Thiazolidinediones in the Treatment of Type 2 Diabetes: A Clinician's Perspective

An interview with John B. Buse, MD, PhD, Associate Professor in the Department of Medicine and Director of the Diabetes Care Center at the University of North Carolina in Chapel Hill, North Carolina

John B. Buse, MD, PhD

In the vacuum left by the removal of troglitazone from the US marketplace, clinicians are asking new questions—and revisiting old ones—about insulin resistance, patient management, cardiovascular risks, cost effectiveness, and the efficacy and comparative safety of thiazolidinediones.

To help clinicians and administrators sort through these issues, we contacted Dr. John B. Buse. Dr. Buse, who has participated in clinical research on several of the newer oral agents for the treatment of diabetes, manages a large practice of approximately 2000 diabetic patients.

His hospital-based academic practice works with all insurers in North Carolina. The central part of North Carolina is a rapidly growing area. Because patients with diabetes are often primarily concerned about diabetes management, many of the new area residents establish their first contact with the healthcare system via the University of North Carolina Diabetes Care Center. The Center is actively involved in the development of new treatments for diabetes via participation in pharmaceutical industry clinical trials and federal and foundation contracts. It is also the site of clinical training for residents, fellows, allied health professionals, and practitioners of all types from the community.

We asked Dr. Buse practical questions about treatment goals for diabetic patients and the role of the thiazolidinediones in the posttroglitazone era.

Therapeutic Goals and Costs

AJMC: Should managed care organizations actively target insulin resistance as a unique disease state in their populations?

Dr. Buse: First, we should realize that treatments that lower insulin resistance may have benefits beyond just that of lowering glucose. For example, results of the United Kingdom Prospective Diabetes Study [UKPDS] suggest that metformin was associated with better cardiovascular outcomes in overweight subjects than was initial treatment with sulfonylurea or insulin. This did not quite reach statistical significance but was a clear trend. Studies with secondary endpoints involving troglitazone suggest a similar role for thiazolidinediones. We are already treating many patients for insulin resistance with certain expectations that cardiovascular outcomes may be improved.

AJMC: Should we treat insulin resistance separately from diabetes?

Dr. Buse: There is definitely a role for lifestyle management in people who are centrally obese, for the management of dyslipidemia in people with initial cardiovascular risk factors, and for the management of hypertension. Do we target insulin resistance as a medical disorder separate from those other disorders? I don't think that there are sufficient data to warrant

drug therapy. There is no evidence that people with insulin resistance who do not have other problems such as dyslipidemia, hypertension, or diabetes are at imminent risk of death or disability. Therapy to treat classical cardiovascular risk factors is certainly warranted, but the transitioning from impaired glucose tolerance to diabetes takes (on average) 5 to 10 years or longer.

Several trials now in progress might answer such questions more definitively. During the next 5 years, we should have much better data that will be used to direct treatment.

AJMC: Which trials are under way?

Dr. Buse: The DPP [Diabetes Prevention Program], which is the main trial, randomizes individuals with impaired glucose tolerance to therapy with metformin, aggressive lifestyle intervention, or standard lifestyle intervention. The troglitazone subgroup arm was disbanded, but those patients are being followed up prospectively. Also under way are European and Canadian trials involving α-glucosidase inhibitors. New trials using thiazolidinediones to prevent the development of diabetes and cardiovascular disease have been discussed and are being designed.

AJMC: From the healthcare system perspective (not the societal perspective), does the potential long-term economic benefit of thiazolidinedione use outweigh the short-term cost?

Dr. Buse: Definitive studies are just now being planned. But given the huge costs of treatment for heart attacks, strokes, and heart failure, the relative expense of thiazolidinediones versus the cost of other medicines used in the treatment of diabetes is fairly modest. For example, using a maximum dose of a thiazolidinedione for a year may cost approximately $1500 to $2000. If we thought this lowered the hemoglobin A1c [HbA1c] level by 1% to 2% and produced the additional cardiovascular benefit suggested by the data discussed above, a 40% or more reduction in cardiovascular endpoints might be expected. The practical economic benefits of insulin-sensitizing treatments—especially if they also affect the cardiovascular outcomes independent of lowering the glucose level—could be tremendous.

If the patient has a heart attack and is disabled, most of those costs may be absorbed by the federal and/or state healthcare system. But that's a problem with our current healthcare system: The costs are shuffled.

