The Rise and Fall of Rezulin

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Rezulin:
Today's Presentation

- Rezulin: A Breakthrough Drug for Diabetes
- Discovery to Approval
- Post-Approval Liver Disasters
- Dear Doctor Letters and Revisions of Labeling
- More Advisory Committee Meetings
- Rosiglitazone and Pioglitazone to the Rescue?
- Rezulin Removed from the Market
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Rezulin:
A Breakthrough Diabetes Drug

- Generic name: troglitazone
- Other brand names: Prelay, Romozin
- First of a new class of diabetes drugs called thiazolidinediones (TZDs) or “glitazones”
- New mechanism of action: “PPAR activators”
- Synergistic with other classes of diabetes drugs
- Safe (“hypoglycemia is not to be expected”)
- Manufacturer in US: Parke-Davis Pharmaceutical Research (Division of Warner-Lambert)

Discovery to Approval: Timelines

- Discovered in 1979 by Sankyo in Japan
- First in man studies in 1987
- US IND opened in 1989
- FDA Advisory Committee meeting December 11, 1996
- Approved by regulators in late 1996 (Japan and UK) and early 1997 (US)

Discovery to Approval: Three-way Development

- Three companies involved in development:

  Sankyo in Japan;

  Glaxo-Wellcome and Sankyo-Europe in Europe;

  Parke-Davis and Sankyo-USA in North America
- All three companies did studies; all studies were included in the US NDA (27 Japan, 28 US, 19 UK)
- Regulatory approval granted in Japan, US, UK, Australia, Philippines. Never submitted in rest of EU.

Discovery to Approval: Efficacy

- Dose-dependent decreases in fasting glucose, HbA1c, and insulin doses
- Many patients came off their insulin
- Drug works slowly: dose increases recommended every 2-4 weeks
- Once daily dosing; oral
- Studied in combination with SUs or metformin, both SU & metformin, and with insulin, and alone
- No studies done in type 1 diabetes, pediatrics, pregnancy or lactation, NYHA Class III or IV cardiac status

Discovery to Approval: Adverse Events

- "Hypoglycemia has not been observed"
- Pregnancy risk in premenopausal anovulatory patients with insulin resistance
- Decrease in hemoglobin, thought due to increased plasma volume
- Weight gain
- No cardiac issues (CHF or ischemic heart disease)
- And…

Discovery to Approval: Hepatic Adverse Events

- "There are transient, reversible increases in liver function tests which are seen in approximately 1 percent of patients. This incidence is comparable to placebo."

  (Parke-Davis presentation to AdCom 1996)

- 1.9% of troglitazone-treated subjects had ALT >3xULN compared to 0.6 percent of placebo-treated subjects, 0.8% had ALT >8xULN, and 0.2 percent (5 subjects) had ALT >30xULN.

  (Review of Rezulin clinical trials per USPI 1999)

Discovery to Approval: Hepatic Adverse Events

- "During all clinical studies in North America (N=2510 patients), a total of 20 Rezulin-treated patients were withdrawn from treatment because of liver function test abnormalities. Two of the 20 patients developed reversible jaundice. Both had liver biopsies which were consistent with an idiosyncratic drug reaction"

(USPI January 1997)

Discovery to Approval: FDA internal disagreement

- FDA medical officer Dr. John Gueriguian stated in August 1996 that troglitazone "offered very little significant therapeutic advantage" over existing therapies for diabetes
- He expressed his concern over the high rates of liver injury and heart failure in 2 Phase III trials
- His report recommended rejection of the drug, and he commented on "the propensity of the company to dismiss a possible association between Rezulin and adverse events"

Discovery to Approval: FDA internal disagreement *(continued)*

- Parke-Davis protested Dr. Gueriguian's "intemperate language"
- The Agency took him off their evaluation panel on 4 November 1996, and removed his medical review from the Rezulin files.

