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IN THIS ISSUE

MAY 2000

VOL. 3, NO. 5 (pages 49-60)

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With demise of Rezulin, FDA says there are safe alternatives

Avandia, Actos offer same benefits without same risks

Three-quarters of a million patients who used the insulin-sensitizing drug troglitazone (sold by Warner-Lambert Parke-Davis under the brand name Rezulin) have viable options in two other drugs in the same class that have not displayed the liver toxicity associated with Rezulin, according to the U.S. Food and Drug Administration (FDA).

At the recommendation of the FDA, The Morris Plains, NJ-based pharmaceutical giant withdrew Rezulin from the market on March 21 amid a firestorm of controversy over increasing evidence of liver toxicity in patients taking the drug.

On March 8, the FDA said it had received 88 reports of liver failure "possibly or probably related to use of the drug [Rezulin]"; 61 patients died and 10 required liver transplants. Three of the liver-transplant patients died. On March 21, the FDA said in a written statement: "FDA took this action after its review of recent safety data on Rezulin and two similar drugs, rosiglitazone [Avandia] and pioglitazone [Actos], showed that Rezulin is more toxic to the liver than the other two drugs. Data to date show that Avandia and Actos, both approved in the past year, offer the same benefits as Rezulin without the same risk."

"When considered as a whole, the pre-marketing clinical data and

KEY POINTS

- Pioglitazone and rosiglitazone are preferable options to the now-withdrawn troglitazone, says the Food and Drug Administration.
- Neither alternate insulin sensitizer has shown the liver toxicity effects that proved to be the downfall of Rezulin.
- Patients who have not been switched to an alternate therapy should be contacted now, says the American Diabetes Association.

post-marketing safety data from Rezulin as compared to similar, alternative diabetes drugs indicate that continued use of Rezulin now poses an unacceptable risk to patients," said **Janet Woodcock**, MD, director of the FDA's Center for Drug Evaluation and Research, in a written statement released several days after the withdrawal of Rezulin from the market. "We are now confident that patients have safer alternatives in this important class of diabetes drugs."

Rezulin also has been pulled from the market in Japan, the only other country where the drug was sold. After the drug was withdrawn from the U.S. market, the Japanese pharmaceutical firm, Sankyo Company Ltd., said it would halt sales of troglitazone, sold there under the brand name Noscal.

In the March 8 statement, the FDA also acknowledged it had received two reports of liver failure in patients taking Avandia, including one death, that FDA medical staff consider "possibly or probably related to use of the drug." The official statement said there have been no reports of liver failure linked to Actos.

The FDA announced it will publicly present the Rezulin data and the rationale for its decision at a meeting of the Endocrine and Metabolic Drugs Advisory Committee, tentatively scheduled for May 18 and 19.

Warner-Lambert, in announcing it was voluntarily discontinuing the sale of Rezulin, said in a written statement, "The company has always believed that it is essential for patients and physicians to receive accurate and objective information regarding benefits and risks of Rezulin. It was for that reason that Warner-Lambert requested a public meeting with the FDA's expert advisory committee. However, repeated media reports sensationalizing the risks associated with Rezulin therapy have created an environment in which patients and physicians are simply unable to make well-informed decisions regarding the safety and efficacy of Rezulin."

In a "Dear Doctor" letter posted on the Rezulin Web site, Warner-Lambert officials said they were making arrangements for wholesale and pharmacy returns of existing stock of the drug. Patients are instructed to contact the company to receive information about reimbursement for unused supplies of Rezulin. A company spokesman said 1.9 million prescriptions had been written for the drug. Its 1999 sales were reported at $625 million.

Many managed care organizations removed Rezulin from their formularies when reports of liver toxicity escalated. Endocrinologists at the Mayo Clinic in Rochester, MN, decided in October to stop prescribing Rezulin because of concerns about the risks, according to **Bruce Zimmerman**, MD, a Mayo endocrinologist and president of the Alexandria, VA-based American Diabetes Association.

Public Citizen calls for revised labeling

The latest round of controversy surfaced in early March after the Washington, DC-based public interest group Public Citizen, which had called for Rezulin's withdrawal from the market in 1998, submitted a petition to the FDA calling for revised labeling on all three drugs in the thiazolidenedione class. "Studies have shown that adverse effects of all three drugs can include liver damage, heart damage, weight gain, fluid retention, low blood pressure, anemia, and possible changes in hormone levels," Public Citizen said in a written statement.

In addition, the organization alleged the class of drugs commonly known as the "glitazones" is not as effective as metformin and sulfonylureas. The FDA has not responded to allegations of toxicities other than liver damage linked to thiazolidenediones. "We're not happy about these results," said **Sidney Wolfe**, MD, director of Public Citizen's Health Research Group, after Rezulin was withdrawn. "Sixty-one people are dead who would be alive if the FDA had acted when they should have."

