DIABETIC
Microvascular Complications
NEWS
Volume 3, No. 4 • July/August 2006

FDA Approved Ranibizumab for the Treatment of Neovascular AMD

The Food and Drug Administration (FDA) approved ranibizumab (Lucentis; Genetech, San Francisco) for the treatment of neovascular age-related macular degeneration (AMD). Lucentis is the first treatment, which when dosed monthly, can maintain the vision of >90% of patients with this type of AMD, according to the FDA. Ranibizumab is a new molecular entity, and as such contains an active substance that has never before been approved for marketing in any form in the United States.

"This approval is of great importance for the 155,000 Americans who are diagnosed each year with AMD," said Andrew von Eschenbach, MD, acting commissioner. "At a time when our elderly population is rapidly increasing, this product preserves quality of life for those affected by this disease, helping them to regain the ability to participate in everyday activities such as reading and driving."

AMD, a retinal disease causing severe and irreversible vision loss, is a major cause of blindness in individuals aged >55 years. Untreated, the majority of eyes affected with neovascular AMD may become functionally impaired. Neovascular AMD, which accounts for 10% of all AMD, is responsible for 80% of the associated vision loss.

The vision loss in neovascular AMD is caused by the growth of abnormal leaky blood vessels that eventually damage the area of the eye responsible for central vision. Ranibizumab is designed to block new blood vessel growth and leakiness, which ultimately lead to disease progression and such vision loss. The agent, administered by injection into the eye, was shown to be safe and clinically effective in three multicenter, randomized studies of patients representative of the population usually affected with AMD. In clinical trials, nearly 95% of the participants who received a monthly injection maintained their vision at 12 months compared with approximately 60% of patients who received the control treatment.

Approximately one-third of patients in these trials had improved vision at 12 months. In a single study carried out for 24 months, these findings have been maintained with continued monthly dosing. The most commonly reported adverse events included conjunctival hemorrhage, eye pain, floaters, increased eye pressure and inflammation of the eye. Serious adverse events were rare and often related to the injection procedure, including endophthalmitis, intraocular inflammation, retinal detachment, retinal tear, increased intraocular pressure and traumatic cataract.

In a related report, researchers looking at data from the Nurse's Health Study have found that dietary glycemic index may be an independent and modifiable risk factor for early AMD. "The likelihood of having abnormalities characteristic of AMD on eye exam more than doubled for women who consumed diets with the highest glycemic index, regardless of other factors already known or suspected to increase the risk of AMD, such as age, high blood pressure, cigarette smoking and obesity," the investigators wrote in the *American Journal of Clinical Nutrition*.

Agents that are used to treat AMD may also be useful in diabetic retinopathy, although this is still under investigation.

ADA Disappointed by President's Stem Cell Veto

Lawrence T. Smith, chair of the American Diabetes Association (ADA) and the parent of a daughter with type 1 diabetes, and Dana Lewis, a teen from Huntsville, Alabama who has type 1 diabetes and is the ADA's National Youth Advocate, issued statements in response to a veto by President Bush of the Stem Cell Research Enhancement Act (HR 810). Miss Lewis presented a petition, signed by approximately 11,000 Americans affected by diabetes, urging the President to sign the bill. The ADA has been a strong supporter of the bill, which would accelerate medical advancements by easing existing restrictions and supporting research that uses embryonic stem cells, while maintaining strict ethical guidelines.

"This is a devastating setback for the 20.8 million American children and adults with diabetes — and those who love and care for them. We truly believe that embry-

onic stem cell research offers the greatest promise for a cure for diabetes. Despite bipartisan support in Congress, the backing of 70% of the American public, and the hopes and prayers of millions of individuals with diabetes and other debilitating diseases, the President has chosen the wrong path," Mr. Smith said.

"I had hoped that the President would have really tried to listen to our voices," Miss Lewis said. I feel let down, and I am very saddened that he shattered my sense of hope and the hope of millions of other children and young adults. I still believe this bill is right for this country, and I will still fight in the future to see it become law."