Diabetes Formulary Management

AJMC: What advice would you give a formulary committee in a managed care organization that is designing the pharmacy benefit for diabetic members?

Dr. Buse: Don't get overly restrictive. Make it as easy as possible for those with diabetes to take care of themselves. In a sense, patients with diabetes who are trying to control their blood sugar level, manage their lipid level, and change their lifestyle are really working for the managed care organization. If the patients don't take care of those things and if we don't make it easy for them to take care of themselves, an essentially guaranteed set of negative outcomes will result, including an increased risk of hospitalization, an increased need for laser eye therapy, an increased incidence of disability caused by neuropathy, and an increased risk of poor vascular outcomes.

AJMC: Can you give an example of what you mean by "overly restrictive"?

Dr. Buse: Denying access to the best glucose monitoring equipment is an

example. Some pharmacy programs do not have a robust understanding of how some meters are more difficult for certain patients to use. The insulin pen is another diabetes care product against which some formularies discriminate. Although those pens cost more than traditional insulin delivery systems, they are really much more convenient and accurate.

AJMC: And for medications?

Dr. Buse: There are often concerns within a drug class about differences in side effects or drug interactions. But most doctors have preferences, and if they cannot prescribe the product to their patient because it's not in the formulary, poor diabetes care could result. The costs of treating the complications of diabetes are so high that having very restrictive policies may cause more harm than good.

AJMC: Many health plans have restricted thiazolidinediones to second-line or third-line therapy and require prior authorization for use of that medication class. From a therapeutic perspective, do these restrictions make sense?

Dr. Buse: No. For example, there are patients who simply don't tolerate metformin. If they are given a sulfonylurea drug, they are at significant risk of hypoglycemia or weight gain. A thiazolidinedione in such cases might be a very reasonable alternative. We do not have the results of long-term trials indicating that treatment with thiazolidinediones can prevent the long-term complications of diabetes. But given their pharmacologic actions and proven glucose-lowering effects, long-term benefits seem very likely. A review of the data indicates that those drugs produce an even greater cardiovascular benefit. The thiazolidinediones are the best tolerated and easiest to take of the medications for diabetes, and (with appropriate patient selection) they are exceptionally effective.

Formulary restrictions are clearly a major barrier to providers' intensification of care. When I present CME [continuing medical education] lectures all over the country, it's clear that doctors are not willing to make an extra phone call to get a restricted drug for their patient. If blood sugar is poorly controlled because patients can't find a drug they can tolerate, if they have problems with hypoglycemia and wreck their car, or if they lose their job, there can be huge consequences for those patients and high costs for the healthcare system.

AJMC: How common are those types of formulary restrictions?

Dr. Buse: In North Carolina, requiring phone calls is rather rare. Quite often, there is a financial disincentive with the copayment. Some sulfonylureas can be obtained for $10 a month. For metformin, there may be a higher copayment. The thiazolidinediones may be a third-tier drug and may cost $30 a month. Some patients cannot afford to pay for the higher-priced agents or for a combination regimen. High-dose insulin regimens are cheaper for patients because they have fewer agents to pay for, but that type of therapy often results in other costs, such as an increased risk of hypoglycemia and increased costs associated with blood glucose monitoring. Also, many primary care physicians are reluctant to prescribe insulin in effective doses, which are usually approximately 100 units per day, and therefore many patients who might be able to control their diabetes on a 3-drug oral regimen may not achieve good control on a straight insulin regimen. Insulin is arguably the best blood glucose-lowering drug, but administering it safely and effectively requires greater provider experience and patient education.

Also, taking care of the average diabetes patient who has hypertension

requires an average of 3 drugs to achieve the current blood pressure targets espoused in national guidelines. A lipid disorder, which occurs in approximately 50% (some estimates suggest 90%) of patients with diabetes, requires another 1 to 2 drugs. If the copayment is substantial (and especially in tiered copayments), then the treatment of diabetes and comorbid conditions can become very expensive for the patient.

Practical Patient Management

AJMC: Which types of patients are the best candidates for monotherapy with thiazolidinediones?

