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Case Report

High-Dose Statin Associated with Rhabdomyolysis, Acute Kidney Injury, Cholestatic Liver Injury, and Thrombocytopenia

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Abbreviations ACS: Acute Coronary Syndromes; AKI: Acute Kidney Injury; ALAT: Alanine Aminotransferase; AlkP: Alkaline Phosphatase; ASAT: Aspartate Aminotransferase; CK: Creatine Kinase; GGT: Gama-Glutamyl Transferase; HD: Hemodialysis; HDL-C: HDL cholesterol; LDH: Lactate Dehydrogenase; LDL: Low Density Lipoproteins; LDL-C: LDL Cholesterol; LFT: Liver Function Tests; WUF: With Unknown Frequency

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Abstract

Introduction: Statins are the drugs of choice to reduce cholesterol and the incidence of cardiovascular events. Although rare, the side effects of these drugs may be severe (especially when given in the high doses recommended by the cardiologists), including: muscle damage, renal and liver injury and compromised function, and polyneuropathy.

Case Report: We report a case of statin-induced rhabdomyolysis, acute kidney and liver failure and thrombocytopenia that developed in a 76-year-old man, who was referred to our department because of severe generalized myalgia and muscle weakness, extreme fatigue, loss of appetite, dark brown urine. Following an acute myocardial infarction 8 months previously he was put on atorvastatin 80 mg once daily. Laboratory evaluation at presentation revealed much increased levels of muscle enzymes, aminotransferases, total and conjugated bilirubin, and nitrogenous waste products, and low platelets. A diagnosis of acute renal and liver failure secondary to the long-term intensive statin therapy was made. Atorvastatin was discontinued and forced alkaline diuresis was started. After five days of oliguria and slight but persistent increase in creatinine levels dialysis was initiated, but discontinued after 4 sessions, once urine output increased. At discharge the patient's serum creatine kinase level was in the normal range, creatinine was significantly decreased the thrombocyte count was better, aminotransferase were much lower but not completely normalized, but the bilirubin remained at the same level. The patient was discharged and instructed to avoid any potentially nephrotoxic and hepatotoxic drugs until next outpatient evaluation.

Conclusions: Our case report is meant to raise concerns about prescribing high dose statins. Unfortunately the prescribing cardiologists may be insufficiently aware of the potential for severe adverse effects as these come to the attention of clinicians from different specialities, especially nephrologists.

Introduction

Statins are the most effective and widely prescribed drugs currently available for the reduction of low-density lipoprotein cholesterol, revolutionizing the treatment of hypercholesterolemia and the management of patients with increased cardiovascular risk. Using statins for primary and secondary prevention of cardiovascular diseases has become commonplace and lipid-lowering therapies have become more intense in compliance with the more aggressive targets set by the trials demonstrating their safety and efficacy in high-risk patients, such as: HPS(Heart Protection Study of cholesterol lowering with simvastatin) [1], AVERT (Atorvastatin versus Revascularization Treatment) [2], PLANET I and II (renal effects of atorvastatin and rosuvastatin in proteinuric patients with and without diabetes) [3]. Although the beneficial effect of the statins is a fact, one cannot ignore their side-effects, ranging from benign and asymptomatic to severe and organ-threatening (jeopardizing especially liver and kidney function). Serious adverse reactions associated with statin treatment include: muscle damage, renal failure, liver dysfunction, and polyneuropathy.

This article describes a case of rhabdomyolysis, acute renal and liver failure and thrombocytopenia, due to long-term intensive lipid-lowering therapy with a target LDL cholesterol (LDL-C) value <70 mg/dl in a patient with very high cardiovascular risk.

Case Report

A 76 year-old white man presented to the hospital emergency department with complaints of severe generalized myalgia and muscle weakness, with difficulty in an assuming upright posture from sitting position and difficulty in walking for the past week. These symptoms were accompanied by a reported paroxysmal dyspnoea and extreme fatigue for 2 days.