COMING IN FUTURE MONTHS

- Syndrome X: Do low carbs and vitamins have as profound an effect on diabetes as claimed?
- Coping skills for teens: Yale study yields better outcomes
- Virtual visits with home health nurses: Helping elderly patients with diabetes do better
- Update on Viagra: Encouraging clinical results and some caveats for men with diabetes
- Exercise regime: Helping stave off the onset of diabetes in menopausal women

The group charged that the problems were well known to FDA medical officers who reviewed the drugs before they were approved. Rezulin entered the market in March 1997, Avandia in June 1999, and Actos in August 1999.

Public Citizen is not calling for the withdrawal of Actos and Avandia, but is requesting labeling revisions to warn of possible liver toxicity and advise liver monitoring for patients on the drugs.

Reports of Rezulin's liver toxicity began to emerge a few months after it entered the U.S. market. The drug was pulled from the British market by medical authorities in December 1998 after reports of 130 cases of liver damage worldwide, including six deaths.

Benefits outweigh risks

In March 1999, an FDA expert panel said Rezulin's benefits outweighed the risks associated with the drug. During hearings before the panel, **Stephen Clement**, MD, an endocrinologist with Georgetown University in Washington, DC, testified as a spokesman for the American Diabetes Association. "The American Diabetes Association believes that Rezulin has been a very useful drug for many patients, and its unique mechanism of action has been invaluable for countless individuals who, for many reasons, cannot achieve good glycemic control with the other drugs available."

Clement noted at the time that, despite its "risk of serious adverse events," Rezulin was the only drug available that offered help to certain patients with severe insulin resistance. He added that new therapies and new drugs would soon become available. "At that time, the FDA may need to reassess the benefits of Rezulin as it should all drugs previously approved to treat diabetes. . . ."

In response to the panel's March recommendation, in June 1999, the FDA ordered labeling changes for Rezulin that warned of liver toxicity and recommended close monitoring of liver function for the first year a patient was using the drug. It also said Rezulin should be used only as a combination therapy with other oral agents.

In the interim, the FDA granted priority review status to Avandia, manufactured by SmithKline Beecham, and Actos, manufactured by Takeda Pharmaceuticals American and Eli Lilly and Co., and approved both drugs within a few months.

The day after Rezulin was withdrawn from the market, Public Citizen presented additional allegations in a letter to Donna Shalala, secretary of the U.S. Department of Health and Human Services. The organization wrote that FDA officials harassed FDA physicians "in the context of the recent controversy over Rezulin," and that the FDA had "lowered safety standards" in 1997 when Rezulin and several other controversial drugs were approved.

"The number of drugs already pulled off the market [Posicor, Duract, Raxar, and Rezulin] from those approved in 1997 is twice as many as in any other previous year of approval," wrote Wolfe in his March 22 letter to Shalala. He also mentioned the withdrawal of the weight loss aid Redux in 1996. "In many of these cases, there was either opposition by FDA employees to the approval of these drugs [Redux and Rezulin], unsuccessful urging of stronger product warnings on approval [Duract], or inadequately heeded opposition from several FDA advisory committee members [Posicor]."

Wolfe said a Public Citizen survey of medical officers at the FDA's Center for Drug Evaluation and Research in late 1998 found 27 instances in which a drug was approved over a medical officer's objection and 14 instances in which FDA officers were told not to present adverse information at FDA advisory committee hearings.

At press time, the FDA declined to comment on Public Citizen's demands for a criminal investigation of alleged irregularities in Warner-Lambert's reporting of evidence of hepatotoxicity that emerged in clinical trials on troglitazone.

Two physicians involved in Rezulin clinical trials say their conclusions were not properly reported by Warner-Lambert.

ADA Statement on Rezulin

The American Diabetes Association strongly encourages patients to work closely with their health care team to help decide the best treatment option. The American Diabetes Association emphasizes that patients should NOT make any medication decisions without the help of their health care team.

Further, the American Diabetes Association encourages physicians to discuss with their patients the withdrawal of the drug from the market, and available treatment options.

Source: American Diabetes Association, Alexandria, VA.

Janet McGill, MD, an endocrinologist, principal researcher and associate professor of medicine at Washington University in St. Louis, says she reported atypical elevated liver enzymes in two of 10 patients in her part of the 1994 Rezulin trials and that a third patient experienced an allergic reaction to the drug. These were downplayed in the data the company submitted to the FDA, she charges.

One patient, McGill says, had liver enzymes five times the normal amount, although none of her patients suffered liver failure. "What does this mean? It means that the FDA is looking only at cases of complete liver failure, and not considering 'sick livers.' I saw two cases of liver problems in patients who had no problem before that. Behind the liver failure, there may be 10 times as many cases of people who were made ill by the drug."

Another physician, Mohammed Saad, MD, deputy chief of endocrinology and diabetes at the University of California at Los Angeles told CBS television that a patient in his study on Rezulin died of liver failure during the trial, but when he cautioned medical students about Rezulin's risks, Warner-Lambert complained.