Dr. Buse: Patients with lower fasting blood sugars (for example, less than 140 mg/dL [~ 8 mmol/L]) have a substantial risk of the development of hypoglycemia when sulfonylureas are used as initial therapy. That risk is reduced when the newer, longer-acting agents are used, but it remains. Those patients in particular are candidates for thiazolidinedione or metformin monotherapy. Many patients cannot remember to take medicines twice a day, or they just don't tolerate metformin; they need an alternative such as the thiazolidinediones. The α-glucosidase inhibitors are usually less well tolerated as a class and thus are not used often as monotherapy.

Any patient with diabetes may be a candidate for thiazolidinedione therapy, but for probably one third of that population (those with early diabetes), the thiazolidinediones are a logical choice. As we learn more about the additional cardiovascular benefits produced by metformin and thiazolidinediones, the use of those agents as a first-line or second-line therapy should increase. In patients with more advanced diabetes, there is clearly a role for thiazolidinediones in combination with other oral agents or insulin. Regardless of the drug used, monotherapy does not control diabetes for most diabetic patients in general clinical practice.

AJMC: How much of a concern is hypoglycemia in type 2 diabetes?

Dr. Buse: That is a real concern, especially for people who work in the public setting; for example, those whose work involves physical labor or the use of heavy equipment. If you try hard to control their blood sugar to accepted target levels with sulfonylureas or insulin, then a substantial risk of hypoglycemia and personal danger (eg, from motor vehicle accidents) may result in those patients. For people with erratic schedules, the inability to eat meals on time can result in a low blood sugar level with often embarrassing consequences, such as profuse sweating or confusion during a late meeting. In the UKPDS, the risk of severe hypoglycemia requiring third-party assistance was 3% per year over the entire study duration, even though tight control was not maintained during the study, in part because of concern regarding the risks of insulin therapy. A combination of the thiazolidinediones and metformin makes hypoglycemia essentially impossible in the patient with diabetes. These insulin-sensitizing agents can offer valuable options, either as monotherapy or in combination with other medications, particularly for those at higher risk of hypoglycemia.

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AJMC: Who should definitely not be taking thiazolidinediones?

Dr. Buse: The only strong contraindication is for those with preexisting or progressive hepatocellular disease (eg, individuals with chronic hepatitis), primarily because troglitazone therapy is associated with hepatocellular failure. In a patient with liver disease and diabetes that cannot be controlled by any other therapy, the risk might be outweighed by the potential benefit of thiazolidinedione therapy. Greater confidence in the lack of liver toxicity of the newer agents will be needed before this is a realistic consideration except in the most extreme cases.

Care is also required in treating those with heart failure, because the thiazolidinediones tend to be associated with fluid retention. I have not seen major problems with edema, but I am aggressive in the way I prescribe diuretics. Some patients have experienced leg swelling and shortness of breath that seemed to be caused by heart failure. These symptoms could have been caused by preexisting heart failure that went unnoticed because the high blood sugar level caused excessive urination—that is, the patients were essentially treating their own heart failure with their out-of-control diabetes.

AJMC: How might the thiazolidinediones lead to edema?

Dr. Buse: We don't know. It's more of a clinical observation. In animal models, high doses of thiazolidinediones cause heart enlargement. This does not seem to be the case in humans. The thiazolidinediones might also cause increased sodium reabsorption in the kidney, possibly by augmenting the insulin action on sodium absorption. The thiazolidinediones may produce effects similar to those of the calcium channel blockers, which as a class are associated with edema via vascular effects.

AJMC: How do you monitor treatment with the thiazolidinediones?

Dr. Buse: It is important to measure the alanine aminotransferase [ALT] level every 2 months for the first year of therapy. I always have people check their legs for edema. Individuals receiving treatment should also be advised that weight gain (part of which is fluid and part fat) will probably occur.

Glucose monitoring depends on the other therapies. The patient taking metformin should just check his or her blood sugar level at different times on different days, but probably no more than once a day. A patient on a more sophisticated insulin regimen might need to check the plasma glucose level 4 times per day.

AJMC: What about glucose monitoring in thiazolidinedione monotherapy?

Dr. Buse: Theoretically, home glucose testing should not be absolutely necessary from a safety perspective. Patients should return to have their ALT level checked every 2 months and should undergo testing to determine the HbA1c level every 2 to 3 months. We want to create patient-centered management in which we can instruct those patients to monitor glucose at home. Knowing which glucose level (~ 100 mg/dL) is associated with good outcomes provides a target for therapeutic achievement and motivates patients.