His medical history included type 2 diabetes mellitus, hypertension, atrial fibrillation, ischemic stroke and coronary artery disease with myocardial infarction (8 months earlier). His current

Table 1: Blood chemistry evolution.

	Day 1	Day 7	Day 12	Day 17
White blood cells [/μL]	6800	8100	9300	5800
Hemoglobin [g/dL]	14.2	12.9	9.5	9.6
Platelets [/μL]	64,000	74,000	57,000	82,000
Serum glucose [mg/dL]	314	180	149	132
Serum creatinine [mg/dL]	4.57	6.61	3.93	2.85
Serum urea [mg/dL]	108.6	257	118	101
Creatine kinase [IU/L]	24432	2055	251	108
Creatine kinase MB [IU/L]	512	104	27	23
Aspartate aminotransferase [IU/L]	1856	573	181	77
Alanine aminotransferase [IU/L]	1183	892	391	170
Serum total bilirubin [mg/dL]	4.2	4.56	4.5	4.18
Serum conjugated bilirubin [mg/dL]	3.2	3.86	3.7	3.13
Serum sodium [mEq/dL]	137.5	133	140	145
Serum potassium [mEq/dL]	4.1	3.4	3.1	3.8
Alkaline phosphatase [IU/L]	150	–	110	–
Gama-glutamyltransferase [IU/L]	779	–	243	–

medications consisted in atorvastatin (80 mg),aspirin (75 mg, which is the most widely available and commonly used dose of antiplatelet aspirin in our country, not the 81 mg dose), clopidogrel (75 mg), rivaroxaban (15 mg), bisoprolol (5 mg), candesartan (16 mg), isosorbide mononitrate (40 mg), pantoprazole (40 mg), gliclazide (30 mg) daily. He had been under treatment with atorvastatin 80 mg for about 8 months.

No information was available about the level of LDL-C at the beginning of atorvastatin therapy. In the medical documents from cardiology only total cholesterol of 147 mg/dl, HDL cholesterol (HDL-C) of 48 mg/dl, andtriglycerides of 133 mg/dl were mentioned. However, we should stress out that the patient had already been taking simvastatin (in an unspecified dose and for an unspecified time interval) when presenting at cardiology 8 months previously. After the myocardial infarction, the cardiologist decided to change the cholesterol-lowering therapy from simvastatin to high-dose atorvastatin.

Physical examination showed jaundice, right upper quadrant tenderness, enlarged liver (lower margin 5-6 cm below the right costal margin), and firm in consistency, enlarged spleen (lower pole 3 cm below the left costal margin). The patient was confused and his vital signs were temperature 36.5°C, pulse 80 beats per minute, dysrhythmic, blood pressure 200/100mmHg, and respirations 20 breaths per minute. Neurologic examination showed 2/5 power in all four limbs and muscle tenderness. His urine was dark brown and turbid.

Laboratory evaluation at admission revealed severe thrombocytopenia, a dramatic increase in serum muscle enzymes levels [Creatine Kinase (CK) 24432 IU/L, creatine kinase MBfraction 512 IU/L, Lactate Dehydrogenase (LDH) 1653 IU/L)], markedly elevated transaminase levels [Aspartate Aminotransferase (ASAT) 1856 IU/L, Alanine Amino Transferase (ALAT) 1183 IU/L] and cholestatic changes [Alkaline Phosphatase (AlkP) 150 IU/L, Gama-Glutamyl Transferase (GGT) 779 IU/L, total bilirubin 4.2 mg/dl, conjugated bilirubin 3.2 mg/dl)] and severe deterioration of renal function (creatinine 4.57 mg/dl, urea 108 mg/dl). Urine analyses showed hematuria and proteinuria >1g/24h. Ultrasonography endorsed the liver and spleen enlargement detected on physical examination. Expectedly, lipid levels were low: total cholesterol = 90 mg/dl, HDL-C = 11 mg/dl, LDL-C = 54 mg/dl, triglycerides = 123 mg/dl.