One in Three Americans Has Diabetes or its Precursor

More than 73 million Americans — one-third of the adult population — now have diabetes or may be on their way to getting it, according to a study published in *Diabetes Care*.

A separate study also found that it may be necessary to lower cholesterol even further than previously believed in order to prevent myocardial infarctions (MIs) in people with type 2 diabetes. A third study reports that teenagers with type 2 diabetes are more likely to develop early symptoms of heart and kidney disease than teens who have type 1 diabetes, even when those with type 1 have been diagnosed with diabetes for a longer period of time and maintain poorer glycemic control.

Prevalence of Diagnosed Diabetes Still Rising. Researchers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Centers for Disease Control and Prevention found the prevalence of diabetes in America continues to climb. The study showed 9.3% of adults aged ≥20 years (19.3 million people) had diabetes in 1999 to 2002. While the prevalence of undiagnosed diabetes has remained essentially stable from 1988 to 1994 at 2.8%, the prevalence of diagnosed diabetes rose sharply during the same period from 5.1% to 6.5% of the population. Another 26% of Americans had impaired fasting glucose (IFG). Prediabetes often leads to diabetes within 10 years, if steps are not taken to prevent it, according to an ADA news release.

"Despite the fact that we now know how to prevent type 2 diabetes in many cases through lifestyle changes that include weight loss and increased physical activity, we continue to see this disease climb," said lead researcher Catherine Cowie, MD, director of the Diabetes Epidemiology Program at NIDDK. "We also need to do a better job of diagnosing the one-in-three people with diabetes who don't know they have it, and the 26% of the adult population who have IFG."

The study compared data from the 1999 to 2002 National Health and Nutrition Examination Survey (NHANES) with that of the 1988 to 1994 NHANES. It found that minorities continue to suffer disproportionately, with prevalence rates nearly twice as high for blacks and Mexican-Americans as whites. The report noted that Americans pay a high price for the rise in diabetes. The disease cost the United States an estimated $132 billion in medical expenses and lost productivity in 2002.

Higher Doses of Medication, Lower Cholesterol, Fewer MIs. Lowering LDL cholesterol to <80 mg/dL with atorvastatin (Lipitor; Pfizer, New York, NY) significantly lowers the risk of MI in people who have both diabetes and heart disease, according to a study conducted by researchers from around the world. The study found that patients who took 80 mg of atorvastatin lowered their LDL levels to 77.0 mg/dL and reduced MIs 25% more than patients who took a 10-mg dose of the drug and lowered their LDL levels to 98.6 mg/dL. The ADA recommends that people with diabetes lower their LDL to <100 mg/dL. This study suggests that people who have both diabetes and heart disease should lower their LDL levels even further. The study was conducted over a 5-year period by researchers at the University of Glasgow, UK; the Heart Research Institute, Sydney; Institut Pasteur, Lille, France; and American universities in California, Texas and New York.

Teenagers With Type 2 Diabetes More Likely Than Those with Type 1 to Develop Disease Symptoms. Teenagers with type 2 diabetes develop more serious complications than teens with type 1 diabetes, even when they have lived with the disease for less time and have better glycemic control, according to a study by Australian researchers.

The study found youth who had type 2 diabetes developed significantly higher rates of hypertension and microalbuminuria. The teens who developed type 2 diabetes were also more likely to be obese, which could be a factor in the development of these complications. Teens with type 1 diabetes were more likely to develop retinopathy.

Poverty, Lack of Health Care Plague Residents Along US-Mexico Border

More than 13 million American and Mexican residents live along the 2,000-mile border between the United States and Mexico, a region that suffers disproportionately from health problems because of poverty and lack of access to health care and health insurance coverage, according to a

news release. In a speech before the Border Conference on Health, National Association of Community Health Centers (NACHC) Director of Policy Dan Hawkins said that picture is unlikely to improve unless the nation acts to counter the trend in several key areas.

