中文題目：以 ezetimibe 成功治療高血脂症於 Statin 不耐性之吉伯特氏症病患-病例報告：

英文題目：Successful treatment of hypercholesterolemia with ezetimibe in a statin-intolerant patient with Gilbert syndrome.

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Introduction

Gilbert syndrome, a disorder, influencing the metabolism of bilirubin due to reduction 10-30% of the enzyme activity, is responsible for conjugation of bilirubin with glucuronic acid. It is one of the most common causes of unconjugated hyperbilirubinemia. The enzyme called Uridine Diphosphoglucuronate (UDP)-glucuronosyltransferases(UGTs) is encoded by the gene uridine diphosphoglucuronate-glucuronosyltransferase 1 A1 (UGT1A1). Recurrent asymptomatic jaundice triggered by some specific condition is the typical manifestation. Since the enzyme UGTs, being responsible for conjugation of bilirubin, was also found to be partially involved in the metabolism of statins, patient with Gilbert syndrome taking statins had more risks to suffer from decreasing ability to conjugate bilirubin than people who had the baseline of a better function with having bilirubin metabolism and taking statins. This may contribute to the competition of enzyme requirement between drugs and bilirubin. Besides, owing to approximately 80% of ezetimibe is glucuronidated by the UGT in enterocytes, the ability to conjugate bilirubin in hepatocytes was not interrupted significantly. We reported the successful treatment of hypercholesterolemia with ezetimibe in a statin-intolerant patient with Gilbert syndrome.

Presentation of Case

A 38 year-old man was presented to the gastrointestinal outpatient clinic in this hospital in Sep. 2019 owing to hyperbilirubinemia with unknown cause being noted. The patient has had underlying disease of pre-diabetes mellitus, moderate fatty liver and hyperlipidemia under rosuvastatin 5mg use per day since Apr. 2019. The alcohol was only used at social event. Smoking and illicit drugs history was negative. There were no known drug allergies. He denied any discomfort noted. According to his record in 2018, the plasma total bilirubin level was 1.9 mg/dL; direct bilirubin level was 0.2 mg/dL; alkaline phosphatase level was 34 U/L; gamma-glutamyl transpeptidase was 35 U/L; alanine aminotransferase level was 35 U/L; aspartate aminotransferase level was 23 U/L; albumin level was 4.6 g/dL. Hepatitis B surface antibody was positive, hepatitis B surface antigen was negative. Blood urea nitrogen level was 13 mg/dL and creatinine level was 0.89 mg/dL. Besides, total cholesterol

level was 273 mg/dL; low-density lipoprotein level was 187 mg/dL;(the LDL level on 2016 showed 202 mg/dL, the LDL level on 2017 showed 181 mg/dL); high-density lipoprotein level was 40 mg/dL; triglyceride level was 228 mg/dL. On physical examination, the weight was 82 kg. He didn't have scleral icterus. The abdomen was non-distended, and no ascites evidence was noted. There was no tenderness when his doctor performed palpation on the whole abdomen, either. The patient didn't have gynecomastia, caput medusae, spider angiomas or flapping tremor. He was alert and oriented. Laboratory tests were arranged in Oct. 2019. The results showed the plasma total bilirubin level was 4.17 mg/dL; direct bilirubin level was 0.8 mg/dL; alkaline phosphatase level was 41 U/L; gamma-glutamyl transpeptidase was 25 U/L; alanine aminotransferase level was 18 U/L; aspartate aminotransferase level was 21 U/L. Albumin level was 5.2 g/dL; haptoglobin level was 86.9 mg/dL. Total cholesterol level was 257 mg/dL; low-density lipoprotein level was 183 mg/dL; high-density lipoprotein level was 42 mg/dL; triglyceride level was 192 mg/dL; HbA1C was 5.6%. Antinuclear antibody (ANA), anti-mitochondria Ab (AMA), anti-Smooth Muscle Antibody (ASMA) were all negative. Ceruloplasmin level was 15.5 mg/dL. Serum thyrotropin(TSH) level was 3.24 uIU/mL; serum free thyroxine (Free T4) level was 1.35 ng/dL; serum thyroid peroxidase Ab (aTPO) level was 13.20 IU/mL; serum thyroglobulin Ab (aTG) level was 10.00 IU/mL. Serum ferritin level was 361 ng/mL. Abdominal sonography showed moderate fatty liver with bright echogenicity, smooth surface and normal margin. Gallbladder, intrahepatic duct and common bile duct were normal without any obstruction presentation.