Suspecting statin-related rhabdomyolysis, atorvastatin was discontinued and intravenous fluids (saline), alkalinization (sodium bicarbonate) and diuretics (furosemide) were started with the aim of limiting tubular myoglobin deposition. The CK level gradually decreased over the next 6 days, but the patient failed to maintain an adequate urine output of >30 ml/hr, lab tests showing worsened in renal function (creatinine 6.77 mg/dl, urea 243 mg/dl). Hemodialysis (HD) was initiated. After 4 sessions of HD, the urine output gradually increased reaching more 120 ml/hr, serum creatinine stabilized at 3.2 mg/dl and renal replacement therapy was stopped. The patient's symptoms and laboratory test values progressively improved throughout his hospital stay, except for jaundice and bilirubin level (reflecting hepatic injury), despite declining cholestatic enzymes levels. On discharge, 17 days after admission, serum CK level was in the normal range, creatinine 2.85 mg/dl, urea 101 mg/dl, ASAT 68 IU/L, ALAT 134 IU/L, total bilirubin 4.18 mg/dl, conjugated bilirubin 3.13 mg/dl, as shown in table 1. The patient was instructed to avoid potentially nephrotoxic and hepatotoxic drugs until next outpatient evaluation.

Discussion

Robust evidence showed that lowering LDL-C with a 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitor (statin) decreases cardiovascular mortality and morbidity when employed as both primary and secondary prevention strategy. Recent trials have supported early intensive statin therapy as the standard treatment for very high-risk patients [such as those with Acute Coronary Syndromes (ACS)] and the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines have set a value of <70 mg/dl as the therapeutic goal for LDL-C [4]. Other authors believe that patients with an ACS should have their LDL-C lowered to approximately 50 mg/dL (1.3 mmol/L) [5]. On the other side, post hoc multivariable analysis of the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial failed to prove the utility of treating individuals with baseline LDL-C <66 mg/dl, suggesting it as the threshold at which the zenith of clinical benefit is reached, not to be surpassed by any supplementary decrease in LDL-C [4]. There are still controversies regarding the impact of baseline LDL-C on the clinical benefit of lipid-lowering therapy, but the current recommendation for ACS patients not already treated with a statin is to start a statin at high dose (80 mg of atorvastatin or 20 to 40 mg of rosuvastatin daily), irrespective of the baseline LDL-C, and to maintain it indefinitely [5].

Among the different types of statins, atorvastatin has been reported to be more effective in decreasing total cholesterol, LDL-C and triglyceride levels than other HMG-CoA reductase inhibitors. In patients with coronary heart disease, atorvastatin was superior to other statins (such as lovastatin, pravastatin, fluvastatin, and simvastatin) in decreasing LDL-C to the desired target. Indeed, under

high doses of atorvastatin LDL-C plummets to very low levels [6]. In a well-designed more than 3000 strong trial (MIRACL), the decrease in LDL-C to 1.9 mmol/L (in ACS patients receiving atorvastatin 80 mg/day for 16 weeks) was reflected in significantly fewer combined primary end-point events as well as fewer hospital admissions for recurrent ischemic events [7]. In the AVERT trial, aggressive lipid-lowering therapy with atorvastatin 80 mg/ day for 18 months at least equalled coronary angioplasty and usual care in decreasing the incidence of ischemic events in low-risk patients with stable coronary heart disease [2,7]. More recently PLANET I and II studies proved the ability of high dose Atorvastatin (but not of Rosuvastatin in either low or high dose) to lower proteinuria [3].

In accordance with the European Society of Cardiology Guidelines for the Management of Dyslipidaemias [8] our patient is a very high risk patient (cardiovascular disease clinically documented by previous myocardial infarction) and should therefore receive statin therapy with the aim to reduce LDL-C below 70 mg/dL (1.8 mmol/L) or by at least 50% if the baseline is between 70 and 135 mg/dL (1.8 and 3.5 mmol/L). The only statins able to decrease LDL-C more than 40% are rosuvastatin and atorvastatin in doses of at least 20 mg per day [9] and the only one able to reduce proteinuria (a much desired goal in a diabetic patient) is atorvastatin 80 mg per day. This was probably the rationale for the 80 mg/day dose of atorvastatin prescribed to our patient by the cardiologist: lipid-lowering treatment consistent with the guidelines for acute myocardial infarction and intensive statin therapy given the high cardiovascular risk of his condition [10-12].

