The last few years have witnessed a growing number of studies and guidelines advocating the need to further lower low density lipoprotein-cholesterol levels in high risk coronary heart disease patients. Updated guidelines recommend a LDL-cholesterol level of less than 100 mg/dl as the goal for patients with stable CHD or equivalent cardiovascular disease (including diabetes mellitus), and even a goal of 70 mg/dl in patients at particularly high risk [1]. The direct implication of this apparent consensus is that lipid-lowering drugs will play an increasing role in achieving the newly set LDL-cholesterol goals. Hand in hand with its beneficial effects, high dose lipid-lowering therapy carries risks. Below we describe our experience with a severe case of adverse reaction related to intensive lipid-lowering therapy.

**Patient Description**

An 84 year old woman with a previous diagnosis of hypertension, unilateral carotid stenosis and hypercholesterolemia was admitted to our department complaining of generalized weakness and severe limb muscle pain, to the point of almost complete immobilization. Her symptoms began a week earlier when she complained of gradually worsening weakness of the limbs. The patient had been treated with statins (simvastatin) for the last few years. Four months earlier her family physician had increased her simvastatin dosage to 80 mg daily. Blood tests drawn following the dosage increase demonstrated normal liver enzyme levels (aspartate transaminase and alanine aminotransferase 56 and 55 IU/L respectively). Two weeks prior to her admission, in order to achieve LDL goals in this high risk CHD patient, ezetimibe (Ezetrol®) 10 mg/day had been co-administered. The patient was also treated with aspirin (100 mg), verapamil, and folic acid and vitamin B supplements.

Blood samples that were drawn upon her admission demonstrated creatine phosphokinase levels > 100 times the normal value, and high aminotransferase levels (with ALT > 20 times the upper limit of normal). Renal function was normal and there were no signs of infection, as represented by fever, leukocytosis or other symptoms and signs. Serial blood chemistry results are shown in Table 1. In light of the clinical picture and the recent drug changes, the patient was diagnosed with severe myopathy and elevated liver enzymes related to the lipid-lowering treatment. With discontinuation of her lipid-lowering therapy and intensive intravenous fluid administration, muscle enzyme levels gradually decreased and the symptoms receded. The patient was discharged following 3 days of hospitalization. On a follow-up visit 2 months after the described hospitalization, both muscle and liver enzymes returned to normal levels (Table 1).

**Table 1. Blood chemistry results**

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>After 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>133</td>
<td>139</td>
<td>137</td>
<td>139</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.3</td>
<td>3.7</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>54</td>
<td>50</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>698</td>
<td>463</td>
<td>255</td>
<td>156</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>–</td>
<td>1039</td>
<td>822</td>
<td>658</td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>–</td>
<td>1626</td>
<td>1107</td>
<td>949</td>
</tr>
<tr>
<td>CPK total (IU/L)</td>
<td>10938</td>
<td>6329</td>
<td>3031</td>
<td>1504</td>
</tr>
</tbody>
</table>

Days represent day number from admission (day 0)

AST = aspartate transaminase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase, CPK = creatine phosphokinase

**Comment**

Ezetimibe, a fairly recent addition to the lipid-lowering drug arsenal at the clinician’s disposal, acts as an inhibitor of cholesterol intestinal absorption. Co-administration of ezetimibe plus statin therapy enabled more patients to reach LDL-cholesterol goals at a lower statin dose [2]. While statins carry a myotoxic potential, ranging from myalgia to overt rhabdomyolysis (reported incidence 1–7%), initial randomized, double-blind studies have not shown this to be true also for ezetimibe monotherapy or statins-ezetimibe co-administration. In a large prospective randomized double-blind trial, only one patient from among 255 patients receiving atorvastatin and ezetimibe had developed myotoxic symptoms coincident with CPK elevations, with resolution of symptoms following treatment discontinuation [3].

Apart from the large clinical trials that have been conducted in the last 5 years on the effectiveness and safety of ezetimibe plus statin co-administration therapy, several case reports have also reported...
clinically significant myopathy attributed to the drug combination. Fux et al. [4] report a patient who developed myopathy following the addition of ezetimibe to ongoing atorvastatin therapy, while Simard and Poirier [5] describe two cases of myopathy—one on ezetimibe monotherapy, and the other, again following the addition of ezetimibe to atorvastatin treatment. In these three cases, unlike the case we have described here, no elevation in liver enzymes was recorded, and CPK levels were elevated to about three to four times the upper limit of normal, while all three exhibited muscle pain and weakness. The severe combined myopathy-elevated liver enzyme reaction, which we encountered in our patient, is indeed rare.

This and other cases raise the question of whether ezetimibe increases the risk of statin-associated myopathy or is the direct causative agent. Although this patient illustrates a rare and severe adverse reaction to lipid-lowering drug therapy, we wish to point out the possibility of this potential life-threatening complication. We also suggest that more caution be taken by clinicians when prescribing high dose statins and ezetimibe co-administration, a combination that will probably gain popularity in face of the aggressive race to further lower LDL levels.

References

Correspondence: Dr. E. Zimlichman, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel. Phone: (972-3) 530-2661 Fax: (972-3) 535-2855 email: zimliche@post.tau.ac.il

Capsule

The molecular pathways of tumorigenesis

Knowing which genes are recurrently mutated in cancer cells helps illuminate the molecular pathways that underlie tumorigenesis. In a pilot study, Sjoblom and co-authors sequenced 13,000 protein-coding genes in human breast and colorectal cancers and developed methods for distinguishing harmless sequence changes from causal mutations. Almost 200 candidate cancer genes (CAN genes) were mutated at significant frequency, many of which had not been previously implicated in tumorigenesis. Notably, there was little overlap of CAN genes mutated in breast and colorectal cancers, nor was there substantial overlap in different tumor specimens derived from the same tissue.

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Eitan Israeli

Capsule

Novel antisense drug for inflammatory diseases

BiolineRx Ltd. has signed an exclusive worldwide license agreement with two Israeli technology transfer companies (B.G. Negev Technologies Ltd. of Ben-Gurion University of the Negev, and Mor Research applications Ltd., of Clalit Health Services) for the development and commercialization of BL-3030. This antisense oligonucleotide, specifically designed to treat inflammatory disease, acts by inhibiting cPLA2. Currently, these diseases are treated by non-steroidal anti-inflammatory drugs or steroids, which either have limited therapeutic benefit or produce severe side effects that prevent long-term use. BL-3030 is expected to be efficacious while avoiding these problems. Inflammation is a critical factor in numerous diseases affecting a significant part of the population worldwide. Rheumatoid arthritis, for example, is one of the most common and severe forms of arthritis. It is a chronic and often debilitating autoimmune disease in which the body’s immune system attacks joint tissue, leading to pain, inflammation, deformity and disability that can be permanent.

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