Troglitazone for Type II Diabetes

Summary

★ There is no conclusive evidence that troglitazone offers any clear clinical advantage over existing drug therapies.

★ Troglitazone is only the first of a number of new antidiabetic agents. The costs of these drugs is likely to be substantially higher than existing drugs. Many other new developments in diabetes treatment, for example, nasal sprays and insulin patches, are also emerging in this field.

★ Results of ongoing trials, and the possible identification of benefits to lowering glucose levels in pre-diabetic individuals, may open up new indications for the use of troglitazone to an even larger segment of the Canadian population.

Diabetes mellitus is a disorder of the pancreas which affects the body’s ability to produce or use insulin. Type II, or non-insulin dependent, diabetes mellitus is the most common form, accounting for over 90 percent of cases of diabetes. 1.5 million Canadians are diagnosed as diabetic, and an estimated 750,000 others have the disorder without knowing it. Diabetes reportedly affects 5 percent of Canadians. The prevalence is higher in certain populations, such as North American Indians and the elderly. Diabetes is associated with an increased risk of macrovascular disease (heart disease and stroke) and microvascular disease (renal impairment, blindness and amputation).

Current Therapy: In many cases diet and exercise can control the disease. Where these are not sufficient, drug therapy relies on oral agents or insulin. Three main drug classes of oral agents are available: sulfonylureas (e.g. glyburide), alpha-glucosidase inhibitors (e.g. acarbose and miglitol), and biguanides (e.g. metformin).

Status in Canada: In May 1997, Health Canada approved troglitazone (Manufacturer: Parke-Davis; Brand name: Rezulin®), the first of a new group of oral anti-hyperglycaemic agents known as thiazolidinediones, for treatment of Type II diabetes poorly controlled by insulin therapy. Thus far, troglitazone is approved for use in Canada only in combination with insulin therapy, but the U.S. Food and Drug Administration has approved troglitazone for use in combination with existing drugs and as monotherapy.

The Evidence: The published literature reports 12 randomized controlled trials of troglitazone
compared with placebo, and one with glyburide. The placebo-controlled trials only report short-term (12-week) results, and are on small sub-groups of patients: nine in only obese patients, and three in pre-diabetics (i.e., those with impaired glucose tolerance), among which two treated non-obese, Asiatic patients. Abstracts of other trials, one with only elderly patients, have been reported. Evidence from long-term trials and trials which compare troglitazone to other drug therapies, such as metformin, are not available. An analysis of randomized controlled trials of troglitazone versus placebo, and metformin versus placebo, prepared by CCOHTA staff as a background document, indicates that troglitazone may not offer any advantages over existing drug treatments in the short-term.

A multicentre trial by the U.S. National Institutes of Health (the Diabetes Prevention Program) is evaluating troglitazone and other antidiabetic drugs in patients with impaired glucose tolerance. Preliminary results are expected early in 1998 and should answer questions about the effectiveness of troglitazone and other drugs in preventing or delaying the onset of Type II diabetes and its complications. One objective of another long-term trial, the U.K. Prospective Diabetes Study, is to determine the effectiveness of drug therapy versus diet for Type II diabetes, and to measure the impact of improved glycaemic control on associated risks, such as heart disease (final results are expected early in 1998). Favorable results from these trials may result in an extension of the indications for drug use.

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<th></th>
<th>METFORMIN</th>
<th>ACARBOSE</th>
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Cost of illness: A 1993 study estimated the direct costs of diabetes in Canada at over $1 billion. Canadian drug expenditures for diabetes were calculated as $161 million. A 1992 American Diabetes Association report indicated that direct and indirect costs of diabetes mellitus in the U.S. were 14 percent of U.S. medical expenditures. Costs including medication and self-monitoring devices were estimated at $9.9 billion (U.S.), or $1,056 (U.S.) per patient. A 1994 study in the U.K. estimated that 5 percent of total health resources were consumed by diabetes related illness, and that annual costs amounted to $338 (U.S.) per patient. A German study showed even higher costs of $1,600 per patient per year.

Drug costs: Prices for troglitazone in Canada are not yet available. However, a U.S. study indicates that troglitazone may cost more than four times the cost of drug treatments such as metformin.

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UPDATE: Troglitazone for Type II Diabetes

Since we published *Troglitazone for Type II Diabetes* (Issues in Emerging Health Technologies, October 1997), important information has been issued by the U.S. Food and Drug Administration (FDA) concerning adverse events associated with use of troglitazone (Rezulin®).

In November 1997, the FDA and the manufacturer of troglitazone announced changes in prescribing information, including a new warning and recommendations for monitoring liver function. This was based on about 35 post-marketing reports of liver damage in American and Japanese patients taking this drug. These reports included one case of liver failure requiring transplantation, and one death. The FDA then asked for reports of additional adverse events and subsequently received about 150 reports.¹

Late in 1997, troglitazone (Romozin®), was voluntarily withdrawn from the market in the United Kingdom. The UK Committee on Safety of Medicines, Medicines Control Agency, cited 130 cases of liver reactions to troglitazone reported worldwide. Six of these cases were fatal.² Troglitazone (Rezulin®) has been approved for marketing in Canada, but has not yet been marketed by the manufacturer.

The issue of drug safety is of key concern to health professionals, policy-makers and, of course, to patients. At the time the CCOHTA summary was prepared, very little information on adverse events associated with this drug was documented in the published trial results. Only short-term (12-week) randomized controlled trial results were available, and evidence of serious adverse events did not appear until patients had been on the drug for several months. This raises the important question of public safety in the rush to get new medical technologies onto the market.

As we examine and synthesize information on new and emerging health technologies, many gaps become apparent in the evidence needed to support rational decision-making. We hope that this series will help to make those involved in health policy and research aware of these issues.

ISSUES IN EMERGING HEALTH TECHNOLOGIES

READER SURVEY

(TROGLITAZONE FOR TYPE II DIABETES)

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☐ This information was not of interest to me.

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Please send comments to: Annie Hall, CCOHTA
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Thanks very much for your assistance.

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