Saad, who could not be reached for comment, told CBS, "I have been teaching young doctors for 20 years now. This never happened before. I thought they were using pressure tactics that were inappropriate."

In May 1997, the FDA's principal Rezulin investigator, Robert Misbin, MD, investigated Warner-Lambert's data, according to reports on CBS News, and found patients with liver enzymes up to 30 times normal. An FDA internal document shows Warner-Lambert privately admitted its report to the FDA was "not correct," according to CBS. Another draft document "shows the FDA allowed the company to cross out mention of the most severe cases," said the news report.

Before Rezulin was withdrawn from the market, Misbin took the unusual step of sending a letter to Congress saying he was "frustrated" in his efforts to persuade his superiors to remove Rezulin from the market. Once a supporter of the drug, Misbin told legislators there are now safer drugs available. ■

Dutch study finds stress increases risk of diabetes

Coping with stress is key element in diabetes care

Psychological stress contributes to physiological stress, which significantly increases the risk of developing diabetes, say Dutch researchers in a study published in the February issue of *Diabetes Care*.

More than 2,000 white adults between the ages of 50 and 74 were asked about stressful life events over the past five years, and their answers were correlated with the number of patients who later developed diabetes.

Previously healthy adults who experienced three or more highly stressful events over a five-year period were 60% more likely to be diagnosed with Type 2 diabetes than those with fewer stressful events, wrote lead researcher Johanna Mooy, MD, PhD, and colleagues at the Institute for Extramural Medicine at Vrije Universiteit in Amsterdam. The risks remained even after Mooy's team factored out family history of diabetes, lack of exercise, and alcohol use.

While other evidence suggests that stress may trigger weight gain in the abdomen, which also is a risk factor for diabetes, the Dutch researchers found no link between stress, abdominal fat, and diabetes. They also found no specific association with stress connected to work-related events such as forced job changes, retirement, or long-lasting problems at work.

The researchers theorized the link is caused by increasing levels of the hormone cortisol and decreasing levels of sex hormones such as testosterone, which have been shown to influence the action of insulin. The study also raises the issue of whether people who are stressed make poor

KEY POINTS

- Stressful life events can contribute to the manifestation of Type 2 diabetes, according to Dutch researchers.
- The expected relationship between stress and visceral adiposity was only weakly present, researchers found, however some clinicians theorize stress hormones may be connected to the propensity to accumulate visceral fat.
- The study raises the as yet unanswered question: "Do people who are stressed make poor health choices and thereby increase their risk of developing diabetes, or is there a causal connection between stress and diabetes?"

health choices and thereby increase their risk of developing diabetes or if there is a causal connection between stress and diabetes.

U.S. diabetes experts weren't surprised at the findings, but they say the strong correlation between stress and diabetes should serve as a warning signal to clinicians to help already-diagnosed patients with diabetes to cope better with stress.

"Stress management should be part of every diabetes care program, but unfortunately, very few clinics or hospitals pay attention to the effects of stress on patients with diabetes," says **Sarah Cook**, RN, a psychiatric and mental health nurse at St. Joseph's Hospital in Towson, MD.

Cook offers a stress management seminar every six weeks as part of the hospital's diabetes management program. "I encourage repeat attendance because dealing with diabetes can become more difficult over time for many people." Having diabetes and learning to manage the disease is in itself a powerful stressor, says Cook. "When you add in the stresses of everyday life, it can become overwhelming."

Experts denote several major causes of stress for patients with diabetes:

- fear, frustration, and anger associated with the diagnosis and unending attention the disease demands as well as the fear of complications, which may develop in coming years;
- lack of support from friends and family;
- lack of education about ways to manage the disease and the resulting emotional stress of not knowing what is happening and what to do about it;
- lack of adequate support from a diabetes care team;
- physiological stress associated with poor eating and exercise habits that can result in episodes of hyperglycemia and hypoglycemia.

"High stress levels can cause the release of cortisol, the fight-or-flight hormone, which speeds up metabolism and causes insulin to be absorbed prematurely, and causing a floating blood sugar that doesn't cover the medications a patient may be taking," Cook explains.

She recommends several stress management techniques to her patients, but one of the most effective is keeping a journal. "I ask them to record their sugars and their feelings. Many of them begin to see a pattern then."

She recalls an elderly woman with diabetes who was under excellent control, with fasting blood glucose around 100 mg/dL. "Suddenly her sugar shot up to 300 in a 24-hour period, and she couldn't figure out a reason why. We took her back step-by-step through the last 24 hours and she finally recalled something she had almost forgotten — at least on the conscious level. There had been a fire alarm in her apartment building, and she was evacuated briefly. The stress of not knowing whether she would lose her home and all her possessions caused this kind of blood glucose response."

"You can see how collectively destructive stress can be," says Cook. "That's why stabilizing their lifestyles is so important to help patients control their diabetes."