The border region encompasses California, Arizona, New Mexico and Texas. In the Texas-Mexico border counties "the uninsured make up 34.6% of the population — more than twice as high as the United States average of 15%," Mr. Hawkins said Consequently, residents face health problems common to developing nations. "Border counties had a tuberculosis rate 192% higher than the entire state of Texas and 271% higher than the United States," Mr. Hawkins said. "The incidence of hepatitis A was 347% higher than Texas as a whole and 694% higher than the United States. Eight percent of people 18 and older who were living in Texas border counties had diabetes compared to 6.2% of people in the entire state."

Cross-border migration and easy mobility between the United States and Mexico make it difficult for providers to track and treat patients who suffer from disease, much less provide follow-up and continuity of care. The nation's farmworkers are among the ones most vulnerable, Mr. Hawkins noted, "because their work requires mobility that makes it all but impossible for them to either secure affordable insurance coverage or receive regular health care. America's farmworkers suffer from some of the highest rates of diabetes, hypertension, asthma, oral and mental health problems, infectious diseases, skin and muscular disorders and cancer."

Endemic poverty and lack of health insurance also play a major role in the shortage of health professionals in the area. Roughly 60% of border counties in Texas are designated as a Health Professional Shortage Area, with a skeletal health care infrastructure that includes fewer public hospitals than in other parts of the country. Also, Mr. Hawkins said changes to the payment structures of both Medicare and Medicaid will make it even more difficult for the few physicians in the area to get adequately reimbursed for treating patients; the price of caring for large numbers of uninsured is skyrocketing in southwest border counties, with "county hospitals reporting uncompensated care totaling nearly $832 million."

Mr. Hawkins said to counter the trend, the United States must invest dollars in building and expanding community and migrant health centers to expand access to health care in underserved areas. He noted that, "Already, the House of Representatives has taken the President's request for a $181 million funding increase for the program — and raised that amount by another $25 million. This new funding would extend care to almost 1.5 million more underserved people next year. So there should definitely be some real money available to improve access to care in key areas next year." He also said Congress must support "more funding for key health professions training programs, including the National Health Service Corps," to address the "the current shortages of physicians, dentists, nurses, mental health specialists and other health care providers."

In the NACHC news release, Mr. Hawkins also said the United States must maintain and grow the reach of both Medicaid and the State Children's Health Insurance Program that are "fast becoming the only affordable sources of health coverage for low-income and even moderate-income Americans." He also said initiatives aimed at supporting the work of the US-Mexico Border Health Commission need more support and cited NACHC's support for pending legislation in the House and Senate, the Border Health Security Act (HR 5412, S 2825), that "would continue the work of the Commission, while also significantly improving the health of border communities, and — I note — would also stimulate the development of more health centers along the border."

ADA, AHA Reinforce Joint Commitment to Preventing CVD and Diabetes

In a joint statement, the ADA and the American Heart Association (AHA) are calling for greater prevention and treatment efforts to stem the continuous rise in diabetes and in the numerous cardiovascular-related deaths that relate to inadequately recognized and undertreated risk factors. Published concurrently in *Diabetes Care* and in *Circulation*, the statement sets forth a proactive collaborative challenge to health care providers to assess their patients' risk factors for cardiovascular disease (CVD) and diabetes more comprehensively to more effectively reduce the risk of heart disease, stroke and diabetes.

According to the statement, the groups are in "100% agreement that more can be done by professionals and patients alike to better understand, anticipate, prevent and manage the commonalities and co-occurrence of diabetes and [CVD]," said Robert A. Rizza, MD, president, Medicine & Science, ADA.

"The importance of identifying a core set of risk factors such as prediabetes and diabetes, prehypertension and hypertension, dyslipidemia and obesity cannot be overstated," said Robert H. Eckel, MD, president of the AHA. "It is long past time to start getting these risk factors under control through lifestyle changes and medication. It's not as if

we don't know how. The research is there. The ADA and AHA recognize that a significant volume of scientific research has contributed to a better understanding of how the clustering of metabolic abnormalities may impact the cardiovascular disease risks of patients.

