metformin and basal insulin. As one can see, the algorithm is a rather conservative approach, and one suspects that costs are a major consideration. This is a logical approach if such an algorithm is to be valuable in a wide range of countries and settings. However, there are advantages with new drugs, less hypoglycemia and weight gain with DPP-4 inhibition compared to sulfonylurea; longer durability of adequate control with rosiglitazone compared to metformin of sulfonylurea. Discussion will remain, and that is to be cherished.

Conclusions

A new dawn has broken for the drug treatment of patients with type 2 diabetes. New agents have been developed, and new combinations tried. The rosiglitazone story has taught us how slippery the road for new

drugs can be, notably in the post-marketing period. The initial meta-analysis by Nissen *et al.* reported that rosiglitazone was associated with increased cardiovascular ischemic events and cardiovascular mortality [23]. The reported potential increase in cardiovascular death reported in the initial meta-analysis has been rightfully questioned for several reasons. Firstly, studies without cardiovascular events were not included. Secondly, two large studies have been combined with more than forty small ones, sometimes in patient groups for whom rosiglitazone was not registered for use.

Similar to the RECORD interim analysis, a subanalysis during the ACCORD trial indicated that rosiglitazone was not associated with an increased risk [24]. However, caution remains necessary, and the general trend in drug registration is for careful long-term data and surveillance. Whether pioglitazone really holds advantage over rosiglitazone remains a matter of debate. In this light, the potential link with pancreatitis with exenatide is worth mentioning. Although much attention has been paid to the new drugs, metformin has taken off only during the last decade, after having been all but banned earlier because of the link with lactic acidosis. Glibenclamide was the center of discussion in the 70's and 80's because of the potential link with cardiac arrhythmias and death, in the UGDP study [25]. Oral DPP-4 inhibitors have not gained a place in the algorithm, because of the lack of long term experience and costs. Pioglitazone obtained a place in the algorithm, based on the positive results of piolitazone on some secondary vascular end points in the PROACTIVE study, and due to recent discussions about the association of rosiglitazone with increased risk of ischemic cardiovascular disease [26].

The three large trials have shown that strict glycemic control does not improve macrovascular outcome in five years follow-up, and the price in ADVANCE was hypoglycemia. One might argue that at least the risk of hypoglycemia could have been less if a DPP-4 inhibitor had been used. Another consideration could be that ADVANCE did not eliminate the possibility that a good effect could have been obtained if treatment had been strict from diagnosis onward. Finally, follow-up studies form the DCCT, the STENO trial, and the recently published follow-up from the UKPDS have all indicated that a period of good control may have long-lasting beneficial effects. Benefits have been seen to continue after the study intervention has ended and when the glycemic control is roughly comparable between previous intervention and control groups. This leaves room for much speculation on causes and consequences [27-29]. Some light has been shed in 2008, but many dark corners remain, shrouding knowledge and opportunities.

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