She recommends asking patients to look at the symptoms that indicate stress may be playing a role in their diabetes control. The most common symptoms are:

- agitation;
- anxiety;
- sleep loss or change in sleep habits;
- change in eating habits — either eating more or less than normal;
- lack of compliance — failure to eat or take medications on time;
- lack of concentration;
- low self-esteem;
- irritability;
- talking too much or withdrawal;
- frequent crying;
- headaches;
- dizzy spells;
- digestive problems;
- depression.

Of these, Cook says depression is the hardest one to pin down. "It's so complicated and manifests itself in so many ways; it's hard to tell where stress ends and depression begins."

Helping patients recognize issues

To clinicians, Cook advises helping patients recognize their "issues," whether those issues are with diabetes or with their everyday lives. "Watch their body language, and it will tell you a great deal about what is going on with them." People under stress may frown, clench their fists, grind their teeth, perch on the edge of their chairs, and drive very aggressively or grip the steering wheel very tightly. Cook has devised a pamphlet for patients, which includes tools on how to recognize stress and how to relieve it.

She first gives patients a psychological stress test, which scores the impact of stressors on their

Stressful Events

- ✔ Death of a spouse
- ✔ Divorce
- ✔ Marital separation
- ✔ Detention in jail or other institution
- ✔ Death of close family member
- ✔ Major personal injury or illness
- ✔ Marriage
- ✔ Losing a job
- ✔ Retirement
- ✔ Major change in health or behavior of a family member
- ✔ Pregnancy
- ✔ Sexual difficulties
- ✔ Birth of a child
- ✔ Financial crisis
- ✔ Death of a close friend
- ✔ Change of job
- ✔ Incurring debt for a major purchase
- ✔ Major change in job responsibilities or hours worked
- ✔ Outstanding personal achievement
- ✔ Change in residence

Stress Reducers

- ✔ Taking time for yourself every day
- ✔ Planning your day, getting organized
- ✔ Talking to a friend or spouse about your feelings
- ✔ Developing a positive attitude
- ✔ Getting as much fresh air as possible during the day
- ✔ Exercising on a regular basis
- ✔ Practicing breathing exercises or meditation
- ✔ Practicing yoga
- ✔ Listening to soothing music, especially at bedtime
- ✔ Enjoying a hobby or involving yourself in volunteer work
- ✔ Avoiding excess alcohol consumption
- ✔ Avoiding caffeine late in the day
- ✔ Eating lightly in the evening
- ✔ Getting plenty of sleep
- ✔ Saying no to responsibilities you don't want or need

Source for both lists: St. Joseph's Hospital, Towson, MD.

lives. Events range from ones usually viewed as negative — the death of a loved one, the loss of a job, or even a move to a new home — to events usually perceived as positive, such as a marriage, the birth of a child, or a job promotion. When patients see their stress scores and add in a value related to being diagnosed with a chronic disease, they begin to understand how important it is to acquire the tools to learn to relax, she says. **(See "Stressful Events" and "Stress Reducers," at left.)**

She uses a variety of techniques depending on each individual patient's need ranging from simple relaxation techniques to organizational and time management skills to breathing techniques and even meditation. "Good nutrition and a regular exercise program, even if is only chair exercise, will go a long way toward relieving stress," Cook says.

One of the biggest stress relievers is to help patients recognize their limits. "I try to help them get a realistic view of what they can do and the events that are not under their control," she says. "I tell them not to judge themselves by others' standards." Cook advises providers to "encourage an optimistic point of view. Negativity complicates life."

Stress probably plays a role in the rising number of cases of diabetes, says **Marion Parrott**, MD, vice president for clinical affairs for the American Diabetes Association in Alexandria, VA. "We have been seeing a huge increase in the number of cases of diabetes in this country, and the increase in obesity and the decrease in physical activity somehow don't seem adequate to explain the increases we are seeing.

"Stress has always been known to be an aggravating factor in diabetes, and stress isn't fun. It's sure not good for you, but it's still not certain if reducing stress would reduce the incidence of diabetes," Parrott adds.

Is depression a link?

Recent studies that show that depression may be a triggering factor for diabetes, Parrott says. "Maybe depression is the link between stress and diabetes. It's an interesting idea."

Patients who are stressed exercise less and eat more and put on more visceral fat, even if they have not been diagnosed with diabetes, so it all seems to lead to the same conclusion, she says.

Members of diabetes care teams can help their patients by recognizing that most people think their lives are more complicated than those of our

ancestors, Parrott says. Most of us also believe we are more overwhelmed by our lives than our parents or grandparents and that we live at a more hectic pace.

The stresses of previous generations may be relative and it may not be fair to compare modern life to the stress of life during the Depression or during wartime, she points out. But there are enormous stresses today that didn't exist a generation or two ago. "My parents didn't worry about somebody going to their kids' school and shooting the place up," she says.

Giving patients the tools to cope with that sense of overwhelm just might help them achieve better glycemic control and ultimately prevent or delay complications, Parrott adds.

