Combination Oral Agent Therapy in the Treatment of Type 2 Diabetes

a report by
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It is well established that type 2 diabetes is a progressive disease, with blood glucose levels rising over time. Most patients will require multiple therapies in order to control their blood sugar levels and maintain glycemia at or below the A_{1c} target of less than 7%. Although studies have been performed to assess the effectiveness of combining oral agents to improve glycemic control, there is no large-scale definitive study on which are the best sequential combinations to use. Therefore, treatment must be individualized based on the clinical circumstances of each individual patient, and new therapies must be initiated rapidly to keep the A_{1c} from rising much above the target range.

Background

The UK Prospective Diabetes Study (UKPDS) was a long-term treatment study evaluating the benefits of intensive glycemic control (the intervention group) and conventional therapy (the control group). In addition to establishing the benefits of better blood glucose and blood pressure control in the treatment of type 2 diabetes, it provided longitudinal data on the progression of type 2 diabetes. In the study, A_{1c}s rose over time, regardless of the treatment used (lifestyle, sulfonylurea agents, metformin, or insulin). By nine years of monotherapy with diet only, 9% had an A_{1c} of less than 7%. Those on oral agents did only slightly better: 13% of those on metformin monotherapy and 24% on sulfonylurea agent therapy were at the target A_{1c} after nine years in the study. Twenty-eight percent of those on insulin monotherapy met the target. Thus, monotherapy with any of the agents studied was not successful long term in nearly 75% of patients. When beta-cell function was assessed it was shown that beta-cell failure progressed steadily over the course of the study, regardless of treatment used.

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In the US, A_{1c} levels remain well above target and patients even less frequently (less than 25%) reach all of their glucose, lipid, and blood pressure targets. One important reason why blood sugar levels remain high is the clinical lag found before adding each new medication. Providers as well as patients resist adding another treatment and as a result A_{1c} levels remain high for many years. Often, A_{1c} levels will rise to well above 8% before a new agent is added. The major factor in predicting response to combination therapy is the level of the A_{1c} at the time the next therapy is added. Each additional new therapy only produces an A_{1c} reduction of approximately 1%, although higher A_{1c} levels will fall further. Therefore, regardless of the order of therapy, adding each new therapy as soon as the A_{1c} is above target is critical to ensure lifelong maintenance of near-normal blood-glucose levels.

Antidiabetes Medications

In recent years, there has been an explosion in the number of new drugs available for the treatment of type 2 diabetes. In addition to the various types of insulin, there are eight classes of additional medication for treating type 2 diabetes (sulfonylurea agents, meglitinides, biguanides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase (DPP)-4 inhibitors and amylin analogs). Except among secretagogues, most drugs from different classes can be combined for an additive effect (although in some cases this is an off-label use). Although some studies have been carried out assessing the effectiveness of various combinations of two or three agents, no systematic trials have been performed to evaluate the most effective stepwise addition of therapeutic agents in the treatment of type 2 diabetes.

The American Diabetes Association and European Association for the Study of Diabetes proposed a stepwise algorithm for the treatment of type 2 diabetes (see *Figure 1, Initiation and Adjustment of Therapy in Type 2 Diabetes, page 17*). In their approach, metformin and lifestyle interventions are started simultaneously at the onset of diabetes. A second drug is added when the A_{1c} begins to rise above 7%, and the choices include a sulfonylurea agent, a TZD, or insulin. The third step can be another oral

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agent, although early initiation of insulin therapy is suggested. Some of the newer agents were not considered in these algorithms, since clinical experience was lacking at the time at which they were developed.

Multiple factors should influence the choice of the second and third agent to add. First, one agent is generally not stopped and another substituted, but the drugs should be progressively combined until the A_{1c} is below 7%. When a new drug is added, the dose should be up-titrated every two to four weeks based on fasting plasma glucose levels and side effects until the maximal tolerated dose is reached. In some cases, in patients with marked hyperglycemia, combination therapy is used at the start with faster improvement of blood glucose levels than when each drug is used individually.

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The choice of which drug to use in an individual depends, in part, on whether or not the patient has any contraindication to the proposed medication and what their specific clinical circumstances are. For instance, a more overweight patient might benefit from drugs that reduce insulin resistance, such as metformin and TZDs, whereas a leaner patient may be more insulin-deficient and require an insulin secretagogue. Cost is often a factor, and often the formulary associated with an individual's health plan has preferred medications that may be more affordable for the patient. Generic metformin and sulfonylurea agents cost only cents a day in most circumstances, compared with the greater expense of all of the newer agents. Adherence is also an important consideration. Daily drugs are often easier to remember to take than drugs that are taken multiple times throughout the day.

