CLINICAL interface

Thiazolidinediones and Slowing the Progression of Diabetes

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A continuing goal of treatment of diabetes is to slow the progression of the disease through the preservation of beta-cell function. To assess efficacious and cost-effective methods of doing this, The Pharmacy & Therapeutics Society (Glastonbury, CT) assembled a study group of health plan medical directors. Based on a review of the data, the group studied the value of earlier diagnosis and the administration of thiazolidinediones. The potential role for health plans to support this approach to diabetes care is outlined below.

In March 2007, The Pharmacy & Therapeutics (P&T) Society, Glastonbury, Connecticut, convened a study group of 11 health plan medical directors to consider data demonstrating the potential for thiazolidinediones (TZDs) to slow the progression of diabetes through the preservation of beta-cell function. Based on the data, the study group assessed the value that earlier diagnosis of diabetes and administration of TZDs could provide for health plans and their members and physicians. A potential role for health plans to support this approach to diabetes care was also outlined.

The study group's medical directors represent a variety of commercial, Medicare, and Medicaid health plans from across the United States. Together, their organizations represent more than 11 million covered lives. Each of the study group's advisors has been employed by a health plan as a medical director for three or more years, is responsible for developing medical and pharmacy policies, and is knowledgeable about the health plan's approach to managing the patient population suffering from diabetes. This approach ensured a breadth of perspective and a base of knowledge for critically evaluating the data presented.

The retrospective study regarding the cardiovascular side effects associated with rosiglitazone was published subsequent to the assemblage of the study group.[1] Therefore, the group did not consider the results of the retrospective

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study when evaluating the data demonstrating the potential for TZDs to slow the progression of diabetes.

At the conclusion of the meeting, it was agreed that the data suggest beta-cell preservation may delay or slow progression of diabetes and that TZD therapy may play a role in beta-cell preservation.

Earlier diagnosis and the opportunity to preserve beta-cell function increases the importance of encouraging patients to comply with therapy.

Thus, earlier diagnosis of diabetes and administration of TZD therapy presents an opportunity to delay the progression of diabetes. Additional data are required to document the direct relationship between TZD therapy, beta-cell preservation, and the progression of diabetes, as well as the resulting effect on the cost of care. Therefore, this is an approach to diabetes diagnosis and treatment that, based upon available clinical evidence, warrants the consideration of health plan P&T Committees.

BETA-CELL PRESERVATION AND DIABETES

Diabetes is a high-priority concern for managed care owing to its prevalence and cost. From 1980 through 2005, the number of Americans with diabetes increased from 5.6 million to 15.8 million.[2] At particular risk are the 5.9 million Americans who are unaware that they have the disease.[3] In 1992, the Centers for Disease Control and Prevention (CDC) estimated that diabetes incurred $82 billion of cost in the United States. The CDC estimates this cost will rise to $156 billion by 2010 and $192 billion by 2020.[4,5]

Beta cells, which are located in the pancreas, are a key marker for the progression of diabetes. These cells make insulin, which is released into the blood stream to affect the metabolism of carbohydrates, lipids, and proteins. Insulin resistance is a condition in which the normal response to a given amount of insulin is reduced. As a result, higher levels of insulin are needed for insulin to have effect.

Insulin resistance increases over time. As long as the pancreas is able to produce enough insulin to overcome this resistance, blood–glucose levels remain normal. When the pancreas can no longer produce enough insulin, blood–glucose levels begin to rise, initially after meals when glucose levels are at their highest and more insulin is needed, but eventually in the fasting state as well. At this point, type 2 diabetes is present.

Insulin resistance and the associated decline in beta-cell function precede the development of type 2 diabetes, sometimes by years. As demonstrated by Goldstein,[6] beta-cell function typically decreases by almost half during the 10 or more years before diagnosis.

The United Kingdom Prospective Diabetes Study reinforced the above results.[7,8] This study showed that beta-cell function continues to decline over time and after diagnosis with diabetes, even with diet modification or when monotherapy with a sulfonylurea or metformin is administered. The study showed that declining beta-cell function is associated with the loss of glycemic control over time.

Based on this evidence, the study group discussed the potential benefits of early diagnosis and preservation of beta-cell function. Therapy that preserves beta-cell function in combination with earlier diagnosis may provide an opportunity to delay the progression of diabetes and the comorbidities associated with a decrease in beta-cell function.

