Liver Enzyme Monitoring in Patients Treated With Troglitazone

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Troglitazone is a thiazolidinedione antidiabetic agent that decreases insulin resistance. It was approved by the US Food and Drug Administration (FDA) in January 1997 for treatment of type 2 diabetes mellitus. Soon after initial marketing in March 1997, troglitazone, the first thiazolidinedione antidiabetic agent, was found to cause life-threatening acute liver failure. The drug was removed from the market in March 2000.

Objective To evaluate the effect of US Food and Drug Administration (FDA) risk management efforts, including repeated labeling changes and “Dear Healthcare Professional” letters, on periodic liver enzyme monitoring of patients taking troglitazone.

Design, Setting, and Participants Claims data from a large, multistate managed care organization were used to establish 4 cohorts of patients (N=7603) with at least 90 days of health plan enrollment before first troglitazone prescription during 4 consecutive periods spanning April 1997 to September 1999 and representing 4 progressively stringent liver monitoring recommendations.

Main Outcome Measures Percentage of eligible troglitazone users in each cohort with baseline, monthly (for up to 6 months of continuous use), and complete (baseline and monthly) enzyme monitoring, based on computerized records of laboratory claims.

Results Baseline testing increased from 15% before any FDA monitoring recommendations (cohort 1) to 44.6% following 4 separate FDA interventions (cohort 4; P.<.001). In cohort 4, 33.4% of users had follow-up testing after 1 month of therapy, falling to 13% after 5 months of continuous use. In all cohorts, less than 5% received all recommended liver enzyme tests by the third month of continuous use.

Conclusions The FDA risk management efforts did not achieve meaningful or sustained improvement in liver enzyme testing. Evaluation of the impact of regulatory actions is needed before such actions can be regarded as effective or sufficient.

METHODS

The issuance of successive warning letters and associated changes in labeling for liver enzyme monitoring provided an opportunity to study their impact on physician and patient behavior and to assess their effectiveness as a risk management tool.

UnitedHealth Group is a national health care company that includes 43 health plans across the United States. A historical cohort study of troglitazone recipients was performed using longitudinal claims data from 12 UnitedHealth Group-affiliated health plans covering about 3 million persons from 10 different states. Data consisted of separate files (pharmacy, facility, physician, and enrollment) linked by unique encrypted identifiers, protecting patient confidentiality.

Members with at least 1 troglitazone prescription between April 1, 1997, and September 24, 1999, and with at least 90 days of continuous enrollment before their first (index) prescription were selected for study (n=9136). The prior en-
LIVER ENZYME MONITORING WITH TROGLITAZONE

Table 1. Description of Study Cohorts With Respect to Period Covered, Liver Enzyme Monitoring Recommendations in Place, and Number of Patients Under Observation

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Inclusive Dates</th>
<th>Liver Enzyme Monitoring Recommendations</th>
<th>Cohort Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Apr 1, 1997-Oct 27, 1997</td>
<td>None</td>
<td>2307</td>
</tr>
<tr>
<td>2</td>
<td>Jul 28, 1998-Jan 26, 1999</td>
<td>Baseline; monthly, 8 times</td>
<td>1673</td>
</tr>
<tr>
<td>3</td>
<td>Mar 26, 1999-Sep 24, 1999</td>
<td>After advisory meeting; baseline; monthly, 12 times, from mid June to end of period</td>
<td>800</td>
</tr>
</tbody>
</table>

The number of patients in each cohort at each month is shown in Table 2.

results

There were 7603 first-time troglitazone recipients enrolled in the 4 study cohorts. The proportion of patients undergoing baseline liver enzyme testing rose from 15% in cohort 1 to 44.6% in cohort 4 ($\chi^2 = 429; P < .001$). Monthly follow-up enzyme monitoring at 1 month of therapy increased from 3.8% for cohort 1 to 33.4% for cohort 4 ($\chi^2 = 325; P < .001$). This level of monitoring was not maintained in cohort 4, falling to 13% by 5 months. The largest increase in monthly testing occurred between cohorts 1 and 2, with successively smaller increases between subsequent cohorts. For the first 5 months of treatment, monthly testing was generally 3- to 4-fold higher in cohort 2 than cohort 1 ($P < .001$ at each month). There was no difference between these cohorts in the sixth month. Monthly testing in cohort 3 was 1.7-fold higher than cohort 2 in the first month ($P < .001$). With each successive month, the differences in monitoring completeness decreased and were gone by month 5. There was no statistical difference in monthly monitoring between cohorts 3 and 4 in any month. Although one third or fewer of patients underwent follow-up testing in any month, the same patients were not typically tested each month. For example, among patients in cohort 4 treated with troglitazone for 3 months, only 10% had all 3 follow-up tests performed, while 60% had at least 1.

Complete adherence to monitoring requirements occurred at low levels (Table 2). In cohort 4, only 18.4% of patients had a liver enzyme test at both baseline and month 1. By 3 months of use, less than 5% of patients in any cohort received the full complement of recommended testing.