Non-glucose Effects of Antidiabetic Agents

Type 2 diabetes is a complex, multi-system disease. Reducing cardiovascular risk is as important as reducing the microvascular complications that stem from hyperglycemia. An ideal drug would lower blood glucose levels and blood pressure, normalize diabetic dyslipidemia, and reduce the risk for thrombosis. In addition, it would help restore beta-cell mass to normal. Unfortunately, there are no agents that even come close to performing all of these metabolic miracles. However, some may be better than others.

For instance, although there was initial concern about sulfonylurea agents increasing the risk of cardiovascular deaths, after many years of use it appears that they do not. Sulfonylurea agents lower blood sugar levels rapidly and appear to be purely glucose-lowering agents. Metformin, on the other hand, when used as monotherapy in obese patients, reduced the risk of a myocardial infarction in the UKPDS and has overall been linked to a slight reduction in cardiovascular diseases (CVDs). This could be due to its small but fairly consistent effects on lipids reduction in low-density lipoprotein cholesterol (LDL-C) with an increase in high-density lipoprotein cholesterol (HDL-C).

TZDs have long been postulated to have cardioprotective benefits. A variety of surrogate markers—such as C-reactive protein and fibrinogen levels, reduction in progression of intimal medial thickness, and improvements in vascular reactivity—have been seen in studies with TZDs. It has been theorized that reducing insulin resistance, a pathogenic feature of the metabolic syndrome, would lower the risk of CVDs. TZDs, as primary insulin sensitizers, appear to be the most likely class of agents to have this benefit.

The largest clinical outcomes study to date has been the PROspective pioglitAzone Clinical Trial in macroVascular Events (PROactive) study. In this trial, 5,238 individuals from study sites around the world with type 2 diabetes and existing CVDs were randomized to add either a placebo or pioglitazone 45mg per day. Their progress was followed for a mean of 2.8 years. The primary end-point had both disease-related end-points (all-cause mortality, non-fatal myocardial infarction (MI), including silent MI, stroke, and acute coronary syndromes) and procedure-related end-points (coronary artery bypass graph or angioplasty, leg amputation, and leg revascularization). Although there was a 10% relative risk reduction for the primary end-point, this did not reach statistical significance (p=0.095). The secondary end-point did show a significant relative risk reduction (16%) for adding pioglitazone (p=0.027).

Moreover, patients in the pioglitazone group had a lower hemoglobin A_{1c} and a longer time until the initiation of permanent insulin therapy, which is a significant benefit when treating patients with type 2 diabetes, who tend to have worse glycemic outcomes when they are on insulin therapy. There are no data on the cardiovascular effects of rosiglitazone, although studies are ongoing.

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Rosiglitazone and pioglitazone are not the same in terms of their effects on lipids. In the GLAI study, which was a head-to-head comparison of rosiglitazone and pioglitazone, the lipid effects differed between the two agents. Rosiglitazone increased triglyceride levels compared with pioglitazone. Plus, although both agents increased both HDL-C and LDL-C levels, pioglitazone increased HDL-C more and increased LDL-C less than did rosiglitazone. Therefore, the overall lipid impact of pioglitazone was more favorable than that seen with rosiglitazone.

Beta-cell Mass

The Holy Grail for the treatment of type 2 diabetes would be to not only

improve blood glucose levels, but also to return the depleted beta-cell mass to normal. If this occurred, type 2 diabetes would not only cease to progress, it would regress. Unfortunately, no agent to date has been shown to do this. As noted above, in the UKPDS sulfonylurea agents, metformin, and insulin were all associated with deterioration in beta-cell function. In the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) study, which was designed to assess the impact of rosiglitazone on the progression of impaired fasting glycemia (IFG) and/or impaired glucose tolerance (IGT) to diabetes, the presence of the drug was found to delay progression. However, once the rosiglitazone was stopped, rates of the development of diabetes returned to the same rate as seen with placebo. Therefore, rosiglitazone stabilized beta-cell function as long as patients were on the drug, but once it was stopped beta-cell function continued to deteriorate with no evidence of restoration of beta-cell mass. It is likely that pioglitazone has the same beta-cell-stabilizing effect seen with rosiglitazone, since in smaller studies it has been shown to delay or prevent progression to type 2 diabetes in high-risk individuals.