"A patient with any cardiometabolic risk factor must be assessed for all others. Either being overweight, having an elevated blood pressure, abnormal glucose level, or any altered lipid value, requires a comprehensive CVD/diabetes risk assessment. And certainly let's not forget to greatly encourage smokers to stop," said Richard Kahn, PhD, chief scientific officer of the ADA.

Rose Marie Robertson, MD, chief science officer of the AHA, went on to indicate that "the steady rise in obesity and overweight in the United States over the past several decades has reached such overwhelming proportions that it now threatens to undermine our hard-won gains in preventing and controlling such chronic illnesses as heart disease, stroke and diabetes. Addressing this issue as well as the overall risk of each individual patient is critical to the health of the public."

Pioglitazone May Also Treat Alzheimer's Disease

New data presented during a press briefing at the 10th International Conference on Alzheimer's Disease and Related Disorders, Madrid, shows that the type 2 diabetes medication pioglitazone (Actos; Takeda Pharmaceuticals, Lincolnshire, Ill) may hold promise in treating Alzheimer's disease.

Recently, several studies have suggested that diabetes increases the risk of Alzheimer's disease and that the two diseases are intertwined. During the past 10 years, several studies have found that, compared with healthy people of the same age and sex, those with type 2 diabetes are twice as likely to develop Alzheimer's. In both conditions, the protein amyloid builds up in the pancreas.

The University of Virginia Health System & Case Western study investigated the effects of pioglitazone on the progression of Alzheimer's. They reported that treatment of high blood sugar may have a scientific connection to memory loss that could, one day, benefit millions of people with Alzheimer's disease, which affects up to 4.5 million older Americans, bringing with it impaired thinking and memory.

"We believe that the drug may reduce the body's inflammatory reaction to one of the toxic components that builds up in Alzheimer's, called amyloid plaque," said David Geldmacher, MD, an associate professor of neurology at the University of Virginia.

Pioglitazone was tested in a placebo-controlled trial involving 25 people with mild-to-moderate Alzheimer's. The study assessed the safety of the drug. Although the treatment appeared to reduce Alzheimer's progression, the study was too small for investigators to be sure of the effects on memory and everyday abilities. The findings are promising enough, however, to carry out larger studies of pioglitazone, the researchers said.

"We don't know exactly how pioglitazone works in Alzheimer's, but there are two possibilities," Dr. Geldmacher said. "It could be that the drug reduces the body's response to the amyloid protein found in Alzheimer's. Or, it could be that this drug helps brain cells function. The real advantage is that it's a completely novel approach to treating the disease."

In the next few years, Geldmacher and his colleagues hope to study the effectiveness of pioglitazone in a group of 200 to 300 Alzheimer's patients nationwide. "If it works, this treatment might allow people to better hold on to memory and brain function over a period of time, despite having Alzheimer's," Dr. Geldmacher said. "It could also complement other treatments and become part of a multipronged approach to Alzheimer's treatment."

The trial was supported by the National Institutes of Health (NIH) and Takeda.

Risk of Kidney Disease Progression Higher in US Than in Europe

The higher rate of end-stage renal disease (ESRD) in the United States compared with European countries, such as Norway, reflects a greater risk of worsening kidney disease in the United States, not a higher number of people in the early stages of chronic kidney disease (CKD), according to a study in the *Journal of the American Society of Nephrology.*

Led by Stein Hallan, MD, of St. Olav University Hospital in Trondheim, Norway, the researchers compared large population databases including 65,000 Norwegian and 20,000 American patients. Their goal was to understand the reason why the incidence of ESRD is so much higher in the United States than Norway, according to a press release from the American Society of Nephrology.

One possible explanation was a difference in the rate of CKD. However, there was no difference in the overall prevalence of CKD, defined by having less than half of normal kidney function or persistently having protein in the urine: 11.0% in the United States and 10.4% in Norway.

Once CKD was present, however, the risk of progression

to ESRD was significantly higher for Americans — 2.5 times higher than for Norwegians. This risk was little affected by adjusted analysis comparing white Americans to Norwegians of similar age, sex and diabetes status.