[Contact Sarah Cook at (410) 337-1580 and Marion Parrott at (703) 549-1500.] ■

Experts say oral insulin product shows promise

Initial studies show it's as effective as injections

The days of multiple needlesticks could be numbered, say researchers working with a new oral insulin product that appears to be as effective as injected insulin.

The small rapid-mist-dispensed insulin, under development by Generex Biotechnology Corp. of Toronto, is "the first and only oral insulin that can be absorbed through the mouth," says **Arthur Krosnick**, MD, a diabetologist and clinical associate professor at Robert Woods Johnson Medical School in Princeton, NJ. "Every patient involved in the trials says he will take it anytime instead of insulin," he says.

KEY POINTS

- Phase II clinical trials indicate new form of oral insulin works like insulin and keeps blood glucose in an acceptable range for patients with Type 1 and Type 2 diabetes.
- Pre-prandial dosages may eliminate as many as 60% of needlesticks patients need to maintain insulin levels.
- Initial patient reaction is positive.

Taking it anytime is not quite in the cards — at least not yet. The product, which will be sold under the name Oralgen in the United States, is intended for pre-prandial use, although the company's researchers are working on a long-acting product to be delivered the same way, Krosnick explains. The short-acting oral product is now at the end of Phase II clinical trials and is expected to begin Phase III trials soon. Patients will still have to inject long-acting insulin once or twice daily.

Studies in Texas, California, and Canada show insulin levels begin to rise within 10 minutes of taking the medication and peak in 30 minutes to one hour, then slowly dissipate over two to three hours, mimicking the normal insulin function. While blood sugar levels drop after the insulin dissipates, the medication does not produce hypoglycemia, he says.

Studies also have shown it is equally effective in producing glycemic control in patients with Type 1 and Type 2 diabetes.

The oral medication is dispensed through a device that looks like an asthma inhaler, but the product does not go into the lungs, and it is not swallowed. Instead, a fine mist comes in contact with the mucous membranes of the mouth. The patient holds it in for a few seconds. "The only unpleasantness associated with it is a slight medicinal taste for about three seconds," says Krosnick.

Patients are more than willing to put up with that minor discomfort, he says. "Needlesticks are hurtful. [Patients] tell me this is a godsend because they only have to inject in the morning and evening now and can use the oral insulin at mealtimes."

"We have to make it easier for patients to live with diabetes," Krosnick says. For 1.5 million patients with Type 1 diabetes and approximately 4 million with Type 2 diabetes who need insulin, not only will quality of life improve, but compliance will likely improve as well since self-management will be less painful, he predicts.

The potential of the new product has generated excitement in the medical community. "It looks impressive," says **William Duckworth**, MD, director of diabetes research at the Veteran's Affairs Medical Center in Phoenix and professor of microbiology and cellular biochemistry at University of Arizona, also in Phoenix.

Duckworth, who has not been involved in any clinical trials of the oral insulin, says absorption of insulin through the oral mucosa would likely be faster than subcutaneously injected insulin.

"That is what is most attractive about it. A patient could take it with a meal or even after a meal and get rapid absorption rather than depend on the sometimes erratic absorption of any subcutaneously delivered insulin." He speculated that the new product could be "more consistent even than Humalog."

"It's a race between inhaled or oral insulin, and certainly oral insulin is a far better way to go than through pills," Duckworth says.

At least two companies are investigating the effectiveness of inhaled insulin, which generated a great deal of excitement a couple of years ago. The medication is delivered as a fine powder, inhaled in measured doses through a device similar to an asthma inhaler.

While Phase III trials were set to begin on at least one of those products last year, some questions from the U.S. Food and Drug Administration are still being addressed, says Duckworth, who has worked on those trials.

[Contact Arthur Krosnick at (609) 683-4655 and William Duckworth at (602) 277-6436.] ■

Annual retinopathy screening: Is it a must?

Biennial screening may be just as effective

At a time when many health care organizations have been judged deficient in their diabetes care because of low compliance on annual retinopathy exams, new studies suggest annual screens may not be cost-effective, or necessary, for patients who show no signs of retinopathy.

The study from the U.S. Veteran's Affairs Health Services Research Center at the University of Michigan in Ann Arbor was published in the Feb. 16 issue of the *Journal of the American Medical Association*. It drew a quick expression of concern from the American Diabetes Association in Alexandria, VA, which immediately issued a written statement reiterating its recommendation for annual eye screenings for all patients with diabetes.

The Michigan team was led by **Sandeep Vijan**, MD, MS, investigator at the VA and assistant professor of Internal medicine at the University of Michigan. The researchers concluded that a high-risk patient who is age 45 and has an HbA_{1c} of 11% gains 21 days of sight when screened annually as opposed to every third year. A low-risk patient who is 65 and has an HbA_{1c} of 7% gains an average of three days of sight.

Their results showed patients in the high-risk group cost an additional $40,530 per quality-adjusted life-year (QALY), while the low-risk group cost an additional $211,570 per QALY gained. In the general population, annual retinal screening vs. every-other-year screening costs $107,510 per QALY gained, and screening every other year vs. every third year costs $49,760 per QALY gained.