(Editorial, *Diabetologia* 2005)

Initial Labeling
January 1997

- Mentioned elevated transaminase levels in clinical trials (2.2% had reversible elevations >3xULN compared with 0.6% on placebo)
- Mentioned the 2 liver biopsies showing idiosyncratic drug reaction
- "Rezulin should be used with caution in patients with hepatic disease"
- No recommendation for any liver monitoring

(USPI January 1997)

Post-Approval Liver Disasters: Liver Failure, Transplant and Death

- "About 500,000 patients in the United States have been treated with Rezulin since it came on the market in January 1997; of those, approximately 85,000 have been taking the drug for six months or more.
- As of October 21, 1997, 35 post-marketing reports of liver injury of various degrees have been received. These reports ranged from mildly elevated blood levels of the liver transaminase enzymes to liver failure leading to one liver transplant and one death."

(FDA Talk Paper, November 3, 1997)

What Was Happening? In Hindsight It Became Clear

- In rare cases (~1:1000?) Rezulin causes idiosyncratic hepatocellular injury
- Serum transaminases (e.g., ALT) are an early and reliable marker of Rezulin-related injury
- Not dose related
- No rash, fever or eosinophilia (hence not an immune mechanism)
- Rarely observed until about 7-10 months of therapy
- Discontinuing usually causes reversal of findings
- Very rarely, hepatic failure led to transplant or death

FDA and Parke Davis Response: Multiple "Dear Doctor" Letters

- October 28, 1997: Warned of liver problems and need for regular monitoring
- December 1, 1997: "you will be reassured to know that the additional reports received since early November do not indicate a greater frequency of liver injury or potential for serious harm than had been previously estimated"

- August 1999: Rezulin no longer approved for use in monotherapy

First Revision of Labeling October 1997

- "FDA and the manufacturer are recommending that serum transaminase levels in patients be checked routinely within the first one to two months of Rezulin therapy, every three months thereafter during the first year of treatment, and periodically thereafter.
- In addition, liver function tests should be performed on any patient on Rezulin who develops symptoms of liver dysfunction…
- Patients on Rezulin who develop jaundice or whose laboratory results indicate liver injury should stop taking the drug."

(FDA Talk Paper, November 3 1997)

Second Revision of Labeling December 1997

- Serum transaminase levels should be checked at start of therapy, every two months during the first year of treatment, and periodically thereafter.

Post-Approval Liver Disasters: Glaxo Wellcome Backs Out in 1997

- Glaxo Wellcome launched Romozin in the UK in October 1997
- After receiving notification from the USA and Japan of 135 cases of serious liver toxicity and six deaths, G-W voluntarily withdrew troglitazone in the UK in December 1997 and didn't pursue approval for the drug in the rest of Europe

Post-Approval Liver Disasters: NIH Study Death in 1998

- A major NIH study of diabetes prevention in patients with impaired glucose tolerance (The DPP) had included Rezulin in one arm of the study
- In 1998, one Rezulin subject (MCN# 001-0991-980812) developed liver failure and died after liver transplant complicated by extensive large bowel necrosis
- In June 1998, the NIH announced discontinuation of the Rezulin arm of the study, and advised all DPP subjects to stop taking the drug

Third Revision of Labeling July 1998

- Check transaminases
  - At start of therapy then
  - Monthly for 8 months then
  - Every 2 months for remainder of first year then
  - Periodically thereafter
  - Don't start if active liver disease or increased transaminase (ALT>1.5 x ULN)

Post-Approval Liver Disasters: LA Times Gets Involved in 1998

- David Willman, investigative reporter for the Los Angeles Times, wrote repeatedly about Rezulin. From a 2000 article:
- *"People were dying as specialists waged war against their FDA superiors. Patient safety was at stake in the scramble to keep a 'fast-track' pill on the U.S. market, research reveals.*
- WASHINGTON — The suffering persisted for more than two years. Initially, there were four known victims. Then 21. Then 33. Finally, 63 confirmed fatalities. All the while, federal authorities watched, waited and hoped the deaths would stop."

Advisory Committee Meeting: March 26, 1999

- FDA classified 35 liver reports from the US as "possibly" or "probably" related to Rezulin (26 deaths, 9 liver transplants)
- Additionally, 8 patients with encephalopathy that did not progress to liver failure or death were classified by FDA as "possibly" or "probably" related to Rezulin
- In Japan: 9 additional liver-related deaths were reported
- Recommendations of AdCom: labeling change, more study. KEEP ON THE MARKET.

