Statins and Clarithromycin : a dangerous combination. Case report and review of the literature

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Introduction

Statins account for the most prescribed drugs around the world. The number of patients treated by statins is estimated at 17% of the population older than 20 years and more (1). Similarly, *Helicobacter pylori (HP)* infection is also very frequent worldwide and estimated to occur at least one over the life in one third of the population in western countries (2). The treatment recommended for *HP* by the Toronto consensus contains the use of clarithromycin (3). Consequently, the possibility that a patient receives concomitantly clarithromycin and a statin is very high.

Case report

A 81-year-old man was admitted to our Emergency Department for a history of nausea, asthenia and muscle weakness, lasting for one week. He didn't complain of abdominal pain, diarrhea, or fever. Muscle weakness was severe in the proximal parts of lower limbs.

His past medical history included past myocardial infarct treated 20years ago by aorto-coronary by-pass, systemic hypertension and dyslipidemia. No history of alcohol abuse. His medical treatment included bisoprolol 10mg, aspirin 80mg, perindopril 5mg, simvastatin 40mg and spironolactone 25mg. All drugs were taken once a day and simvastatin was taken for many years. Recently, a treatment for *HP* gastric infection has been started and he received the first line quadruple therapy (proton pump inhibitor, amoxicillin, metronidazole and clarithromycin. This therapy ended one week ago.

Usual clinical parameters at admission were as follows: blood pressure 130/80mmHg, heart rate 52/minute, body temperature 35,5°C and oxygen saturation 96%.

At the clinical examination, the patient was icteric. The examination of heart, lungs and abdomen was normal. The palpation of lower limb muscles was painful and bilateral quadricipital paresia was found. The rest of the neurological examination was normal.

Laboratory results are reported in Table 1. A conjugated hyperbilirubinemia and marked elevation of liver enzymes and creatine phosphokinases were noticed (Figure 1).

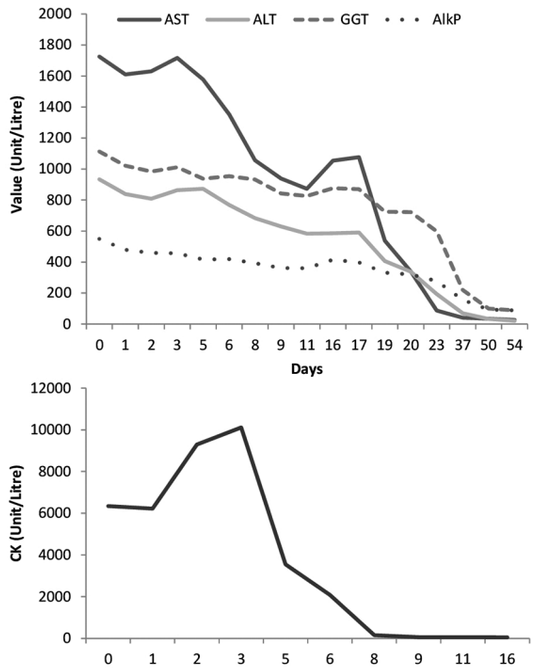

Fig. 1. — **Evolution of the liver enzymes and the creatine phosphokinase. 1.A Evolution of the liver enzymes. Liver enzymes decreased slowly and reached normal values after weeks. ALT : Alanine aminotransferase. AST: Aspartate aminotransferase. G-GT : Gamma-glutamyl transferase. AlkP : Alkaline phosphatase. 1.B Evolution of the level of creatine phosphokinase (CK). The evolution was more rapidly favorable, than the liver enzymes, when the incriminated drugs were stopped.**

Serologies for viral hepatitis (HBV, HCV, HEV, CMV, EBV) and auto-immune hepatitis were all negative at the exception of previous contact with HAV.

Hepatic ultrasonography and MRI were without abnormalities of the liver.

A liver biopsy demonstrated a severe portal and lobular inflammation associated with eosinophilic infiltration.