American and Norwegian patients with ESRD were similar in most characteristics, including age and level of remaining kidney function when starting dialysis.The US patients had strikingly higher rates of obesity. "Obesity and physical inactivity lead to high blood pressure and type 2 diabetes, which are now the most important causes of ESRD," Dr. Hallan said.

In addition, the American patients made their first visit to a nephrologist significantly later — that is, at a lower level of kidney function. "Early referral to a nephrologist is important," said Dr. Hallan. "It often results in better control of diabetes and high blood pressure, as well as early and more adequate correction of anemia and disturbances in electrolyte balance. This reduces the rate of kidney disease progression, and in many patients postpones the start of dialysis."

Progressive kidney disease requiring dialysis is an increasingly common problem, with a major impact on health and health costs. Decisions about screening and other public health interventions require more data on the frequency and natural course of kidney disease. Previous studies have established the high rate of CKD in the United States — more reliable data are needed from European countries, where the prevalence of ESRD requiring dialysis is much lower.

"Our results show that the lower incidence of ESRD in Norway reflects a lower rate of progression from the early stages of CKD to dialysis, rather than a smaller pool of individuals at risk," Dr. Hallan concluded. "Although we did not evaluate predialysis care directly, we think that strong programs to prevent diabetes and obesity and manage [CKD] are needed to preserve the favorable situation in Norway and turn the tide on the current dialysis epidemic in the United States."

Researchers Focus on Overnight Hypoglycemia

Overnight hypoglycemia — a condition that has baffled physicians and type 1 diabetes patients alike — is the focus of current research in the journal *Countdown*, according to a news release from the Juvenile Diabetes Research Foundation (JDRF).

The overnight period is particularly dangerous because it has the potential to cause a drop in blood sugar that can lead to seizures and coma. New clinical trials are seeking to understand what happens to the body during sleep, when patients are unable to monitor their blood glucose levels.

"Due to the lack of overnight monitoring, there has been insufficient information to explain what exactly happens while the body sleeps. With the new tools and technology available to diabetes researchers today, prescribing a daily regimen to manage a moving target should become easier," said Aaron Kowalski, director of Strategic ResearchProjects for JDRF. "Continuous glucose monitoring systems may well be a key player in controlling overnight hypoglycemia."

Important correlations have been established between exercise and overnight hypoglycemia. For example, patients who exercised during the day were twice as likely to experience severe blood sugar lows overnight. In addition, researchers are investigating various bedtime snacks and their effects on overnight lows.

The effort to manage overnight hypoglycemia has created opportunities to broaden exploration of the benefits of the new continuous glucose monitoring systems, the release noted. Since 2001, researchers participating in the Diabetes Research in Children's Network (DirectNet) have conducted seven studies investigating continuous glucose monitoring systems and overnight hypoglycemia. A research effort led by William Tamborlane, MD, from Yale University is looking at children over a 36-hour hospital stay where blood sugar levels are regulated through an external sensor and a subcutaneous pump — an early prototype of a closed-loop artificial pancreas system.

According to Dr. Tamborlane, "The ultimate answer to managing blood sugar levels is to have a closed-loop system in which the sensor adjusts to differences."

Contributing factors to overnight lows may include the natural decrease in brain activity during sleep, as well as the release of growth hormones, which both reduce the need for insulin.

NEWS FROM THE ADA MEETING

Positive Phase 2 Results with Novel BGP-15 Insulin Sensitizer

Positive phase 2 data for BGP-15, a novel insulin, were presented in a poster session at the ADA 66th Scientific Sessions in Washington, DC.

The clinical trial, conducted in Hungary, used an agent from N-Gene Research Laboratories (New York, NY) in a double-blind, placebo-controlled study involving 42 patients in three arms. Jesse Roth, MD, professor of medi-

cine, Albert Einstein College of Medicine, and former scientific director of NIDDK of NIH, and Kalman Tory, MD, head of Cellular and Molecular Pharmacology at N-Gene Research Laboratories were the study authors.

