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Case Report: Alirocumab Resistance in a Patient with Arteriosclerotic Cardiovascular Disease and Hepatic Dysfunction

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Alirocumab resistance; Case report; Total cholesterol; Low-density lipoprotein cholesterol

1. Abstract

1.1. Introduction: Patients with Alirocumab resistance has not been confirmed in the current literature.

1.2. Case Report: We reported case of Alirocumab resistance with CAD and hepatic dysfunction for the first time. During Alirocumab lipid-lowering treatment, the patient's LDL-C levels did not decrease at all time points within 2 months.

1.3. Discussion/Conclusion: The temporal relationship and laboratory data support the probability of Alirocumab resistance, and genetic testing is suggested to support diagnosis. Alirocumab decreases LDL levels by blocking the binding of PCSK9 and LDLR. The etiologies of Alirocumab resistance include unidentified high Lp(a) levels, mutations in various of genes, anti-drug antibodies(ADA), and other causes related to lifestyle habits and treatments. Combination therapy with statins and Inclisiran bring more options and therapeutic effect to patients.

2. Introduction

Patients with long-term high levels of cholesterol, especially total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), are at the highest risk of atherosclerotic cardiovascular disease (ASCVD). At present, The proportion of patients with acute coronary syndrome (ACS) on lipid-lowering treatment (LLT) is 94.8%, and the rate of LLT with statins among these patients is 93.1%. However, the lipid-lowering treatment goal attainment rate is only 36.60% [1]. As reported by an 8-year follow-up study, lipid-lowering regimens after cardiovascular events had been in need of optimization, and many individuals were reported having poor adherence to statin therapy or the emergence of some side effects [2].

Alirocumab, as an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9), is a novel lipid-lowering drug. It binds to liver LDL receptor (LDLR) and promotes the degradation of LDLR in the endosomal/lysosomal pathway [3]. Alirocumab can reduce LDL-C level by up to 61 per cent and Lp(a) by up to 26 per cent [4].

Nowadays, Alirocumab has been demonstrated playing an important role in combined lipid-lowering regimen. Patients with ACS have exhibited good adherence and significant reduction of LDL-C level [5]. Based on the results of available studies, very few patients (0.5%) classified as unusual responders [6]. But it hasn't been reported any case of Alirocumab resistance, which is defined as the patient who has LDL-C measurements before and after initiation of Alirocumab , exhibit no changes in LDL-C level at all time points.

In this article, we aimed to represent a 55-year-old woman with ASCVD and hepatic dysfunction who showed no decrease in LDL-C level after the treatment of Alirocumab. She was considered as Alirocumab resistance.

3. Case Presentation

A 55-year-old woman with poor lipid control reported to the department of cardiovascular medicine. Her clinical symptoms and physical examination were normal. In March 2023, based on the history, clinical manifestation and biochemical analysis, she was

diagnosed with coronary artery disease (CAD) and hepatic dysfunction. Patient history of hepatitis or alcohol use causing liver damage were negated. Patient history of hepatitis and alcohol use were negated. Immediately after diagnosis, she underwent coronary arteriography and percutaneous coronary intervention. Simultaneously, her laboratory and aided examination resulted that TC 5.26mmol/L, LDL-C 3.72mmol/L (Figure 1). After taking Rosuvastatin 10 mg PO at bedtime daily for 4 months, the re-examination resulted that TC 2.83mmol/L, LDL-c 2.32mmol/L. After maintaining the original lipid-lowering regimen for 1 month, the patient's Rosuvastatin was discontinued without physician's order. More than 20 days after stopping the medication, the patient had marked elevation of serum cholesterol with TC 6.84mmol/L, LDL-c 4.6mmol/L (Table 1). Soon after that, Alirocumab 75mg i.h. q2w was started on early October 2023, and had been continued for next 2 monthes regularly. The patient had given consent to the treatment of alirocumab for 4 times so far. During new lipid-lowering treatment, the patient accepted re-examination every month, and the results are as shown in Table. Unexpectedly, the levels of TC and LDL-C were elevated shown by the in a recent blood test (Figure 2). Besides, Hepatoprotectors, Clopidogrel, Aspirin, Rabeprazole, Metoprolol were also applied for therapies of CAD and hepatic dysfunction at the same time. Her dietary habit did not increase risk of blood lipids elevation. The operations of hypodermic injection were performed In medical institutions. Now the patient was diagnosed with Alirocumab resistance.