The study group suggested that the implementation of programs to encourage earlier diagnosis of diabetes faces challenges. Earlier diagnosis and the opportunity to preserve beta-cell function increases the importance of encouraging patients to comply with therapy. The study group noted that improving therapy compliance can be challenging, especially as acute symptoms are not readily apparent before diagnosis or during the early stages of diabetes. Addressing this challenge requires patient-centric educational initiatives that may be implemented through an insurer's health plan, integrated health system, or medical group. They could be part of a community-based initiative aided by the media. Another approach is to establish financial incentives for health plan members. For example, a member's monthly insurance premium or drug copay could be based on the individual's glycated hemoglobin score as well as weight, blood pressure, and cholesterol level.

An extensive educational program would be required to change the paradigm for care. Primary care physicians provide care for the majority of patients suffering from diabetes. This is a sizable number of physicians to educate.

The challenge of reaching physicians and potential diabetes sufferers is illustrated by the fact that approximately one quarter of all diabetes sufferers (5.9 million/> 20 million) remain undiagnosed. A new paradigm could further raise diagnosis hurdles.

The study group suggested that one approach to earlier diagnosis of diabetes is to identify patients with impaired glucose tolerance who also suffer from one or more risk factors for cardiovascular disease. The Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease showed

the risk of cardiovascular disease increases significantly for patients suffering from diabetes with one or more risk factors.[9]

The study population included men aged 35 to 57 years with or without diabetes who had been screened for risk factors for cardiovascular disease. Risk factors included high serum cholesterol, systolic blood pressure elevation, and cigarette smoking.

In men with diabetes, the absolute risk of death from cardiovascular disease was greater for all age strata, ethnicity, and risk-factor levels. When adjusted for age, race, income level, serum cholesterol, systolic blood pressure, and number of cigarettes smoked each day, the relative risk for cardiovascular disease and congestive heart disease was 3.0 and 3.2 times higher, respectively ($P < .0001$), for men with diabetes.

THIAZOLIDINEDIONES AND THE PRESERVATION OF BETA-CELL FUNCTION

The study group reviewed two clinical trials that illustrate TZDs preserve beta-cell function: (1) Troglitazone in the Prevention of Diabetes (TRIPOD)[10] and (2) a follow-on study Pioglitazone in Prevention of Diabetes (PIPOD).[11] The TRIPOD study was a randomized, placebo-controlled trial in which 236 of 266 randomized subjects had at least one follow-up visit and 126 women completed 3.6 years of treatment and eight months of postdrug washout. The main findings were: (1) a 55% reduction in the incidence of diabetes during a median of 30 months on troglitazone 400 mg/day, (2) close association between reduction in insulin output during intravenous glucose-tolerance tests (IVGTT) at three months on trial and protection from diabetes, (3) persistent protection from diabetes eight months postdrug, and (4) stable glucose and beta-cell function for 4.5 years in women who did not develop diabetes during troglitazone treatment.[12]

For patients in the placebo group who did not develop diabetes, a significant reduction was noted in the acute insulin response in association with worsening of insulin resistance. In the troglitazone group, the correlation between insulin secretion and insulin resistance was stable. The difference between the groups was consistent with diabetes prevention. As such, those individuals who were able to maintain a tight correlation between the acute insulin response and insulin resistance (or insulin sensitivity) were able to prevent the development of diabetes.

The PIPOD study was an open-label treatment with pioglitazone 45 mg/day in women who completed TRIPOD. In this study, 89 of 95 eligible women without diabetes enrolled for three years of drug treatment and six months postdrug washout. The annual diabetes rate was 4.6%. Multivariate analysis revealed two independent predictors of diabetes: (1) oral glucose tolerance test (OGTT) glucose area at baseline (higher = greater risk) and (2) change in IVGTT total insulin area at one year (fall = lower risk). Beta-cell function (disposition index) did not change significantly during PIPOD ($P = .81$) even in women who had manifested a 33% fall in disposition index ($P = .003$) during placebo treatment in the TRIPOD study.[12]

Both pioglitazone and troglitazone have a stabilizing effect on beta-cell deterioration in people at high risk of developing type 2 diabetes.