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Table 1. — **Biological results**

	Admission	*Day one*	*Laboratory reference range*
Hemoglobin (g/dL)	*15.5*		*12.6-17.4*
Hematocrit (%)	*49*		*37-51*
MCV (fl)	*98.7*		*81-103*
Platelets (/nL)	*187*		*150-400*
WBC (/nL)	*6.36*		*4.50-11.00*
Neutrophils (/nL)	*4.07*		*1.51-7.07*
Lymphocytes (/nL)	*1.65*		*0.65-2.80*
Monocytes (/nL)	*0.57*		*0.10-0.82*
Eosinophils (/nL)	*0.06*		*0.00-0.42*
Basophils (/nL)	*0.00*		*0.00-0.16*
INR	*1.1*		*0.8-1.2*
Sodium (mmol/L)	*136*		*132-146*
Potassium (mmol/L)	*5.2*		*3.7-5.4*
Chloride (mmol/L)	*101*		*96-106*
Carbon dioxide (mmol/L)	*22*		*24-30*
Urea (mg/dL)	*70*		*10-50*
Creatinine (mg/dL)	*1.6*		*0.20-1.20*
Total protein (mg/dL)	*68.9*	*63*	*58.0-80*
Albumin (mg/dL)	*9.09*	*32*	*32-46*
Total bilirubin (mg/dL)		*8.16*	*0.20-1.20*
Direct bilirubin (mg/dL)		*8.1*	*< 0.3*
ALT (U/L)	*934*		*< 45*
AST (U/L)	*1725*		*< 40*
Alkaline phosphatase (U/L)	*549*		*40-130*
Gamma GT (U/L)	*1113*		*8-61*
LDH (U/L)	*638*		*< 225*
CK (U/L)	*6343*		*39-308*
CRP (mg/dL)	*8.90*		*< 10*
Alpha1-antitrypsin (mg/dL)		*223*	*72-143*
Ceruloplasmin (mg/dL)		*37.3*	*22-38*
IgA (g/L)		*2.67*	*1.10-3.51*
IgG (g/L)		*11.50*	*6.65-12.36*
IgM (g/L)		*1.04*	*0.51-1.45*
Antinuclear antibody		*Negative*	
Smooth-muscle antibody		*Negative*	
Mitochondrial M2 antibody		*Negative*	
Hepatitis A antibody		*Positive*	
Hepatitis A IgM		*Negative*	
HBs antigen		*Negative*	
HBs antibody (mUI/mL)		*743*	
HBc antibody		*Positive*	
Hepatitis C antibody		*Negative*	
EBV IgG		*> 750*	
EBV IgM		*Negative*	
CMV IgM		*Negative*	
HIV		*Negative*	

MCV : mean corpuscular volume. WBC : white blood cells count. INR : international normalized ratio. ALT : Alanine aminotransferase. AST : Aspartate aminotransferase. Gamma-GT : Gamma-glutamyl transferase. LDH : Lactate dehydrogenase. CK: Creatine phosphokinase.

Clusters of ceroid macrophages in the pericentrilobular area were also seen. Fibrosis was observed but not at the stage of septal fibrosis or nodularity, probably the result of submassive necrosis (Figure 2).

A diagnosis of drug induced liver injury (DILI) was made thanks to this histology. The decrease of liver enzymes was slow and the patient was discharged to his home after twelve days. Follow-up at the outpatient clinics was uneventful and the statin were not retried.

Discussion

DILI is a frequent cause of acute hepatitis particularly in elderly patients (4,5). Indeed, older patients are either immunized, either at low risk of viral hepatitis and, overall, they take often several drugs. The diagnosis can be suspected by the history of drug intake and the liver histology as well as by exclusion of other etiologies of acute liver injury (6). Histological features are variable (cholestatic, cytolytic or mixed). The first step is to discontinue the causative agent and, then, to manage the possible complications of hepatic failure. Improvement and healing occur most of the time but this can take several weeks particularly in case of cholestatic injury (6). In some cases, DILI may result in chronic injury of the liver, defined as persistent liver abnormality after one year. Its prevalence is estimated at 8% in the following retrospective study, and occurred especially among old patients, or patients having suffered of DILI induced by statins and anti-infective drugs (7).