Nonetheless, the potential for adverse events of statin treatment should not be lost from view: myopathy (resulting in sore, tender, stiff, functionally declining muscles), liver toxicity (abdominal pain, jaundice), acute kidney injury (AKI) [11,13]. Interestingly several signs/ symptoms may have multiple substrates: weakness may be explained by both muscle and liver pathology, the dark-colored urine may be dark-brownish when due to the myoglobinuria of rhabdomyolysis or rather dark-yellowish in cholestatic liver disease, while both liver and kidney injury may explain, if severe enough, the appetite loss. Not even central nervous system seems to be spared by the statins' pleomorphic toxicity: the forgetfulness and/or "fuzzy" feeling some patients are complaining about are interpreted as possible signs of cognitive deterioration secondary to statin therapy [14].

Beside the more wide-spread use of the higher doses, the risk of adverse events may also be increased as a consequence of drug interactions [11]. The risk of statin toxicity is higher in patients co-medicated with a drug altering statin metabolism by inhibiting or competing for the involved enzymes [15,16]. Two or more different substrates may compete for the same metabolizing enzyme leading to protracted inactivation and hence increased likelihood of toxicity. In our patient there were three drugs (atorvastatin, clopidogrel, rivaroxaban) jostling each other on the catalytic sites of the same hepatic enzyme (CYP450 3A4). The result may have been delayed metabolism of atorvastatin [17].

The risk for developing muscle injury during statin treatment seems to be influenced by both non-modifiable factors such as advanced age, and modifiable factors including general debility, multisystem diseases (such as diabetes), and polypharmacy [15] – our 76 years old diabetic on multiple medications met all these factors.

Skeletal muscle necrosis, alias rhabdomyolysis, results in sarcoplasm content spilling out into systemic circulation, leading to CK plasma levels in excess of10-25 the upper limit of normal (which may be used as diagnosis criterion, regardless the renal function), accompanied or not by symptoms. Aching muscles, weakness, and brown urine constituted the classical triad of rhabdomyolysis [15], accompanied by elevated enzyme (CK reaching up to extremely highlevels such as 50,000 and beyond), electrolyte disorders, and AKI [18]. The latter may be the consequence of prerenal as well as renal mechanisms; the most characteristic being acute tubular necrosis secondary to the direct tubular toxicity of myoglobin associated with tubular obstruction by myoglobin casts [19]. Decreased renal blood flow results from an increase in the volume of circulating blood redirected to the damaged skeletal muscle.

The incidence of AKI after high-dose atorvastatin suggested by the large controlled studies is about 1% [3]. No definite conclusions can be drawn from the mishap of one patient, but the clinician experiencing such a case becomes understandably reluctant to prescribe such doses.

Among the various statins, simvastatin was the most frequently reported as engendering muscle injury, usually at high doses (40 mg/day). The second place goes to atorvastatinin surprisingly low doses of 10 mg/day [15]. A characteristic shared by most reported cases of myopathy associated with statins was co-treatment with one or more other drugs [15,20]. This information (and its putative implications) should be taken with a grain of salt, because, although it might seem sensible to assign at least some of the statin toxicity to the interaction with these other drugs, one should keep in mind that most of the patients eligible for statin therapy have serious reasons to be prescribed other medications especially for cardiovascular and metabolic conditions.

