Prolonged cholestasis after raloxifene and fenofibrate interaction: A case report

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Abstract
Assigning causality in drug-induced liver injury is challenging particularly when more than one drug could be responsible. We report a woman on long-term therapy with raloxifene who developed acute cholestasis shortly after starting fenofibrate. The picture evolved into chronic cholestasis. We hypothesized that an interaction at the metabolic level could have triggered the presentation of hepatotoxicity after a very short time of exposure to fenofibrate in this patient. The findings of an overexpression of vascular endothelial growth factor in the liver biopsy suggest that angiogenesis might play a role in the persistence of toxic cholestasis.

CASE REPORT
A 60-year-old woman was started on raloxifene hydrochloride (60 mg/d) in 2000 for the prevention of osteoporosis. On December 1st, 2003 she was prescribed fenofibrate (250 mg/d) for hypertriglyceridaemia (triglyceride level 423 mg/dL). Her liver function was normal and she had no toxic habits, no drug allergies and was not taking other drugs. There was no family history of cholestatic and non-cholestatic diseases of the liver and biliary tract. She did not suffer from diabetes mellitus or pancreatitis and was moderately obese (BMI 26.7). On December 14th she noticed dark urine and both drugs were discontinued, no attempt of drug reintroduction was recorded. On admission (December 16), she was afebrile and jaundiced. Aspartate aminotransferase (AST) was 153 U/L (normal < 30), alanine aminotransferase (ALT) 241 U/L (normal < 36), aspartate transaminase (AST) was 153 U/L (normal < 30), alkaline phosphatase (AP) 174 U/L (normal < 104), gammaglutamyltransferase (GGT) 271 U/L (normal < 32), and total bilirubin 11.07 mg/dL with direct bilirubin 9.6 mg/dL. The leucocyte count was 3.3 \times 10^9/L with 17.7% lymphocytes. Serology ruled out viral causes and screening for autoantibodies was negative. Imaging testing including a magnetic resonance cholangiography showed cholelithiasis with no other pathological findings (i.e. gallstones, tumour). A liver biopsy showed a moderate inflammatory infiltrate of lymphocytes with hepatocellular cholestasis and focal necrosis. Immunohistochemistry showed that expression of vascular endothelial growth factor (VEGF) (clone C-1, Santa Cruz Biotechnology, IC, USA) resulted in mild to moderate granular staining in hepatocytes of zone 3 (Figure 1A). Immunohistochemical staining was performed as previously described[10]. Ten days later a morphiliform and very pruriginous rash appeared in the lower extremities that progressively generalized to the trunk, upper extremities and face.

Liver enzymes decreased initially but on January 20, 2004, the total bilirubin peaked at 21.84 mg/dL (direct
bile duct were absent in three out of the seven portal tracts present in the biopsy. In this biopsy VEGF showed diffuse positivity which was more intense in zone 3 (original magnification 200 x).

### DISCUSSION

Assigning a causal relationship to a drug associated with hepatic injury remains a major challenge, especially when it is the first report of a particular reaction and when more than one drug could be the culprit. If treatments are not started simultaneously, common sense and causality assessment methods tend to incriminate the last drug introduced, as the fenofibrate in our patient. Actually, fenofibrate scored higher than raloxifene when the CIOMS scale was applied to yield 9 and 6 points which fell in the category of highly probable and probable, respectively.

However, this issue may not always be so straightforward and other considerations should be born in mind. Acute hepatitis is rarely related to fenofibrate and the reported cases do not reflect the type of injury that is presented here. Most cases present with hypergammaglobulinemia and high titers of anti-nuclear antibodies, and on liver biopsies a lympho-plasmocytic infiltrate, resembling type I auto-immune hepatitis, is evident. The chronic forms of liver damage are more exceptional, usually appearing after long periods of exposure. They show different histopathological findings such as chronic active hepatitis with bridging necrosis or a reduction in the number of interlobular bile ducts in a clinically asymptomatic patient. On the contrary, the only published case of raloxifene-associated hepatitis did exhibit a late peak of bilirubin one month after drug withdrawal, similarly to our patient.