项目	英文缩写	结果	异常提示	参考值	单位
总蛋白	TP	74.0		65.0-85.0	g/L
白蛋白	ALB	42.3		40.0-55.0	g/L
球蛋白	GLO	31.7		20.0-40.0	g/L
白蛋白/球蛋白比值	A/G	1.33		1.20-2.40	
总胆红素	TBIL	11.12		0-23	μmol/L
直接胆红素	DBIL	1.47		0-4	μmol/L
间接胆红素	IBIL	9.65		0-19	μmol/L
丙氨酸氨基转移酶	ALT	145.0	↑	7-40	U/L
天门冬氨酸氨基转移酶	AST	72.0	↑	13-35	U/L
碱性磷酸酶	ALP	106.0		50-135	U/L
γ-谷氨酰基转移酶	GGT	101.0	↑	7-45	U/L
乳酸脱氢酶	LDH	197.0		120-250	U/L
前白蛋白	PA	224.0		100-400	mg/L
总胆汁酸	TBA	9.40		0-13.00	μmol/L
尿素	BUN	4.19		2.60-7.50	mmol/L
肌酐	CRE	54.9		41.0-73.0	μmol/L
尿酸	UA	265.0		155-357	μmol/L
胱抑素C	Cys C	0.99		0.50-1.07	mg/L
估算的肾小球滤过率	eGFR	107		>90	ml/(min·1.73m^2)
钾	K	4.74		3.50-5.30	mmol/L
钠	Na	140.1		137.0-147.0	mmol/L
氯	Cl	104.1		99.0-110.0	mmol/L
碳酸氢根	HCO3	28.2		21.0-31.0	mmol/L
钙	Ca	2.40		2.11-2.52	mmol/L
磷	P	1.14		0.85-1.51	mmol/L
镁	Mg	0.97		0.75-1.02	mmol/L
葡萄糖	GLU	7.68	↑	3.89-6.11	mmol/L
总胆固醇	TC	5.26		2.86-5.98	mmol/L
甘油三酯	TG	2.18	↑	0.56-1.70	mmol/L
高密度脂蛋白胆固醇	HDL-C	1.03	↓	1.29-1.55	mmol/L
非高密度脂蛋白胆固醇	non-HDL	4.23	↑	1.92-3.98	mmol/L
低密度脂蛋白胆固醇	LDL-C	3.72	↑	0-3.36	mmol/L
极低密度脂蛋白胆固醇	VLDL	0.81	↑	0.21-0.60	mmol/L
载脂蛋白A1	APOA1	1.08		1.05-2.05	g/L
载脂蛋白B	APOB	1.26		0.55-1.30	g/L
脂蛋白(a)	LP(a)	829.0	↑	0-300	mg/L
游离脂肪酸	FFA	0.47		0.10-0.77	mmol/L