Our patient presented to the hospital one week after the onset of the symptoms. We cannot be certain when the toxic effects really had started – it may have been weeks (rather than months) before becoming symptomatic. Although many (but not necessarily most) patients who develop statin-related adverse events do so relatively soon after starting the statin, many others still are slower in developing such side effects (the muscle symptoms may be noticed years into the statin therapy) [21], the acknowledged range of the delay being a few weeks to more than 2 years [22]. Therefore a latency interval of 8 (or maybe 7) months, as was the case in our patient, is not at all unheard of.

Altered Liver Function Tests (LFT) is another adverse reaction commonly found during statin therapy. Nevertheless there are very few reports of liver failure directly attributed to statins. This may be because clinicians, being aware of possible liver toxicity, monitor LFT and stop treatment when abnormalities in the LFT occur [23]. However routine LFT monitoring is not currently recommended because of the rarity of significant statin-induced liver injury [24]. Increased transaminases levels as enzymatic markers of liver toxicity occur in approximately 1 to 3% of the statin-treated patients and in some cases the liver injury is more serious [25]. Although rare, statin-induced idiosyncratic hepatopathy can be severe [26].

Statins seem to be responsible for about 1 to 3% of all cases of drug-induced liver injury [25]. In a comprehensive study about drug-related hepatotoxicity, statins were incriminated in about 1% [8] of

the cases, with numerically equal distribution between simvastatin and atorvastatin (an equality difficult to interpret in the absence of data regarding the relative proportion of patients prescribed each of the two statins). Remarkably, two of the eight cases progressed to extremely severe liver injury leading to death in one case and to liver transplant in the other [27]. Among the drugs incriminated for severe liver injury leading to acute liver failure, the proportion of the statins seems to be even higher (6 out of 133 cases, again with equal distribution between simvastatin, atorvastatin and cerivastatin) [28]. An autoimmune mechanisms (suggested by high ANA) seems to be involved in some cases, and an idea corroborated by several other researchers [29,30]. Autoimmune hepatitis was reported to be triggered by simvastatin and by (no longer used) cerivastatin [28] or by atorvastatin in a genetically predisposed individual [31] or revealed by atorvastatin [32] or by rosuvastatin [33].

Expectedly, the higher doses (40-80 mg) are more likely than the lesser ones (10-20 mg) to determine liver injury [25] which might suggest a toxic/ cumulative rather than allergic mechanism. Atorvastatin seems to be more toxic than simvastatin especially at higher doses [25].

The increase in muscle enzymes attributed to muscle injury includes, besides CK (the most characteristic one), the transaminases, especially ASAT (in almost 95% of rhabdomyolysis cases), which has both a cytosolic and a mitochondrial form and is found in the muscle (skeletal and cardiac), as well as in liver, pancreas, kidney, and brain. By contrast ALAT has a more restrictive distribution, dwelling mostly in the cytoplasm of the liver cells; consequently, it is increased in only three out of four patients with damaged muscles [34,35]. The dynamic of the two enzymes is also different, paralleling that of CK in the case of ASAT, but not in the case of ALAT [35]. Given the uncertain origin (muscle or liver) of the elevated transaminases, they cannot be taken as a marker of hepatic injury per se in cases of rhabdomyolysis [35], leaving serum bilirubin level as the most reliable indicator of liver damage [36] especially in association with increased cholestatic enzymes. In our patient, the clinically detected (and ultrasonographically confirmed) hepatosplenomegaly associated with the elevated serum bilirubin level made us reasonably confident in asserting the harmful effect on the liver of the high-dose statin.

Several researchers reported a cholestatic pattern in association with the liver injury caused by atorvastatin [37-40]. Indeed, atorvastatin induces more frequently cholestatic liver injury [41] (as was the case in our patient given the elevations in conjugated bilirubin and cholestatic enzymes), which may be severe enough to become subjectively and objectively apparent (jaundice and itching) [42]. By contrast, simvastatin provokes more often hepatocellular injury [43]. The liver damage associated with atorvastatin, varying from a mere cholestatic pattern to frank hepatocytolysis and including the inbetween range of mixed pictures [41], may become sufficiently serious to result in death, although this is an uncommon occurrence: there were four reported deaths in 8 years in UK [44]; during a 3 years period, one centre reported seven patients with significant statin-elicited liver injury, including one fatality in a patient on atorvastatin [44].