The trial took place in insulin-resistant, nondiabetic patients who had no previous treatment for their disease. Insulin sensitivity was measured by hyperinsulinemic euglycemic clamp. Results from the study indicate that BGP-15 significantly improved insulin sensitivity at both doses. No serious adverse events were observed.

According to a company news release, BGP-15, with its novel mechanism of action, should be a valuable addition to agents currently used to treat type 2 diabetes, as it can be given along with one or more of these agents, including metformin. Along with diet and exercise, BGP-15 could have a significant impact on the health of diabetic patients.

BGP-15 is designed to restore constitutive nitric oxide synthase and inducible heat shock protein functions resulting in correction of the impaired function of mitochondria.

Encouraging Results for SB-509 in Development for Diabetic Neuropathy

Positive findings for SB-509 were reported from a phase 1a and 1b clinical trial in patients with diabetic neuropathy at the ADA meeting. According to a company news release, Sangamo (San Diego) is developing SB-509, a formulation of a zinc finger DNA-binding protein transcription factor designed to upregulate the expression of the gene encoding vascular endothelial growth factor (VEGF-A) for the treatment of diabetic neuropathy.

Data demonstrated that a single treatment of SB-509 was well tolerated and that no severe adverse events were observed. Importantly, patients in the phase 1b study and in the top-dose cohorts of the phase 1a trial were treated within the pharmacologically effective dose range that had been demonstrated to be efficacious in preclinical animal studies. Injection site reactions were the most common adverse events reported and were mild and reversible.

Clinicians also observed anecdotal clinical improvements in quantitative sensory testing (QST), which measures detection of vibration and improvements in average total neuropathy score (TNS), a composite of several measurements including neurologic exam, QST, electrophysiologic studies and neurologic symptoms. A placebo group of six patients, treated in both legs, provided a control group and showed a mean deterioration in their average TNS over 2 months.

In contrast, all patients treated with SB-509 in one leg in the phase 1a portion of the study, and all patients treated in both legs in the phase 1b portion of the study showed anecdotal improvements in neurologic exams with improved average TNS from baseline. This positive trend in neurologic function highlights the potential for SB-509 to address the nerve damage and its potential for nerve regeneration in the treatment of diabetic neuropathy. The top dose level of 60 mg of SB-509 will be extended to treat nine patients with SB-509 and nine patients with placebo to provide additional clinical data on the effects of SB-509 on the neurologic exam in diabetic neuropathy patients.

Combination Agent Superior to Atorvastatin for LDL Reduction in Type 2 Patients

Results from a clinical study conducted in 1,229 type 2 diabetes patients with high cholesterol showed that the combination agent ezetimibe/simvastatin (Vytorin; Merck/Schering Plough, Whitehouse Station, NJ and Kenilworth, NJ) provided greater reduction in LDL compared with atorvastatin in comparisons of the recommended usual starting doses. The data, presented at the ADA, were based on a primary efficacy endpoint of a percentage change from baseline to the end of a 6-week treatment period in LDL cholesterol.

According to a company news release, the combination product is the first and only agent approved to treat the two sources of cholesterol by inhibiting the production of cholesterol in the liver and blocking the absorption of cholesterol in the intestine, including cholesterol from food. The drug Vytorin is marketed as Inegy in many countries outside the United States.

At the recommended usual starting doses of both agents, ezetimibe/simvastatin 10/20 mg demonstrated a 53.6% mean reduction from baseline in LDL cholesterol as compared with a 38.3% reduction observed with atorvastatin 10 mg and a 44.6% reduction with atorvastatin 20 mg. At the alternative starting dose for patients requiring greater LDL lowering for the two agents (>55% for ezetimibe/simvastatin and >45% for atorvastatin), ezetimibe/simvastatin 10/40 mg, decreased LDL significantly more than atorvastatin 40 mg: 57.6% compared with 50.9%, respectively, (P<.001 for all three comparisons).

This study showed that ezetimibe/simvastatin was significantly more effective than atorvastatin in reducing LDL when comparing the recommended usual starting doses and the alternative starting doses for those patients that need greater LDL lowering.