For this patient's hyperbilirubinemia with indirect type in 2019, we had done survey for it. Anti-HCV antibody checked and history of HBV were all negative. Hyperbilirubinemia related to hepatitis B or C was not likely. Haptoglobin was not elevated, hemolysis related hyperbilirubinemia was not likely. ANA, AMA, ASMA showed negative. The hyperbilirubinemia was not related to autoimmune hepatitis. Ceruloplasmin was between normal limit. Wilson's disease was not considered. TSH and free T4 were not decreased or elevate. Therefore, the decreasing rate of bilirubin conjugation was not related to abnormal thyroid function. Because this patient also had hyperbilirubinemia with indirect type in 2018, Baseline abnormal bilirubin metabolism was suspected. After the survey we had done in 2019, gilbert syndrome was diagnosed after excluded other causes of hyperbilirubinemia. Because of the progression of hyperbilirubinemia in 2019, we have prescribed ezetimibe instead of rosuvastatin since Nov. 2019 on suspicion of statin-related hyperbilirubinemia. The follow up data in July. 2020 showed the plasma total bilirubin level was 2.04 mg/dL; alkaline phosphatase level was 37 U/L; gamma-glutamyl transpeptidase was 35 U/L; alanine aminotransferase level was 36 U/L; aspartate aminotransferase level was 31

U/L; Total cholesterol level was 220 mg/dL; low-density lipoprotein level was 161 mg/dL; triglyceride level was 168 mg/dL. Although we noticed that the bilirubin level mild fluctuation when time passed between 2019 and 2020, we still noted that the level of bilirubin in July. 2020 showed decreased more significantly than the fluctuation degree. The later value became approximately half of the original value collected about one year ago. Besides, follow up laboratory data on July. 2020 showed his serum total cholesterol, and low-density lipoprotein level decreased as we expected.

Conclusion

In the nutshell, viewing all the details of this case, abnormal higher bilirubin level was found after taking rosuvastatin than the abnormal level noted before rosuvastatin taken. This patient was diagnosed with Gilbert syndrome by the establishment of intermittent mild unconjugated hyperbilirubinemia without any symptoms or physical examination abnormal found after excluding other causes of hyperbilirubinemia. We report this case to show that ezetimibe, mostly glucuronidated by the UGT in enterocytes, may successfully treat hypercholesterolemia in a statin-intolerant patient with Gilbert syndrome.

Lab data / Variable	Reference Range	2018 04.16	2019. 10.03	2019 10.18	2019 10.28	2019 11.11	2020 01.30	2020 04.21	2020 07.15
Total bilirubin (mg/dL)	0.2- 1.6	1.9	4.17	2.25		1.89	1.81	1.19	2.04
Direct bilirubin (mg/dL)	0.00 ~ 0.45	0.2	0.8						
Alkaline phosphatase (U/L)	10 - 100	34	41				42	38	37
Gamma-glutamyl transpeptidase (U/L)	4 ~ 60	35	25				50	32	35
Alanine aminotransferase (U/L)	0 - 40	35	18	22		24	30	28	36
Aspartate aminotransferase (U/L)	5 - 45	23	21	21			33	28	31
Albumin (g/dL)	3.7 ~ 5.3	4.6	5.2						
Blood urea nitrogen (mg/dL)	7 - 20	13							
Creatinine (mg/dL)	0.7 - 1.5	0.89					0.95	1.09	0.99
Total cholesterol (mg/dL)	125 - 240	273	216		257		207	204	220
Low-density lipoprotein (mg/dL)	<160	187	158		183	159	152	149	161
High-density lipoprotein (mg/dL)	30 - 70	40			42	37			
Triglyceride (mg/dL)	20 - 200	228	157		192	186	184	218	168
Glucose (mg/dL)	65 - 115	111	91				119	119	113
Hemoglobin (g/dl)	14-18			14.8					
White-cell count (per μl)	4500-11000			5300					
Differential count (%)									
Neutrophils (%)	45%-75%			56.1					
Lymphocyte (%)	20%-45%			34.2					
Monocytes (%)	0%-9%			4.2					
Eosinophils (%)	0%-8%			4.1					
Basophil (%)	0%-1%			1.4					
Platelet count (per μl)	150000 - 350000			293000					
Hepatitis B surface antibody(mIU/ml)	<10	(+)							
Hepatitis B surface antigen (IU/ml)	<0.05	(-)							
Anti-HCV antibody	<1.00		0.13						
Haptoglobin (mg/dL)	30~200			86.9					
Antinuclear antibody (ANA) Anti-mitochondria Ab (AMA) Anti-Smooth Muscle Antibody (ASMA)				(-) (-) (-)					
Ceruloplasmin(mg/dL)	15-30			15.5					
Ferritin (ng/mL)	30 ~ 400			361					
Thyrotropin(TSH) (uIU/Ml),					3.24				

Thyroxine free(Free T4) (ng/dL),					1.35				
Thyroid peroxidase Ab (aTPO) (IU/mL)					13.20				
Thyroglobulin Ab (aTG) (IU/mL).					10.00				