Our patient had a clinical history compatible with DILI and at first view, clarithromycin should be suspected as the causative drug. Indeed, clarithromycin has been the only drug recently added to the treatment of the patient and it

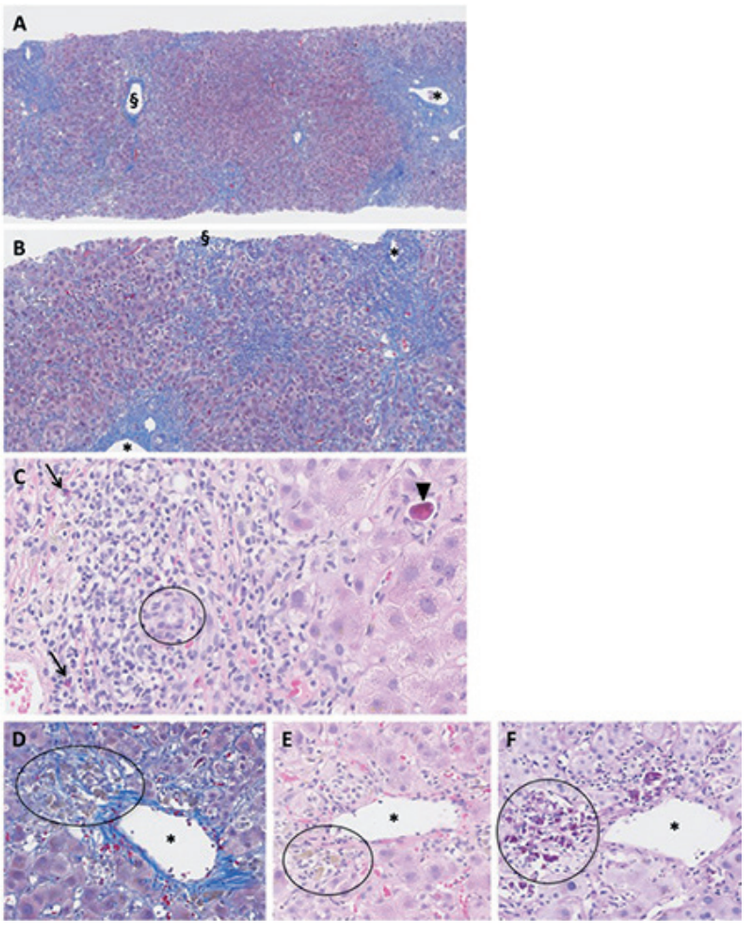

Fig. 2. — **Liver biopsy. 2.A The general architecture was preserved. There was neither septal fibrosis nor nodularity. This indicated a (sub)acute condition. Masson trichrome (MT) staining. 2.B Periportal, pericentrilobular, and pericellular fibrosis was present indicating a subacute condition. MT staining. 2.C Portal tracts showed severe inflammation with mild bile duct damage (circle). We could also observe few eosinophils (arrows) and an apoptotic body (head of arrow). Hemalun eosine (HE) staining. 2.D Pericentrilobular necroinflammation associated with clusters of ceroid macrophages (circle). MT staining. 2.E Central vein showed endotheliitis and pericentrilobular inflammation. Ceroid macrophages are encircled. HE staining. 2.F This PAS-D staining highlights the ceroid macrophages (circle). Portal tracts (*) and central vein (&).**