PROACTIVE: Pioglitazone Reduced Major Cardiovascular Events

In other pioglitazone news, new analyses from the landmark Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) Study found that pioglitazone significantly reduced the occurrence of major adverse cardiovascular events such as MI, nonfatal stroke, acute coronary syndrome and cardiovascular death in high-risk patients with type 2 diabetes. Additionally, pioglitazone significantly decreased the progression to permanent insulin use. These results were presented as three separate abstracts at the ADA.

"What is unique about these new data is that while earlier PROACTIVE results found a combined risk reduction of [MI], stroke and death by 16% in high-risk patients treated with [pioglitazone], we saw a greater risk reduction when we looked at the wider scope of major adverse cardiovascular events, in this high-risk population," said Erland Erdmann, MD, chairman of the PROACTIVE Executive Committee, and director of the Clinic III for Internal Medicine, University of Cologne, Germany.

Two additional analyses from PROACTIVE examined the effects of pioglitazone on insulin use. The results demonstrated that the agent reduced the number of patients on insulin and mean daily insulin dose, and delayed need for permanent insulin use, according to a news release. In one analysis, the one-third of patients who were treated with insulin at baseline (pioglitazone = 864, placebo = 896) were evaluated. A rapid and sustained decrease in insulin doses was observed with patients taking pioglitazone compared with a progressive increase with placebo. By study end, the mean insulin dose was lower with pioglitazone (42 U/day) than with placebo (55 U/day; $P<.0001$), and insulin had been discontinued in 9% of patients in the pioglitazone group versus 2% in the placebo group ($P<.0001$).

In the second analysis, the two-thirds of PROACTIVE patients (pioglitazone =1,741 and placebo = 1,737) who were not on insulin at baseline were evaluated. The study demonstrated that pioglitazone delayed the need for permanent insulin use. In fact, twice as many placebo patients progressed to permanent insulin use, as compared with pioglitazone patients (n=362 and n=183, respectively) with projected rates for time to permanent insulin use 11% and 21% for the pioglitazone and placebo groups, respectively ($P<.0001$).

In addition, pioglitazone patients not on insulin at baseline showed improved HbA1c values compared with placebo patients at final visit (6.97% vs 7.49%, $P<.0001$). Overall, progression to permanent insulin use was reduced by 50% at 3 years with pioglitazone versus placebo, and better glycemic control was seen with pioglitazone.

Large-Scale Study to Evaluate Pioglitazone, Cardiac Risk Factors in Type 2 Diabetes

Researchers at the ADA presented a new initiative that will show the relationship between baseline characteristics and cardiac risk factors in patients enrolled in a trial called CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone).

This is the largest and longest study to examine the effects of pioglitazone on measures of the atherosclerotic disease process in patients with type 2 diabetes, most of whom had no clinical evidence of heart disease, according to a company news release.

"While earlier and smaller studies found that [pioglitazone] reduced carotid intima-media thickness, given the size and duration of the CHICAGO trial, we hope to gather further information about the effect of [pioglitazone] on blood vessel health and atherosclerosis," said Theodore Mazzone, MD, professor of medicine and director of the Section of Endocrinology, Diabetes and Metabolism at the University of Illinois at Chicago. "We look forward to further study findings, as we hope they can provide important information and insight about management of [CVD] in people with type 2 diabetes."

The CHICAGO trial is an 18-month, multicenter, randomized study that has enrolled 439 patients with type 2 diabetes, all from the Chicago area. The primary goal is to compare the effects of pioglitazone versus glimepiride, a sulfonylurea, on carotid intima-media thickness defined as the thickness of the inner lining of a patient's neck arteries.

It is also assessing the occurrence of cardiovascular events and CVD risk factors among patients with type 2 diabetes.

Mix Comparable in Safety, Efficacy to Basal-Bolus Therapy

The PREFER study demonstrated type 2 diabetes patients reached nationally recognized glucose targets with less hypoglycemia and only twice-daily dosing with 70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin) NovoLog Mix 70/30 (Novo Nordisk, Princeton, NJ). These data were presented at the ADA.