Annual screening not cost-effective

"Annual retinopathy screening has always been the gold standard in diabetes care, but it's not really based on scientific analysis," says Vijan. He suggests biennial or even triennial screening would save money and be just as medically effective.

The ADA fired back. "The . . . study relies on computer modeling, not clinical results, so its relevance to actual outcomes may be less certain."

Ronald Klein, MD, professor of ophthalmology at the University of Wisconsin in Madison, echoes the concerns of the ADA and adds a few of his own. "I have no difficulty with the data they present, but the interpretation needs to be carefully examined."

The data are based on computer modeling, and there is a lack of what Klein calls "good epidemiological data to support what the authors suggest needs to be done." He also expresses concern that the subjects in the trial were from a predominantly white population from the Third National Health

KEY POINTS

- A Michigan computer-modeled study suggests annual retinopathy screenings may not be medically necessary or cost-effective for patients with diabetes who have manifested no signs of retinopathy.
- Researchers recommend tailoring the recommendation to individual patients.
- The American Diabetes Association (ADA) continues its recommendation for annual screening because such screenings may prevent or delay other consequences short of blindness.
- ADA also expresses concern that reduced recommendations for screening might further reduce the numbers of patients who need screening.

and Nutrition Examination Survey (NHANES III), by the National Center for Health Statistics. "Diabetic retinopathy may behave differently in other ethnic groups, particularly in Hispanics and blacks."

Klein agrees with Vijan that the timing of screenings should be determined on a case-by-case basis. "The ADA guidelines [on retinopathy] were developed in the 1980s based on epidemiological studies at a time when people were coming to ophthalmologists late in the game after they had already developed retinopathy."

The ADA statement expressed concerns that Vijan's study "only examined the value of screening to prevent blindness, but there are serious consequences of visual impairment short of becoming blind. These consequences also can be prevented or delayed by early detection [i.e. annual screening]. Thus screening to prevent or delay a reduction in visual acuity should, we believe, be quite valuable for most patients with diabetes."

The ADA statement also said the current annual rate of eye exams is estimated to be only 40% to 50% of eligible patients, despite the current recommendation to screen annually. "As such, it is uncertain whether a recommendation to reduce the frequency may lead to even less screening of those eligible or in need of screening." The ADA also expressed concern about the ability of health care professionals who treat people with diabetes to easily identify high-risk vs. low-risk diabetic patients and that follow-up to monitor eye exam referrals is not common.

"We don't want less compliance. But if we lower the burden on both patients and physicians, I think we might actually get increased compliance," Vijan counters.

[Contact Sandeep Vijan at (734) 930-5100 and Ronald Klein at (608) 263-0280. The American Diabetes Association may be reached at (703) 549-1500. The ADA Web site is: http://www.diabetes.org] ■

Early tight control reduces long-term complications

Eye, kidney complications curtailed in Type 1

There's another reason to add tight control to your list of prevention-based measures. The latest analysis of the Diabetes Control and Complication Trial (DCCT) shows dramatic long-term reductions in microvascular complications for patients who undergo intensive therapy early in their disease.

The results provide strong support for beginning intensive therapy as early as possible in the course of Type 1 diabetes and maintaining it for as long as possible, says a DCCT research group in a paper published Feb. 10 in the *New England Journal of Medicine*.

"The results probably apply to Type 2 diabetes as well, although there are no comparable data available yet," says lead researcher **David Nathan**, MD, an endocrinologist and professor of medicine at Harvard Medical School and director of Massachusetts General Hospital's Diabetes Center in Boston.

His team found that even though blood sugars crept up over the years after the trial ended, Type 1 patients who began receiving intensive therapy at the time of diagnosis had a 71% lower risk of developing early microvascular complications over an average of 6.5 years than those in the conventional therapy group.

"This doesn't mean that intensive therapy should be short-term," says Nathan. "What it means is that early efforts to get sugars under control pay off in the long run."

The DCCT intensive therapy group got at least three daily injections of insulin or treatment with an insulin pump, with the dose adjusted frequently on the basis of self-monitored blood glucose values and diet and exercise. Conventional therapy consisted of one or two insulin injections per day with one urine or blood test each day.

At the end of the DCCT, all patients were offered intensive therapy supervised by their own physicians. Nearly all patients in the former intensive therapy group and 75% of the patients

KEY POINTS

- Newly analyzed results of the Diabetes Control and Complications Trial (DCCT) show tight glycemic control reduces the risk of complication for years, even if blood sugars begin to rise over time.
- While DCCT involved patients with Type 1 diabetes, researchers suggest the same benefits translate to Type 2 patients as well.
- Patients on initial tight control had a 53% lower risk of developing mild kidney disease and 83% less chance of developing serious kidney disease.

in the former conventional therapy group were treated intensively throughout the follow-up Epidemiology of Diabetes Interventions and Complication (EDIC) study.