is recognized as a cause of DILI. A study reported even clarithromycin as one of the top 20 drugs responsible for DILI with a fatal outcome (8). There is no typical pattern of liver enzyme elevation with clarithromycin but it most often results in a cholestatic pattern with clinical jaundice. DILI related to the use of clarithromycin is estimated to happen in around 3.8 per 100.000 prescriptions. The DILI occurs after one to three weeks of treatment but can also occur after the discontinuation of the treatment as in our patient. Some evidences suggest that it results from a reaction of hypersensitivity. In the case of our patient, clarithromycin might not be the only drug responsible for this episode of DILI: simvastatin may have play also a role, even though it was taken for several years. First, simvastatin and other statins are well recognized drugs potentially harmful for the liver (9). Second, a rhabdomyolysis not reported in case of DILI due to clarithromycin was present. Thirdly, the potential toxicity of simvastatin and other statins could be enhanced by the adjunction of clarithromycin. The explanation is that clarithromycin and simvastatin are both mainly metabolized by the microsomal cytochrome P450 system. The interaction between these two drugs at the level of metabolization has been well demonstrated (10). Clarithromycin is a strong inhibitor of the cytochrome P450 3A4 (CYP3A4). Therefore, the concomitant intake of clarithromycin induces a decreased of simvastatin metabolism (also metabolized by the CYP3A4) and then an increased blood level potentially dangerous (10).

We performed an exhaustive review of case reports published in the literature on the interaction between clarithromycin and simvastatin (Table2). The first observation is that all of these cases were focused on rhabdomyolysis. No one of the described patients developed a clinical significant hepatitis. Approximately, the half of the patients developed hepatic enzymology disturbance attributed, in two publications, at the rhabdomyolysis. We were the first to prove by biopsy the existence of a DILI with this drug interaction.

Table 2. — **Review of the cases reported in the literature**

Author (date)	Gender/ age (years)	Patients history	Clarythromycin indication, dose and timing of introduction before admission	Simvastatin dose	Symptoms at admission	Creatinine kinase (peak) and time to normalization	Hepatic enzymology	Complication ?
Lee et al. (2001) [1]	M/64	Protein C deficiency, recurrent deep vein thrombosis, type 2 diabetes mellitus, hypertension, severe CKD, not hemodialysed and gout.	Acute sinusitis. 500mg b.i.d. 3 weeks.	80 mg.	Diffuse severe muscle pain (morphine needed) and weakness.	213.978 U/L. 3 weeks.	ALT 301 U/L, AST 981 U/L. ALkP 128 U/L. Bilirubin, GGT : NS.	- Cardiac arrest on hypocalcemia (day 4). - CVVH (day 6). - Death of infectious complications (day 117).
Stirling et al. (2001) [2]	F/62	Renal transplantation, CABG.	Respiratory. 250mg b.i.d. 20 days.	20mg.	Muscle weakness.	7.500 U/L. NS	NS.	No complication.
Kahri et al. (2004) [3]	M/49	Familial combined hyperlipidemia.	Respiratory. 500mg b.i.d. 4 days.	80mg.	NS.	43.200 U/L. 2 weeks.	NS.	Hemofiltration.
Valero et al. (2004) [4]	M/71	Renal transplanta-tion, hypertension, and chronic anemia.	Respiratory. NS. 14 days.	40mg.	NS.	19.819 U/L. NS.	NS.	No complication.
Chouhan et al. (2005) [5]	M/56	CABG.	Respiratory. 500mg b.i.d. Few days.	40mg.	Difficult motility and muscle pain.	20.000 U/L. NS.	NS.	No complication.
Molden et al. (2007) [6]	M/78	CHD, strokes, atrial fibrillation,	Respiratory. NS. 2 weeks.	80mg.	Myalgia, weakness.	24.547 U/L. 1 week.	ALT 690 U/L, AST 1307 U/L. Bilirubin, AlkP, GGT : NS.	No complication.
Cooper et al. (2009) [7]	F/68	NS psychiatric ilness, neuroleptic malignant syndrome.	Respiratory. 250mg b.i.d. 3 weeks.	80mg.	Confusion, increased muscle tone.	884 U/L. 2 days.	NS.	No complication.
Speck et al. (2008) [8]	M/62	Renal transplantation for IgA nephro-pathy.	*Rhodococcus equi* infection. 250mg t.i.d. NS	40mg.	Subacute bilateral proximal paraparesis.	2.976 U/L. 1 week.	NS.	No complication.
Wagner et al. (2009) [9]	F/77	Not specified. Use of cardiovascular drugs (AAS, sartan, diuretic, beta blocker), anti-diabetic (glibenclamid) and allopurinol.	Infected foot ulcer. 500mg b.i.d. 17 days.	20mg.	General weakness and unability to walk.	19.486 U/L. 2 weeks.	ALT 405 U/L, AST 600U/L. Bilirubin, AlkP, GGT : NS.	No complication.
Arnold et al. (2010) [10]	F/88	Ischemic, hypertensive and rhythmic cardiopathy, hypoparathyroidism and stroke.	Respiratory. NS. 10 days.	40mg.	Myalgia, muscle weakness and inability to walk.	11.126 U/L. NS.	ALT 315 U/L, AST 377 U/L. Bilirubin, AlkP, GGT : NS.	No complication.
Page et al. (2014) [11]	F/83	COPD, ACS, CABG, hyperpara-thyroidism.	Respiratory. 250mg b.i.d. increased at 500mg b.i.d. 1 month.	80mg.	Diffuse muscle pain and bilateral leg weakness.	23.246 U/L. 8 days.	ALT 328 U/L. GGT 70U/L. Bilirubin, AST, AlkP : NS.	No complication.