Figure 1: Patient's first laboratory test results on 2 March 2023

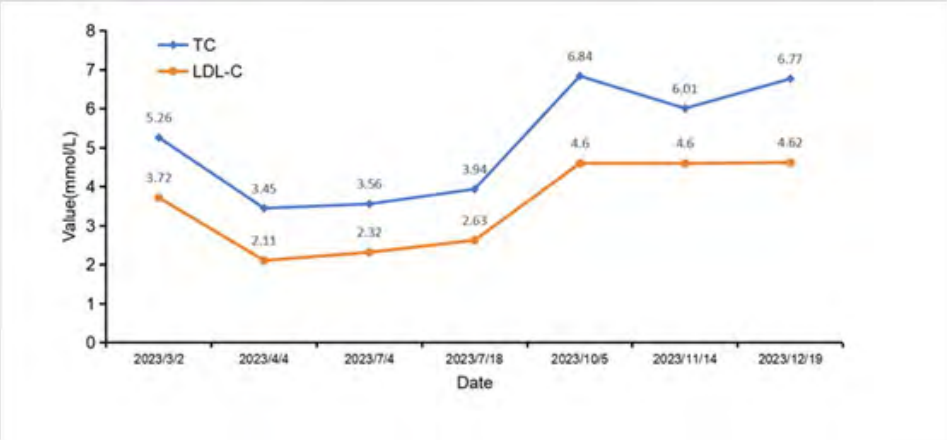

Figure 2: Line graph: Dynamics of total cholesterol and LDL-C in this patient

Table 1: Pertinent labs throughout the whole lipid-lowering treatment

Variable Tested	Date							Reference Range
	2023/3/2	2023/4/4	2023/7/4	2023/7/18	10/5/2023	2023/11/14*	2023/12/19 **	
Alanine aminotransferase (ALT), U/L	145	86	119	80	110	59	96.8	7-40
Aspartate amino transferase (AST), U/L	72	100	74	54	92	54.2	83.2	13-35
Alkaline phosphatase (ALP), U/L	106	101	131	126	109	95.9	91.9	50-135
γ-glutamyl transpeptadase (GGT), U/L	101	88	80	56	57	82.7	71.3	7-45
Glucose (GLU), mmol/L	7.68	6.52	17.32	16.84	6.42	6.2	7.71	3.89-6.11
Total cholesterol (TC), mmol/L	5.26	3.45	3.56	3.94	6.84	6.01	6.77	2.86-5.98
Triglyceride (TG), mmol/L	2.18	3.15	2.83	2.4	4.43	2.9	5.83	0.56-1.70
High density lipoprotein cholesterol (HDL-C), mmol/L	1.03	1.08	1.01	1.04	0.94	1.27	1.3	1.29-1.55
Low density lipoprotein cholesterol (LDL-C), mmol/L	3.72	2.11	2.32	2.63	4.6	4.6	4.62	0-3.36
Very low density lipoprotein cholesterol (VLDL), mmol/L	0.81	1.17	1.05	0.89	1.64	1.07	2.16	0.21-0.60

*Laboratory test results on 14 November 2023 after 4 weeks of lipid-lowering therapy with Alirocumab, **Laboratory test results on 19 December 2023 after 8 weeks of lipid-lowering therapy with Alirocumab

4. Discussion

Alirocumab is one of the monoclonal antibodies of PCSK9. It is also an inhibitor of PSCK9. PCSK9 is a glycoprotein encoded by human PCSK9 gene, after releasing into the extracellular space through the autocleavage process, it binds to the epidermal growth factor-A (EGF-A) domain of LDLR and promotes its degradation in the endosomal/lysosomal pathway [3]. As is the main pathway for LDL clearance, liver LDL receptor (LDLR) can bind and internalize apoB-containing lipoprotein, including LDL, via receptor-mediated endocytosis [7].

According to the latest research, familial hypercholesterolemia(F-H)-phenocopy genes included low density lipoprotein receptor adaptor protein 1 (LDLRAP1), apolipoprotein E (APOE), lipase A (LIPA), ATP-binding cassette (ABC) transporters G5 (ABCG5) and G8 (ABCG8). Meanwhile, polygenic hypercholesterolemia and hyper-Lp(a) can also mimic a clinical FH phenotype [8].

Alirocumab achieves decreasing LDL levels by blocking the binding of PCSK9 and LDLR and indirectly reducing of LDLR degradation. Unusual responder is defined as the individual undergoing

lipid lowering therapy whose LDL-C level decreases by less than 30%. No response, delayed response, reduced response and lost response are included [9,10]. Previous studies demonstrated that unidentified high Lp(a) levels, mutations in LDLR and mutations in FH-phenocopy genes would cause Alirocumab resistance [9,11].

Meanwhile, there are also other influencing factors that affect the efficacy of Alirocumab: 1. drugs simultaneously applied with effect for serum cholesterol levels; 2. high-fat diet; 3. standardization of injection operation; 4. poor adherence of statins/PCSK9 inhibitor therapy; 5. therapeutic plasma exchange after the injection of Alirocumab; 6. the presence of Anti-drug antibodies (ADAs).

We excluded the possibility based on the consultation results that abnormal levels of cholesterol was caused by the influencing factors listed above. The patient we reported hasn't shown reduction in LDL-C at all time points within 2 months of LLT, which meets the definition of Alirocumab resistance. Because of the unidentified high Lp(a) levels, the patient's plasma PCSK9 levels needs further assessment for pathogeny analysis. Genetic testing has also been considered. The reasons of long-term hepatic dysfunction may contain the use of Rosuvastatin. Another concern is that abnormality of liver LDLR is also an influencing factor of Alirocumab resistance.

In recent years, due to the widespread use of Alirocumab in the clinic, more and more patients with CAD are found of poor response to or even resistance to Alirocumab.

Enhancement of statin combination therapy is something that needs to be emphasize. More importantly, lipid-lowering drugs for different targets are also of interest. Inclisiran is a novel siRNA therapy that inhibits the synthesis of PCSK9 by targeting the PCSK9 mRNA, as a result, it reduces LDL-C levels in the blood of patients [12]. Safety and tolerability of inclisiran for treatment of hypercholesterolemia is approved [13]. Inclisiran brings more options to patients with CAD, hepatic dysfunction and renal insufficiency.

5. Conclusion

This article reports a case of a patient with CAD and hepatic dysfunction who is diagnosed with Alirocumab resistance. The basis for the diagnosis is discussed, and the next steps in diagnosis and treatment are planned. It also provides ideas for diagnosis of Alirocumab resistance in future clinical settings, which has implications for further validation and research.

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