COMMENT

Liver transaminase monitoring was infrequently and irregularly performed despite repeated FDA regulatory interventions, including labeling changes, “Dear Healthcare Professional” letters to physicians, and heightened national publicity and awareness of liver failure risk associated with troglitazone. Although baseline testing increased from 13% to 45%, more than half of the patients who started taking troglitazone during the last period did so without a baseline test. Monthly follow-up testing also increased somewhat between the baseline and last period studied, but was modest and not sustained. Differences in testing rates between cohorts quickly waned and were indistinguishable by months 5 or 6 of continued use.

Liver enzyme monitoring was chosen by the FDA as the primary means of reducing ALF risk with troglitazone. Testing was not performed consistently or frequently enough to provide meaningful protection to patients. It is unknown whether monthly monitoring would have prevented the development of ALF had it been performed as recommended. A review of 43 ALF cases reported to the FDA found 12 in which monthly monitoring was performed. Of these, 9 (75%) went from normal enzyme levels to irreversible liver injury within a 1-month interval. In the other 3, troglitazone use continued for a month beyond the first detected abnormality, so that it is unknown whether ALF would
have been avoided had the drug use been stopped a month earlier. Also, 1 case of ALF occurred in each of 3 separate post-marketing studies, despite monthly monitoring. These data call into question the utility of enzyme monitoring for the prevention of ALF with troglitazone. In addition, the risk of ALF did not abate with continued use of the drug, suggesting that if monitoring were capable of preventing liver failure, it would need to be performed at high levels of completeness for as long as patients continued treatment. If monitoring were shown to be protective against ALF, linkage of drug dispensing with normal laboratory test results might be considered. This approach worked well in reducing the incidence of granulocytopenia with clozapine.

The influence of labeling recommendations and warning letters on physician and patient behavior is poorly understood. Walker et al found that the cumulative incidence of liver function testing during the first 8 weeks of diclofenac use was below 20%, despite recommendations in the “warnings” section of its label. Recently, Smalley et al found that an FDA “black box” warning for cisapride, with an accompanying “Dear Healthcare Professional” letter, did not meaningfully reduce the high level of contraindicated use of this product.

There are several potential study limitations. Data were obtained from computerized records, and it is possible that not all laboratory claims were submitted to UnitedHealth Group. However, because facility reimbursement depends on filing of claims, this probably did not occur frequently. Claims lag is another means by which laboratory tests might be undercounted. To minimize this, data collection was performed 6 months after the end of the final cohort period. More than 95% of facility claims typically are filed within 6 months of the date of service.

This study suggests that labeling changes, including “black box warnings” and instructions to monitor patients closely, as well as repeated “Dear Healthcare Professional” letters to physicians, cannot be assumed to be effective means of risk management. More effective strategies are needed if drug risk management programs are to benefit patient safety. Such methods should be pilot-tested and evaluated before they are presumed successful.

REFERENCEs


Author Contributions: Study concept and design: Graham, Drinkard, Shatin. Acquisition of data: Drinkard, Burgess. Analysis and interpretation of data: Graham, Drinkard, Shatin, Tsong. Drafting of the manuscript: Graham. Critical revision of the manuscript for important intellectual content: Graham, Drinkard, Shatin, Tsong, Burgess. Statistical expertise: Tsong. Obtained funding: Shatin. Administrative, technical, or material support: Graham, Drinkard, Shatin, Burgess.

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Table 2. Percentage of Patients Undergoing All Liver Enzyme Monitoring for Which They Were Eligible (Baseline and Testing Each Month)*

<table>
<thead>
<tr>
<th>Month of Eligibility for Liver Enzyme Testing</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>Cohort 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 (1641)</td>
<td>0.5 (1011)</td>
<td>0.2 (621)</td>
<td>0 (414)</td>
<td>0 (255)</td>
<td>0 (95)</td>
</tr>
<tr>
<td>2</td>
<td>6.7 (2318)</td>
<td>3.0 (1554)</td>
<td>1.4 (1089)</td>
<td>0.5 (763)</td>
<td>0.2 (480)</td>
<td>0.4 (240)</td>
</tr>
<tr>
<td>3</td>
<td>14.8 (1381)</td>
<td>7.3 (913)</td>
<td>4.1 (606)</td>
<td>3.3 (367)</td>
<td>1.3 (160)</td>
<td>†</td>
</tr>
<tr>
<td>4</td>
<td>18.4 (713)</td>
<td>10.6 (442)</td>
<td>4.8 (314)</td>
<td>3.1 (194)</td>
<td>2.7 (91)</td>
<td>†</td>
</tr>
</tbody>
</table>

*Numbers of eligible patients at each time point are shown in parentheses. The number eligible at month 1 was less than the total enrolled in the study because 1350 patients had less than 1 month of drug use. At 6 months, there were only 6 eligible patients in cohort 3 and 2 eligible patients in cohort 4. None had complete testing.