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In the recently published A Diabetes Outcome Progression Trial (ADOPT) study, patients with new-onset type 2 diabetes were randomized to glyburide, metformin, or rosiglitazone. Patients treated with rosiglitazone were the slowest to reach the primary end-point of a fasting plasma glucose level greater than 180mg/dl. In addition, they were slower to reach an A_{1c} level greater than 7%, although metformin was a close second in terms of progression to hyperglycemia. Therefore, in this study as well, the effects of TZDs appear to be to lower glucose levels and help preserve beta-cell function. It is important to note that TZDs have found to be associated with a greater risk of fractures in women. These fractures are not the typical osteoporotic fractures, but are in the distal extremities (hands, feet, and ankles). They also increase plasma volume and can precipitate congestive heart failure in individuals prone to develop it.

Drugs such as the GLP-1 receptor agonists and DPP-4 inhibitors have been shown to protect and restore beta-cell mass in animal models, but long-term studies need to be performed in humans to determine the clinical relevance of these findings. Additionally, the lipid profile improved in patients treated with exenatide, but outcomes data are needed to assess whether or not this agent provides CVD benefit.

Summary

Nearly all patients with type 2 diabetes will need combination therapy for management of their diabetes, particularly if tight control is desired. Drugs should be started early, before beta-cell mass is exhausted, and should always be combined with lifestyle modification (which helps whether patients are on oral agents and/or insulin). Each new drug should be added in quick succession in order to be sure the A_{1c} level does not rise much above 7%. Drugs should be chosen based on the patient's clinical status, with consideration of some of the non-glycemic effects of the medications available. Once-daily drugs and appropriate combination pills may be preferable, but the latter should be used with care because drugs cannot be titrated individually, and if side effects occur the patient may end up off two drugs instead off one. However, once a stable dose of medication is reached, conversion to fixed combination pills may be helpful.

Newer agents add increasing benefits and more therapeutic options. However, it is the effective clinical utilization of diabetes treatments that will lead to success. Side effects need to be closely monitored and expectations set prior to initiating therapy. Patients should not be kept on therapies that are not working and do not add significantly to their medication regimen. As patients with type 2 diabetes often need to be on medications for lipid and blood pressure lowering, as well as on aspirin, it is important to balance risks, benefits, and side effects in all individuals taking medication. However, if carried out appropriately, most of the complications of diabetes can be delayed or even prevented, which is a goal worth striving for. ■

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1. Turner RC, Cull CA, Frighi V, et al., Glycemic Control With Diet, Sulfonylurea, Metformin, or Insulin in Patients With Type 2 Diabetes Mellitus, Progressive Requirement for Multiple Therapies (UKPDS 49), *JAMA*, 1999;281:2005–12.
2. Gæde P, Vedel P, Larsen N, et al., Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes, *N Engl J Med*, 2003;348:383–93.
3. Inzucchi SE, Oral antihyperglycemic therapy for type 2 diabetes: scientific review, *JAMA*, 2002;287:360–72.
4. Hanefeld MK, Brunetti P, Schernthaner GH, et al., One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes, *Diabetes Care*, 2004;27:141–7.
5. Varroud-Vial M, Simon D, Attali J, et al., Improving glycaemic control of patients with Type 2 diabetes in a primary care setting: a French application of the Staged Diabetes Management programme, *Diabet Med*, 2007;21:592–8.
6. Rosenstock J, Rood J, Cobitz A, et al., Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes, *Diabetes Obes Metab*, 2006;8:650–60.
7. Brown JB, Nichols GA, Slow response to loss of glycemic control in type 2 diabetes mellitus, *Am J Managed Care*, 2003;9:213–17.
8. Cefalu WT, Waldman S, Ryder S, Pharmacotherapy for the treatment of patients with type 2 diabetes mellitus: rationale and specific agents, *Clin Pharmacol Ther*, 2007;81:636–49.
9. Brown JB, Nichols GA, Perry A, The burden of treatment failure in type 2 diabetes, *Diabetes Care*, 2004;27:1535–40.
10. Riddle M, Glycemic management of type 2 diabetes: an emerging strategy with oral agents, insulins, and combinations, *Endo Met Clinics North America*, 2005;34:77–98.
11. Triplitt C, Glass L, Miyazaki Y, et al., Comparison of glargine insulin versus rosiglitazone addition in poorly controlled type 2 diabetic patients on metformin plus sulfonylurea, *Diabetes Care*, 2006;29:2371–7.
12. Nathan DM, Buse JB, Davidson MB, et al., Management of hyperglycemia in type 2 diabetes: a consensus algorithm of the initiation and adjustment of therapy, *Diabetes Care*, 2006;29:1963–73.