The troglitazone–pioglitazone group was able to maintain or sustain the improvements in the disposition index. The pioglitazone–placebo group realized improvement or at least stabilization and no further deterioration in the disposition index. This suggests both pioglitazone and troglitazone have a stabilizing effect on beta-cell deterioration in people at high risk of developing type 2 diabetes.[13]

The study titled A Diabetes Outcome Progression Trial (ADOPT) provided a much-needed update to the UKPDS, which preceded the availability of TZDs and included only two of the three oral agents evaluated in ADOPT—metformin and sulfonylurea.[14] The ADOPT researchers assessed the time interval of loss of glycemic control once a participant reached the maximum effective dose of each therapy and allowed investigation of the effects of beta-cell function and insulin resistance on disease progression and long-term glycemic control, among other outcomes. This international study included 4,360 patients who were followed for four to six years.

Results from ADOPT demonstrated that initial treatment with rosiglitazone reduced the risk of monotherapy failure by 32% compared with metformin ($P < .001$), and by 63% compared with glyburide ($P < .001$) at five years.[15] Similarly, rosiglitazone was more effective in delaying the progressive loss of glycemic control as measured by fasting plasma glucose and HbA_1c levels. Risk reduction of decreasing glycemic control was 34% compared with metformin ($P = .002$) and 62% compared with glyburide ($P < .001$). Additionally, mean HbA_1c levels of less than 7% were maintained at 60 months with rosiglitazone compared with only 45 months for metformin and 33 months for glyburide.

The ADOPT study also demonstrated rosiglitazone improved insulin sensitivity versus metformin or glyburide ($P < .001$ at 4 yr) and reduced the loss

of beta-cell function versus metformin ($P = .02$) and glyburide ($P < .001$). This was the first long-term study to demonstrate that progressive loss of glycemic control can be delayed and that durable control of targeted glycemic levels can be maintained for a longer duration with rosiglitazone than with metformin or glyburide. Therefore, these results provide evidence that suggest earlier treatment with a TZD in the management of type 2 diabetes may be warranted.[15]

A key issue underlying payer acceptance of a modified approach to care is the magnitude of the cost offsets from delaying the progression of diabetes.

Method of Action. The TZDs increase insulin sensitivity at the level of adipose tissue, skeletal tissue, and the liver, allowing for increased glucose disposal and beta-cell rest.[16] They improve insulin sensitivity by activating the gamma isoform of the peroxisome proliferator-activated receptor (PPAR-gamma). This activation alters the transcription of several genes involved in glucose and lipid metabolism and energy balance, including those that code for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, malic enzyme, glucokinase, and glucose transporter 4.[17,18]

THIAZOLIDINEDIONES AND DELAYING THE PROGRESSION OF DIABETES

Based on the TRIPOD and PIPOD studies, the study group believes that TZDs may conserve beta cells. However, they would like to see data that directly show the effect of TZD therapy on the progression of diabetes and associated comorbidities. It is the comorbidities—such as retinal disease, heart attack, and stroke—that are of concern to managed care as these outcomes drive the cost of care and affect the patient's quality of life.

A key issue underlying payer acceptance of a modified approach to care is the magnitude of the cost offsets from delaying the progression of diabetes. Insurers require outcomes data demonstrating which costs are delayed or eliminated, the magnitude of the cost savings, and the time period for which they are delayed. The data should show that the prevention or delay in the onset of diabetes through earlier TZD therapy is more cost effective than lifestyle management alone as encouraged through any various disease management programs.

Member turnover may cause health plans to identify shorter-term effects on comorbidities. Some health plans might be concerned about investing today in costly TZD therapy if they might not realize cost offsets beyond when the average member leaves for another plan. The study group suggested conducting pharmacoeconomic or outcomes research with a health plan that has a significant number of members at high risk for diabetes. Such an approach might expedite the outcomes research, which could accelerate the timeframe in which evidence is available on the benefits of earlier diagnosis of diabetes and administration of TZD therapy.

Populations and related health systems that might be particularly suitable for such research and for whom the research might have greater effect than the general population are Native-American and Alaskan-native communities and the closed health care systems that deliver much of their care. Many Native-American communities have a higher incidence of type 2 diabetes than other communities. This might permit early observation of a difference between a placebo and a treatment group. The importance of diabetes to Native-American and Alaskan-native communities might ease acceptance of outcomes research by the respective communities and individual patients.

The Indian Health Service (IHS) provides free care to many Native-American and Alaskan-native communities. Also, free tribally based health care is provided to many other such communities. This reduces potential leakage of study participants to health care settings where contact and study follow-up would be lost. Reliance on IHS and tribal-based health care also reduces the number of records depositories, potentially easing the monitoring of studies and verification of investigator entries. Similar benefits for structuring outcomes research apply to other closed or integrated delivery systems.