Fourth Labeling Revision June 1999

- Monotherapy indication withdrawn
- Liver testing (ALT) recommended monthly x1 year, then quarterly
- If ALT's increase to 1.5-2.0 x ULN, they should be repeated immediately and weekly; if the patient develops jaundice or ALT over 3.0 x ULN, the drug should be discontinued
- It was recommended that patients with the following not be started on troglitazone:
  - Patients with ALT over 1.5x ULN; or prior liver disease; or active liver disease; or alcohol abuse

(USPI June 1999)

Post-Approval Liver Disasters: More FDA Dissention

- FDA epidemiologist Dr. David Graham sends an email in March 2000 to 14 FDA officials with his opinion that Rezulin is unsafe and should be stopped
- Graham stated there were no existing data to support the idea that monitoring can prevent the Rezulin liver failures from occurring
- Contents of his e-mail were leaked to the LA Times soon afterward

Rosiglitazone and Pioglitazone to the Rescue?

- Two other "glitazones" were approved for sale in 1999
- Despite close look, neither have shown significant liver issues

  but years later,
- Rosiglitazone (Avandia) has major concern about increased risk of heart disease; now off the market in Europe, and severely restricted in US
- Pioglitazone (Actos) has major concern about increased risk of bladder cancer ; now off the market in France and Germany, and under review in US

Rezulin
Withdrawal March 21, 2000

- FDA pressured Warner-Lambert to voluntarily withdraw Rezulin, or have the FDA remove it
- Pfizer, who was in active negotiations to purchase W-L (to get control of Lipitor), pressured W-L to agree to withdraw Rezulin
- Rezulin was simultaneously withdrawn in the US by W-L and in Japan, Australia, and the Philippines by Sankyo

Warner-Lambert Announcement March 21, 2000

- "Warner-Lambert Company announced today that it is voluntarily discontinuing the sale of REZULIN (troglitazone) Tablets… although the Company continues to believe that the benefits of the drug outweigh its associated risks.
- Patients taking REZULIN should consult with their physicians as soon as possible to discuss alternative therapies…"

Warner-Lambert Announcement March 21, 2000 *(continued)*

- "The Company has always believed that it is essential for patients and physicians to receive accurate and objective information regarding the benefits and risks of REZULIN. It was for this reason that Warner-Lambert requested a public meeting of 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. Under these circumstances, and after discussions this evening with the FDA, we have decided it is in the best interests of patients to discontinue marketing REZULIN at this time."

Rezulin
After Effects

- In June 2000, Pfizer purchased Warner-Lambert/Parke-Davis to obtain control of Lipitor (and got Rezulin as a bonus)
- Numerous lawsuits and class action suits filed against Pfizer re Rezulin
- In 2003, Pfizer took a charge to earnings of $975 million before tax in connection with all known personal injury cases and claims relating to Rezulin (per Pfizer annual report 2005)
- That charge did not cover other pending Rezulin litigation (per Pfizer annual reports)

Rezulin
After Effects *(continued)*

- David Willman of the LA Times awarded 2001 Pulitzer Prize "for his pioneering expose of seven unsafe prescription drugs… and an analysis of the policy reforms that had reduced the agency's effectiveness."
- All ongoing Rezulin trials halted
- Supplies dried up and all patients eventually transitioned to other drugs
- Dr. David Graham of the FDA continued to act as whistleblower on safety issues for other approved drugs: Vioxx, Accutane, others

Rezulin After Effects: Another AdCom May 19, 2000

- FDA finally announced (publicly and to Parke-Davis) what their criteria were for "liver failure"
- FDA had assessed 90 Rezulin cases as meeting their criteria
- Incidence of troglitazone-induced liver failure possibly around 1:2,000 – 1:20,000
- Rosiglitazone and pioglitazone appear to have a better safety profile than troglitazone and offer patients same efficacy benefits

Rezulin Conclusions

- Rezulin had become an outmoded drug:
- Its benefits outweighed risks at time of initial approval; but with newer drugs with better safety profiles, that perspective changes
  - Not a failure of the system
  - Would be a failure not to take off once convinced that a safer alternative available

(Dr. Murray Lumpkin, May 2000)

Rezulin
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