Acute hepatotoxicity secondary to atorvastatin is quite a rare event. However any ensuing abnormalities in LFT should be carefully considered, especially if persistent [44].

The time interval until the onset of liver injury may be weeks to months to years even [41] (some sources indicate an average of 9 weeks [44], others a median of 3-4 months [43]), but is generally 6 months or less [41] and most liver abnormalities usually occur in the first 3 months of treatment [22]. Regrettably, we cannot be sure when this adverse reaction started in our patient. The resolution of the cholestatic picture after drug withdrawl may be protracted (a couple of months in one of the reported cases [45]), lagging well behind that of rhabdomyolysis, a feature also present in our case.

Interestingly, despite this propensity to induce hepatobiliary injury, attempts have been made to use atorvastatin for hepatobiliary diseases, although with limited success. It was tried in primary biliary cirrhosis we the aim or alleviating cholestatis, but resulted in statistically significant increases in AlkP (but not in GGT) and also elevate transaminases levels in several patients [46]. Nevertheless it might be useful in alcoholic steatohepatitis, where it significantly lowered transaminases [47] and GGT by mitigating inflammation (as reflected by a drop in tumour necrosis factor-α) [48]. More interestingly yet, the same inflammation-averting effect (as indicated by a decrease in the adhesion molecules) was noticed in the arterial atheromatous plaques, this time associated with a fall in the GGT level, nowadays accepted as a cardiovascular risk factor [49].

Another characteristic of our patient was thrombocytopenia, for which a plausible (but rather far-fetched) explanation might be the hepatopathy-associated hypersplenism, a hypothesis made more credible by the spleen enlargement is present in our patient taken into consideration. However thrombocytopenia may be a side effect of the statins – a rare one, but sometimes quite severe. Only a handful of reported cases may be found in the literature [50-54]. On the other hand statins impair coagulation by interfering with platelet aggregation, adhesion, and activation both indirectly by modulating nitric oxide synthase activity, and by direct platelet inhibition [52].

Table 2: Frequency of the relevant side effects of the other drugs our patient was taking ("w.u.f." = with unknown frequency).

	Myalgia	Rhabdomyolysis/ elevated CK	Elevated ALAT, ASAT	Cholestasis	Liver failure	Renal dysfunction	Thrombocytopenia
Bisoprolol	w.u.f.	-	w.u.f.	-		-	rare
Candesartan	-	w.u.f.	common/ uncommon	-		common	-
Isosorbide mononitrate	very rare	- (myositis)	w.u.f.	-		-	w.u.f.
Pantoprazole	rare	w.u.f.	common	very rare	very rare	very rare	very rare
Clopidogrel	w.u.f.	-	w.u.f.	-	w.u.f.	w.u.f.	rare
Aspirin	-	w.u.f.	hepatotoxicity w.u.f.	w.u.f.		with high doses	rare
Rivaroxaban	-	-	common	rare		common	rare

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All the side effects we attributed to atorvastatin have been actually described in relation with quite a few of the other drugs our patient was taking [in the parentheses after each drug we've mentioned the frequency with which the particular side effect is occurring in that particular drug; if unknown, "W.U.F" (with unknown frequency) was mentioned] [55-61] (Table 2):