Researchers evaluated retinopathy on the basis of centrally graded fundus photographs in 1997, four years after the DCCT ended and they measured nephropathy on the basis of urine specimens during the third or fourth year after the DCCT ended. The conventional therapy group had nearly twice the incidence of microalbuminuria as the tight control group had.

Those on initial tight control had a 53% lower risk of mild kidney disease and an 83% lower risk of severe kidney disease. Forty-nine percent of the conventional therapy group had a progression in retinopathy of three steps or more from baseline, while 18% of the tight control group had deteriorated that far. With adjustments for levels of retinopathy at the end of the DCCT, researchers projected a 75% reduction in the likelihood of progression with early tight control.

At the time of enrollment, the mean HbA_{1c} in each group was about 9%. During the 6.5 years of follow-up, patients in the intensive therapy group had a median HbA_{1c} of 7.2%, and the conventional therapy group's was 9.1%. However, during the EDIC, the two groups' values had almost converged at a median value of 8.1% for conventional therapy and 7.7% for the intensive group.

Nathan says those results demonstrate the value of early control since the microvascular comorbidity rates of the two groups remain very different. "This suggests that while there is clearly a momentum to complications, once there is a benefit, it remains a benefit."

He notes there was a high level of compliance among all patients in the DCCT and EDIC — 98% in the intensive therapy group and 97% in the conventional therapy group. "This was a highly motivated group of volunteers. They were carefully selected and had a high level of education. It's also important to remember that 15% of the participants were adolescents, and that's a group that generally has difficulty with adherence."

To clinicians, the DCCT and EDIC are particularly important because this group of patients and their physicians did not have the benefit of knowing all their hard work would pay off, Nathan says.

"For patients now, this should be a tremendous motivator, to know that they can get a 50% to 75% reduction in the instance of loss of vision by intensive therapy at the outset," he says. "Even if they can't get their HbA_{1c} [levels] down to 6% or give themselves four insulin shots a day, the lower they keep their average glucose levels, the better chance they stand against complications. It is not an all-or-none phenomenon. If they do the best they can, they'll get positive results."

Clinicians should be "cheerleaders" for their patients, he says. "Every patient needs to be treated uniquely and individually. Find out what works for that individual patient, and you'll have the key to his successful treatment."

Follow-up is always a problem

In the real world of diabetes treatment, follow-up is always going to be a problem, both in terms of patients' time and in terms of cost, says **Barbara Schreiner**, RN, MN, CDE, associate director of the diabetes care center at Texas Children's Hospital in Houston.

Nathan's group's findings are not really surprising, especially in terms of the control "flip" that took place after the DCCT ended, she says. "What happened? Life got in the way. They weren't so intensively involved and didn't have to talk to someone on the diabetes care team every week."

After an initial period of intensive control, the presence of a support team is essential to long-term diabetes management, Schreiner says.

Texas Children's Hospital continues to provide telephone follow-up even though insurers refuse to pay for it. "We've just stopped charging for the phone contacts," she says. "Our institution decided it was worth it to continue, but managed care's attitude from a financial standpoint is that they question whether it should cost $1,000 or $5,000 to help a patient lower his HbA_{1c} by 1%."

While there is voluminous evidence to support the cause for tight control over the long term, managed care has not yet acknowledged the short-term benefits, although at least one study has demonstrated clear short-term dollar savings, Schreiner says. The person-to-person contact is clearly a boon to patients struggling with the ongoing challenges of their disease, but she suggests that interactive Web sites and chat rooms may serve some of the same purposes at a lower cost. Ongoing support groups are also helpful.

[Contact David Nathan at (617) 726-2873 and Barbara Schreiner at (713) 770-1000.] ■

Autoimmune Type 2 may need early treatment

Autoimmunity to pancreatic islet cells has always been believed to be a characteristic of Type 1 diabetes, but there is growing evidence of a subset of Type 2 diabetes in which patients develop autoimmunity similar to what is seen in Type 1.

Universal antibody screening of patients with Type 2 diabetes should be considered to determine if early insulin treatment might stave off the development of this subset as the patient ages, says the lead author of a study published in the January 2000 issue of *Diabetes*.

"This appears almost to be a different disease in some patients," says **Massimo Pietropaolo**, MD, associate professor at the University of Pittsburgh School of Medicine and a staff member at Pittsburgh Children's Hospital.

"Screening for GAD65 and IA-2 antibodies might help, since we have determined that 10% to 15% of Type 2 patients display these antibodies," he says. "This subgroup likely will develop a requirement for insulin over time. Early treatment with insulin may reduce the risk of coronary artery disease connected to the immune system pathogenesis."

Pietropaolo's most recent study showed a 12% incidence of GAD65 and IA-2 antibodies among 290 patients older than 65, but the autoimmune response has been detected in younger patients as well. "We've seen it in people with Type 2 diabetes who are in their 30s and 40s."