The 70% insulin aspart protamine suspension and 30% insulin aspart injection is clinically comparable in safety and efficacy with basal-bolus therapy in helping type 2 patients currently treated with oral antidiabetic agents alone or in combination with glargine or NPH insulin to reduce HbA1c levels for diabetes control.

Data from the treat-to-target PREFER study found that >60% of patients using the mix achieved ADA postprandial glucose targets with equivalent fasting control. The endpoint HbA1c levels were 7.17% for the 70/30 mix patients and 6.96% for basal-bolus patients. Fifty percent of the mix patients in the trial, and 60% of patients treated with basal-bolus therapy, achieved the HbA1c target of ≤7%. Minor hypoglycemia rates were reported at 28% and 31% for patients in the mix and basal-bolus groups respectively.

"Diabetes is often referred to as an epidemic — due in large part to the growing number of type 2 patients," said Andreas Liebl, MD, of the Center for Diabetes and Metabolism in Bad Heilbrunn, Germany. "This study suggests that those type 2 patients taking oral antidiabetic agents or glargine/NPH insulin may benefit from initiating monotherapy treatment with an insulin therapy such as NovoLog Mix 70/30."

Positive Results from DPP-IV Inhibitor, PSN9301, in Phase 2a Clinical Trial

Positive results from a phase 2a proof-of-concept study with the dipeptidyl peptidase-IV (DPP-IV) inhibitor PSN9301 (OSI Pharmaceuticals, Melville, NY) were presented at the ADA. The study demonstrated that with prandial dosing, 14-day administration of PSN9301 reduced blood glucose levels in patients with type 2 diabetes and was generally well-tolerated with no episodes of hypoglycemia, according to a company news release.

Also presented were preclinical data on novel, orally available agonists of the G-protein coupled receptor GPR119 for the potential treatment of obesity, diabetes and associated metabolic disorders.

PSN9301 is an orally available, small molecule inhibitor of DPP-IV, an enzyme involved in the breakdown of the hormone glucagon-like peptide-1, or GLP-1. Unlike other DPP-IV inhibitors, PSN9301 demonstrated a fast onset and relatively short duration of action, supporting the unique meal-related dosing regimen.

This phase 2a randomized, double-blind, placebo-controlled, 2-week, in-clinic dosing trial explored the effects of several different doses of PSN9301 in 56 patients with type 2 diabetes. In the three highest-dose groups, 240 mg, 360 mg and 480 mg, each three times daily with meals, the data showed that the glucose area under the curve in response to an oral glucose tolerance test was reduced significantly. The reduction ranged from 24% to 42% compared with placebo. No serious adverse events were reported. The most frequent treatment-related adverse events reported, which were all mild to moderate, were fatigue, headache and abdominal pain.

In another presentation, researchers described preclinical studies with novel agonists of the G-protein coupled receptor GPR119. The prototypical novel agonist PSN632408 showed appetite and weight reduction effects similar to those obtained with the prescription weight-loss agent sibutramine (Meridia; Abbott Medical, Abbott Park, Ill).

GPR119 has been found to be expressed mainly in the endocrine cells in the pancreas and gastrointestinal tract. GPR119 agonists increase cyclic AMP levels in cells expressing the receptor, which is accompanied by increases in glucose-stimulated insulin release in pancreatic beta cells.

In subchronic studies in rodent models of obesity, the data showed that the reductions in food intake induced by daily oral treatment with novel GPR119 agonists lead to body weight reductions that can be accounted for by a specific loss of fat tissue and, as a result, reductions in plasma triglyceride and leptin levels. Moreover, 21 days of treatment also lead to improvements in glucose tolerance and insulin sensitivity. Improvements in oral glucose tolerance were also found on acute oral administration of GPR119 agonists in several rodent models, including diabetic models. OSI is continuing to study additional, more potent orally available GPR119 agonists for the potential treatment of obesity, diabetes and associated metabolic disorders. ■