AJMC: How much of a clinical concern is drug-related weight gain?

Dr. Buse: We are not certain about weight gain related to the 2 newer thiazolidinedione agents, but with troglitazone, the weight gained is not central obesity, which is associated with cardiovascular risk. It is weight gain in the subcutaneous space. That weight gain is a cosmetic issue and may cause significant patient

concern or predispose him or her to arthritis but is probably not of cardiovascular significance.

AJMC: How soon do you expect to see the effect of treatment?

Dr. Buse: If you see no glucose-lowering effect after 2 to 4 weeks of therapy, it is reasonable to increase the dose of the thiazolidinedione. Some patients do not respond at all to the initial dose but respond very well to a maximal dose. The maximum effect of any dose is seen in 2 to 3 months. If a patient has responded well during the first 2 to 4 weeks of treatment, wait 2 months to see if that dose is fully effective. If only a modest response has occurred 2 to 4 weeks after treatment was started, then you might increase the dose without waiting the entire 2 to 3 months.

AJMC: Do patients tolerate the thiazolidinediones well?

Dr. Buse: In general, I find them to be very well tolerated. The thiazolidinediones have no dose-limiting side effects. With monotherapy, there is no hypoglycemia. They are rarely associated with constitutional symptoms such as malaise, headache, or nausea. In some individuals, edema and some weight gain may develop, but other than that, there's not much of anything. I am aware of cases of neuropsychological symptoms with troglitazone, but those are quite rare and, to my knowledge, have not been reported with the newer agents. In general, thiazolidinediones are also very easy to use, and the dose can be administered once a day, which is convenient.

Focus on Thiazolidinediones

AJMC: What is the mechanism of action of those drugs?

Dr. Buse: The leading hypothesis is that thiazolidinediones sensitize fat cells to insulin, which reduces free fatty acid levels, improves glucose use in muscle, and decreases plasma glucose. Those drugs also reduce hepatic glucose output, thereby reducing the amount of glucose delivered into the circulation. They may also reduce dyslipidemia and may cause positive changes in the endothelium via action on free fatty acids. The seed mechanism from which all of the rather magical properties of the thiazolidinediones may emanate is the change in free fatty acids.

AJMC: Can we expect more thiazolidinediones to be approved soon?

Dr. Buse: There is a product in phase 3 trials, and there are a large number in phase 1 or phase 2 trials. Nothing will be approved this year, and there will probably be no approvals in 2001.

AJMC: Which clinical benefits have been documented as a result of thiazolidinedione use? Is there evidence of anything other than improvements in surrogate measures such as plasma glucose or lipid levels?

Dr. Buse: No. Because of the withdrawal of troglitazone from the market, many long-term studies that are under way are in jeopardy. Those studies attempted to distinguish the glucose-lowering ability of these drugs from their insulin-sensitizing effects. One such study by Dr. Tom Buchanan at the University of Southern California in Los Angeles was reported at the American Diabetes Association meeting in June. His study demonstrated the effectiveness of troglitazone in preventing diabetes, reducing established cardiovascular risk factors such as hypertension and lipid disorders, and minimizing the thickening of major blood vessels in atherosclerosis. Studies of the newer thiazolidinediones, including BARI [Bypass Angioplasty Revascularization In-vestigation] 2 and follow-up studies to

the UKPDS and ACCORD [Angioplastie Coronaire CORvasal Diltiazem], are now being designed, but study results won't be available until approximately 2005 to 2010.

AJMC: Is the clinical evidence for the use of thiazolidinediones based on their ability to lower glucose and on their potential additional benefits associated with insulin sensitization?

Dr. Buse: Yes, but those hints of cardiovascular benefit are not trivial. For example, the changes in lipid panels in patients treated with pioglitazone are clearly beneficial: reductions in triglycerides, combined with a dramatic increase in high-density lipoprotein [HDL] cholesterol and a neutral effect on low-density lipoprotein [LDL] cholesterol. A similar pattern was seen in patients treated with troglitazone, which was also shown to help patients with refractory vasospastic angina and reduce the rate of restenosis after stent placement. The studies providing that information were small, but the evidence was clear.

AJMC: Are there practical differences in the 2 agents on the market now?