1. Elevated transaminases with: bisoprolol (slight increases are common but abate despite continued administration of the drug and are probably due to the underlying condition of the patient, more severe increases are rare), candesartan (ALAT common, ASAT uncommon), isosorbide mononitrate (w.u.f.), pantoprazole (common), clopidogrel (hepatitis w.u.f.), aspirin (hepatotoxicity w.u.f.), rivaroxaban (common);
2. Cholestasis with: pantoprazole (rare to very rare), aspirin (cholestatic hepatitis w.u.f.), rivaroxaban (rare);
3. Liver failure with: pantoprazole (very uncommon), clopidogrel (w.u.f.);
4. Thrombocytopenia with: bisoprolol (rare, not clinically significant), isosorbide mononitrate (w.u.f.), pantoprazole (very rare), clopidogrel (rare), aspirin (rare), rivaroxaban (rare);
5. Muscle pain with: bisoprolol (pain or weakness probably due to decreased cardiac output and diminished muscle perfusion), isosorbide mononitrate (very rare), pantoprazole (rare), clopidogrel (w.u.f.);
6. Rhabdomyolysis/ elevated muscle enzymes with: candesartan (w.u.f.), isosorbide mononitrate (myositis w.u.f.), pantoprazole (w.u.f.), aspirin (w.u.f.);
7. Renal dysfunction with: candesartan (common), pantoprazole (interstitial nephritis is very rare, but may progress to renal failure), clopidogrel (glomerular disease with renal dysfunction w.u.f.), aspirin [renal dysfunction (due to decreased glomerular perfusion in the absence of the vasodilatory prostaglandins) is reported in patients given high doses, not the tiny cardiac doses], rivaroxaban (renal dysfunction is common, aside from the acute impairment induced by the hypotension provoked by a massive bleeding);

No other drug can account for all the side effects our patient experienced, with the possible exception of Pantoprazole. However, with Pantoprazole most of these side effects are rare or very rare (assuming that "with unknown frequency" means at least "not common"), therefore the combination of all of them in one patient is probably exceedingly rare. There is still the possibility that the side effects were not all the consequence of a single drug, but that several drugs contributed to the picture. This is also rather improbable as all the side effects, but for elevated transaminases and renal dysfunctions are rare or very rare and therefore, again, their combinations in one patient should be quite uncommon.

Regarding the most appropriate course of action in this patient after the adverse effects will have completely remitted; the FDA recommendations are rather drastic: "If an alternate etiology is not found, the statin should not be restarted" [62]. However, the European recommendations are less radical and include starting again the same statin in a lower dose (and carefully increasing the dose aiming to get as close as possible to the target LDL-C without side effects), using a non-daily treatment schedule (such as every other day or two days per week), and trying a different statin [63]. The strategy we intend to apply in our patient includes all these recommendations: first we are going to prescribe again atorvastatin 20 mg per day and closely (say, monthly) monitor liver and muscle enzymes, bilirubin, thrombocytes and kidney function. In the rather unlikely case that the target LDL-C is not reached, we might have a go with the 40 mg per day dose, but we deem this rather hazardous and therefore we plan to switch to rosuvastatin (in agreement with the recommendation of the European Primary Care Cardiovascular Society of choosing "a high-intensity statin with a long half-life" [63]) in a low dose such as 5-10 mg per day [64]. Should this statin-based strategy fail, we will take into consideration alternative lipid-lowering medication, such as bile acid sequestrants, ezetimibe, fibrates, and niacin, alone or in combination, although the evidence about their efficiency in improving the cardiovascular outcome is lacking [64]. Of course a diet change would be ideal, but realistically speaking this is hardly ever the case in our country and relying on the all too easily made promises from the patient would be unduly optimistic if not unsensible.

Conclusion

The incidence of liver and kidney injury induced by high dose atorvastatin may be higher than suggested by the results of randomized controlled studies. One should put in balance the clinical significance of the decrease in albuminuria attributed to the 80 mg per day dose of atorvastatin with the risk of severe kidney (and liver) toxicity, as these aggressive therapy might harm precisely the organ it is supposed to protect. Erring on the cautious side, we might wonder whether at such high-doses serious side-effects are mere isolated, rare incidents or should be rather expected, making mandatory close monitoring of kidney function, liver and muscle enzymes, bilirubin, and even thrombocytes. If done routinely, a tight follow-up of patients given high doses of atorvastatin would bring a better understanding of the real potential for harm of this aggressive cholesterol-lowering therapy and, if higher than presently acknowledged, should alter the prescribing practices accordingly.

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