To our understanding, this patient suffered from hepatic toxicity due to an interaction between raloxifene and fenofibrate that could result in liver toxicity by altering the threshold for exposure to toxic metabolites. Both compounds are highly protein bound to albumin with the potential of competitive drug displacement, and an irreversible inhibition of CYP3A4 by raloxifene has been described which is more frequently associated with unfavorable drug-drug interactions.

The prolonged course of the abnormalities in liver biochemistry deserves further consideration. Indeed, an immune mechanism is suggested in the patient by the presence of a severe toxic cutaneous reaction and cytopenia. In these circumstances, a self-propagating immune response may persist, which might explain the outcome.

An interesting finding in this case was the over-expression of VEGF (the most potent proangiogenic growth factor) in the liver and increased plasma VEGF levels, when the clinical and biological picture was in remission and the hepatic lesion evolved into a chronic

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**Table 1 Liver tests while on raloxifene therapy and follow-up after raloxifene and fenofibrate interaction during 14 d of coadministration**

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<tbody>
<tr>
<td>Serum Bilirubin (mg/dL)</td>
<td>-</td>
<td>11.07</td>
<td>14.91</td>
<td>14.33</td>
<td>21.84</td>
<td>8.31</td>
<td>2.81</td>
<td>0.72</td>
<td>0.78</td>
<td>0.65</td>
<td>0.83</td>
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<tr>
<td>Total</td>
<td>-</td>
<td>9.58</td>
<td>14.07</td>
<td>13.69</td>
<td>19.72</td>
<td>7.27</td>
<td>1.79</td>
<td>0.14</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Direct</td>
<td>26</td>
<td>153</td>
<td>88</td>
<td>36</td>
<td>321</td>
<td>97</td>
<td>106</td>
<td>84</td>
<td>84</td>
<td>45</td>
<td>53</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>16</td>
<td>241</td>
<td>167</td>
<td>50</td>
<td>382</td>
<td>160</td>
<td>162</td>
<td>91</td>
<td>74</td>
<td>45</td>
<td>60</td>
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<tr>
<td>ALT (U/L)</td>
<td>21</td>
<td>271</td>
<td>239</td>
<td>97</td>
<td>1246</td>
<td>1387</td>
<td>539</td>
<td>1279</td>
<td>1255</td>
<td>751</td>
<td>666</td>
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<tr>
<td>GGT (U/L)</td>
<td>72</td>
<td>174</td>
<td>236</td>
<td>240</td>
<td>800</td>
<td>420</td>
<td>490</td>
<td>1195</td>
<td>793</td>
<td>493</td>
<td>444</td>
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<tr>
<td>Lymphocytes (%)</td>
<td>26</td>
<td>17.7</td>
<td>13.8</td>
<td>11.5</td>
<td>5.9</td>
<td>14.3</td>
<td>17.7</td>
<td>-</td>
<td>27.7</td>
<td>33.9</td>
<td>32.20</td>
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<tr>
<td>VEGF (pg/mL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>144</td>
<td>-</td>
<td>-</td>
<td>244</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Treatment was stopped on 14 December 2003. Total bilirubin (< 3 mg/dL); AST: Aspartate aminotransferase (< 30 U/L); ALT: Alanine aminotransferase (< 36 U/L); GGT: Gamma-glutamyl transpeptidase (< 32 U/L); Alkaline phosphatase (< 104 U/L); lymphocytes (< 104 U/L); VEGF: Plasma vascular endothelial growth factor.
cholestatic phase. This suggests that angiogenesis may be an important mechanism involved in the persistence of toxic cholestasis which is up-regulated in response to tissue damage and release of pro-inflammatory cytokines. This has been recently shown in primary biliary cirrhosis[10]. Indeed, angiogenesis is a novel mechanism involved in chronic liver damage and its role in drug-induced liver injury also deserves to be defined.

In summary, an interaction between raloxifene and fenofibrate may occur in a postmenopausal woman with resulting hepatotoxicity. Clinicians should be aware of this adverse reaction and patients should be followed up closely. Clinical judgment of the attribution of causality must be made, especially in particularly troublesome cases in which major drug metabolism mechanisms and the potential for pharmacokinetic drug interactions should always be kept in mind.

REFERENCES
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