Hill et al. (2015) [12]	M/68	Hypertension, CKD (stage 3a), gastro-oesophageal reflux disease, thrombo-penia of unknown origin.	*Mycobacterium marinum* infection. NS. 5 weeks.	40mg.	Diffuse muscle pain and progressive proximal myopathy.	216.440 U/L. NS.	NS	- CVVH at the intensive care unit (ICU). - 12 hemodialysis sessions after ICU discharge.
Current case	M/81	ACS, CABG, hypertension, right carotid endarteriectomy.	*Helicobacter pylori* infection. 500mg b.i.d. 14 days.	40mg.	Muscle weakness (quadriceps) and nausea/vomiting.	10.108 U/L. 2 weeks.	ALT 934U/L, AST 1725 U/L. GGT 1113 U/L, AlkP 549 U/L. Bilirubin 9.09 mg/dL.	No complication.

ACS : acute coronary syndrome, AlkP : alkaline phosphatase, ALT : alanine aminotransferase, AST : aspartate aminotransferase, b.i.d: two times daily, CABG : coronary artery bypass grafting, CHD : coronary heart disease, CKD : chronic kidney disease, COPD : chronic obstructive pulmonary disease, CVVH : continous venovenous hemofiltration, GGT : gamma-glutamyl transferase, NS: not specified, SVT : supraventricular tachycardia, t.i.d.: three times daily.

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The statin induced rhabdomyolysis can occur even after the discontinuation of the treatment and also at low dosages of these drugs.

Most of the time there were no complication. Acute kidney injury needing renal replacement therapy was seen in three of these patient. Two of these three patients had already a chronic renal failure.

Interestingly, three of the patients were had a renal transplant and therefore, treated by cyclosporine. It is important to notice that cyclosporine is also an inhibitor of the CYP3A4.

Conclusion

In conclusion, as illustrated by this case report, the association between clarithromycin and simvastatin is a dangerous one. We estimated that this case warranted to be reported because of the probable high frequency of the association of those two drugs frequently used and because it was our feeling that the harmful risk of this association was largely ignored. As an advice, we could recommend to withdraw temporally the treatment by simvastatin during the treatment by clarithromycin. Another possibility is to replace simvastatin by another statin not metabolized by CYP3A4 (rosuvastatin, pravastatin or fluvastatin).

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