Dr. Buse: We haven't had head-to-head studies, so it's impossible to draw firm conclusions. The separate full datasets indicate a fairly consistent pattern with rosiglitazone, including increased LDL cholesterol, modest increases in HDL cholesterol, and uncertain effects on triglycerides. With pioglitazone, there appear to be no changes in LDL cholesterol, dramatic increases in HDL cholesterol, and a significant lowering of triglycerides. Those differences, if borne out in head-to-head trials, could be clinically significant.

In terms of potential drug interactions, rosiglitazone is not metabolized by anything that has been associated with a risk of drug interactions. With pioglitazone, though, approximately 17% of the dose is metabolized by a microsomal enzyme called CYP3A4, which is involved in the metabolism of many other drugs. The possibility that this would cause major drug interactions is, however, extremely low, and early studies bear that out. We need head-to-head studies and greater publication of the completed clinical trials to evaluate both drugs more thoroughly.

AJMC: What about dosing differences?

Dr. Buse: Pioglitazone has active metabolites and a longer effective half-life, so there is absolutely no need for twice-a-day dosing. With rosiglitazone, the glucose-lowering effect is boosted by 20% to 30% when it is taken twice a day versus once a day, so some patients will receive the twice-a-day dose.

Hepatic Injury

AJMC: Why was troglitazone removed from the market?

Dr. Buse: Politics. After March 1999, to my knowledge, there were no additional deaths reported to the FDA [Food and Drug Administration] that were thought to be caused by new exposures to troglitazone. My understanding is that the only person who died of a "probable or possible" case of thiazolidinedione-related liver failure after that date was treated with 1 of the 2 newer agents.

AJMC: But 40 liver deaths occurred in patients taking troglitazone.

Dr. Buse: True. When not used appropriately (soon after its approval, when troglitazone was given to patients who had not undergone liver screening or monitoring), more than 40 people died. But I think that clinicians have finally learned how to use that drug

safely. The FDA made a leap of faith and said that the 2 other agents were safer. They certainly seem safe from the perspective of possible effects on the liver. Now that we don't use troglitazone and we monitor patients taking rosiglitazone or pioglitazone, the concern about liver damage has practically gone away. Only time will tell if rosiglitazone and pioglitazone are safer agents than troglitazone.

AJMC: Overall, how does the risk of serious side effects from treatment with thiazolidinediones compare with that produced by other agents?

Dr. Buse: I believe all 3 of the thiazolidinediones are extraordinarily safe drugs when used appropriately. Even troglitazone may be as safe as the sulfonylureas or metformin, because the risk of death from hypoglycemia caused by sulfonylureas is approximately the same as the risk of liver damage. The metformin-related risk of death from lactic acidosis is also similar. It may be that troglitazone was even safer than the sulfonylureas or metformin, but when someone dies of liver failure, it's impressive—and it's unusual in the treatment of diabetes. Poorly treated diabetes is dangerous; it produces a 2% to 5% annual risk of death from cardiovascular disease.

AJMC: What is the liver testing schedule for patients treated with a thiazolidinedione?

Dr. Buse: Physicians need to determine the ALT level before initiating treatment with the drug, every other month for the first year, and intermittently thereafter. Patients should also be warned about the symptoms of liver diseases, such as fatigue, nausea, dark urine, yellow eyes, or abdominal pain. Those with chronic elevations of ALT greater than 2 times the upper limit of normal should not be treated with the drug, and if the ALT level is ever greater than 3 times the upper limit of normal, therapy should be terminated.

AJMC: How do you counsel patients who are concerned about the risk of liver damage from taking a thiazolidinedione?

Dr. Buse: I tell them that those drugs are incredibly safe, and that I couldn't prescribe a safer drug. Troglitazone was very safe, and the 2 new thiazolidinediones and metformin might be even safer.

AJMC: Any other thoughts as you look ahead to the future of thiazolidinedione therapy in the treatment of diabetes?

Dr. Buse: I'm delighted to have the opportunity to write prescriptions for a thiazolidinedione. The main concern I have is that these other 2 drugs may not have the cardiovascular promise that troglitazone had. They may, but it will take years to find out. Now, we are 3 years behind where we were in those kinds of studies.

My fear is that there will be deaths in patients taking the newer thiazolidinediones. It is unlikely that such deaths will be related to drug therapy. I just don't want advocacy groups or newspaper reporters taking chance occurrences and publicizing them out of context, because that could destroy our chance of using a class of drug that is so valuable in a disease that is both devastating and deadly in its complications.