Pietropaolo and his colleagues will soon begin a larger study with 11,000 patients to determine if the prevalence holds true with larger numbers of subjects.

The medical community is far from convinced that universal screening would change the treatment options for patients who display autoimmune-type diabetes. "Clinically, the concept of universal screening is premature at the moment," says **Jerry Palmer**, MD, professor of Medicine at the University of Washington at Seattle and director of endocrinology, metabolism, and nutrition at the Department of Veterans Affairs Puget Sound Health Care System. He says it is clear there is a subset of patients with Type 2 diabetes who display antibodies usually associated with Type 1 diabetes, but it is not clear if they should be treated differently than patients who are antibody-negative. Palmer says it is possible that patients with the antibodies that indicate beta cell failure tend to have a more severe disease process. "But we don't really know."

There is also no defining evidence to show that starting insulin early would have a protective effect, although he says researchers are currently conducting clinical studies in hopes of finding an answer to that question. "To make clinical recommendations for millions of people with diabetes is jumping the gun a little right now, although we may find out that this screening would be beneficial." The take-home message is that all Type 2 diabetes is not the same and there are subsets of the disease which may ultimately require different treatment, "but the evidence just isn't out there right now," Palmer says. "[In practice], people who are antibody-positive are more likely to need insulin, and you would increase their meds anyway if they are not responding."

Diabetes Management™ (ISSN# 1098-0032) is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Application to mail at periodical rates is pending at Atlanta, GA 30304. POSTMASTER: Send address changes to **Diabetes Management**™, P.O. Box 740059, Atlanta, GA 30374.

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Subscription rates: U.S.A., one year (12 issues), $279. With approximately 18 contact hours CE/CME credit, $329. Outside U.S., add $30 per year, total prepaid in U.S. funds. One to nine additional copies, $223 per year; 10 to 20 additional copies, $167 per year. For more than 20 copies, contact customer service for special arrangements. Missing issues will be fulfilled by customer service free of charge when contacted within 1 month of the missing issue date. **Back issues**, when available, are $47 each. (GST registration number R128870672.)

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Editor: **Kathleen Barnes**, (828) 883-5695, (foxfire@brinet.com).

Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@medec.com).

Editorial Group Head: **Leslie Coplin**, (404) 262-5534, (leslie.coplin@medec.com).

Managing Editor: **Kevin New**, (404) 262-5467, (kevin.new@medec.com).

Production Editor: **Ann Duncan**.

Editorial Questions

For questions or comments, call **Kevin New** at (404) 262-5467.

The concept of latent autoimmune diabetes in adults (LADA) is not a new one, says **Steven Elbein**, MD, an endocrinologist and professor of medicine at the University of Arkansas in Little Rock, who says he suspects this subset is really a late onset Type 1 diabetes.

Elbein considers Pietropaolo's data to be "pretty strong," and agrees that about 10% of patients with Type 2 diabetes will show signs of an autoimmune reaction. He still doesn't recommend universal GAD65 and IA-2 screening. "There's a question whether GAD is the best indicator, and there is no commercially available IA-2 screen now. GAD screenings aren't very useful anyway unless they are done by a lab you can trust."

In practical terms, Elbein echoes Palmer's recommendations. "You can tell when someone is not responding to oral agents and take the steps you need to help them get into glycemic control."

[Contact Massimo Pietropaolo at (412) 692-65570, Jerry Palmer at (206) 764-2495, and Steven Elbein at (501) 257-5814.] ■

FDA recalls herbs with high glyburide levels

The U.S. Food and Drug Administration (FDA) recalled two herbal preparations found to contain "dangerously high" amounts of glyburide in late March. Dianolyn capsules, made by Diabetic Capital of Alhambra, CA, and Dimelstat, manufactured by SciQuest Lab Inc. of Brea, CA, were sold over the counter as herbal remedies.

The two companies announced the recalls in statements released by the FDA with the warning, "People who have low blood sugar or those with diabetes run the risk of serious or life-threatening complications if they consume these products." The recall statement further cautioned consumers to stop using the products and to seek medical advice, "especially if they are currently being treated with other anti-diabetic drugs or if they have symptoms of fatigue, excessive hunger, profuse sweating, or numbness of extremities."

Dianolyn capsules were sold nationally and promoted in Chinese-language radio commercials and newspapers. Dimelstat is sold by mail order and through specialty herb stores.

Both companies told the Associated Press there had been no reported illnesses connected with the products. ■

CE objectives

After reading this month's issue of *Diabetes Management*, the continuing education participant should be able to:

- Identify particular clinical, administrative, educational, or managerial issues related to the disease management of diabetes patients.
- Describe how those issues affect diabetes patients, diabetes management programs, and diabetes costs.
- Cite practical solutions to disease management problems associated with diabetes, based on overall expert guidelines from the National Institutes of Health, the American Diabetes Association, the American Association of Diabetes Educators, or other authorities, or based on independent recommendations from clinicians at individual institutions. ■