The advisors recommend identifying local physician champions to assume leadership roles in educating colleagues regarding the importance of beta-cell preservation in delaying the progression of diabetes and exploring the role of TZDs in beta-cell preservation.

CRITICAL ELEMENTS OF A PHARMACY AND MEDICAL POLICY

Based on currently available data and the potential results of outcomes research, future changes in pharmacy and medical policy encouraging the earlier diagnosis of diabetes and administration of TZDs could be an interesting prospect to discuss at the P&T Committee and medical staff levels. The policy could include provisions and programs focused on patient adherence to therapy, dosing guidelines for TZDs based on any quantity limits and/or the

identification of specific dosages, and indicate the frequency of follow-up care.

Step therapy could be a component of the medical and pharmacy policy. Guidelines could require the failure of a physician-supervised diet and exercise program before TZDs could be prescribed. The study group suggested the guidelines are not likely to require physicians to obtain prior authorization before initiating TZD treatment. Rather, organizations could pursue an approach of retrospectively auditing particular claims and patient charts after payment to determine if the requirement for step therapy is being met overall in a certain physician's practice.

Earlier diagnosis of diabetes and administration of TZDs incurs costs covered under both medical and pharmacy benefits. One challenge health plans will face is to gain support across multiple departments as the pharmacy and medical budgets are managed separately.

THE VALUE PROPOSITION

The study group suggested that the earlier diagnosis of diabetes and initiation of TZD therapy to delay disease progression offers value to health plans, physicians, patients, and employers. The value propositions differ for each of these constituencies.

For health plans, the earlier diagnosis of diabetes and administration of TZDs offers an opportunity to reduce the cost of care, improve Health Plan Employer Data and Information Set (HEDIS) scores, and offer beneficiaries suffering from diabetes an improved quality of life. This is offset to a degree by a concern that one health plan may invest in TZD therapy whereas another health plan recognizes the benefits owing to member turnover.

Primary care physicians benefit from the improved health status of their patients with diabetes, which may result in fewer and less complicated and time-consuming examinations and treatment. Delaying the progression of diabetes provides physicians with more time to convince patients to change their lifestyles to help further delay the progression of diabetes. Also, physicians could be motivated by the improved health status and quality of life for their patients.

Patients benefit from avoiding the health consequences of diabetes and realizing the long-term saving of copays and coinsurances from delaying or avoiding the incidence of comorbidities associated with diabetes.

Employers will benefit from reducing the cost of care for patients with diabetes—either through reduced claims for self-funded plans or potentially a reduction in the rate of increase for premiums—enhanced productivity, and reduced absenteeism from a healthier workforce.

EDUCATING PHYSICIANS AND MEMBERS

The study group identified a number of approaches for educating physicians and patients about the benefits of earlier diagnosis of diabetes and administration of TZDs to preserve beta-cell function. For patients, these approaches include member newsletters, website postings, waiting room material, and disease-oriented advertising in the general community. For physicians, these approaches include clinical newsletter content, treatment guideline updates, continuing medical education, grand rounds case presentations, and scripted conversations to help physicians more effectively communicate the benefits of earlier diagnosis and administration of TZD therapy to patients. At the same time, study group members believe health plans should be wary of intervening directly in the doctor–patient relationship.

Earlier diagnosis of diabetes and initiation of thiazolidinedione therapy to delay disease progression offers value to health plans, physicians, patients, and employers.

CONCLUSION

The benefit of earlier diagnosis of diabetes and administration of TZDs to preserve beta-cell function and delay the progression of diabetes has the potential to help managed care address the cost, quality of life, and HEDIS issues surrounding the management of members suffering from diabetes. Whereas additional outcomes data that document the effect of this approach on the costs associated with diabetes are required to encourage managed care's interest, this approach to care and the supporting data outlined above warrant further evaluation by P&T committees committed to supporting evidence-based care.

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DISCLOSURE

Dr. Jackson has disclosed he serves as a consultant for Takeda, and serves on the speakers' bureau for Takeda, Sanofi-Aventis, Merck, and Pfizer. Mr. Kaminsky, Dr. Salom, and Dr. Guerra-Garcia disclosed they serve as consultants for Takeda. Dr. Bloom and Dr. Tzeel have indicated they have no financial or commercial affiliations to disclose.

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