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Research Article

Lomitapide: A Medication Use Evaluation and a Formulary Perspective

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ABSTRACT

Introduction: Lomitapide is approved for lowering low-density lipoprotein cholesterol (LDL-C) in homozygous familial hypercholesterolemia, which is a rare genetic disorder. The evidence regarding its safety and efficacy from a small clinical trial requires further validation for effectiveness and safety in the real world. This study aimed to use institutional data on the effectiveness and safety of lomitapide to assist in formulating a perspective on adding it to the formulary. **Methods:** This was a retrospective review of patients who were actively prescribed lomitapide at King Abdulaziz Medical City, Riyadh, Saudi Arabia, from 2019 to 2022. Data collection included demographics, confirmed gene mutation results, duration of lomitapide therapy, baseline, on-treatment, last LDL-C levels, percent reduction in LDL-C after 1-3 months of therapy (whichever was first available), other LDL-C lowering therapies used, liver function tests, adverse effects, and compliance. **Results:** Eight adult patients were included in the review, with a mean age of 25.5 years. Approximately 75% were female, and the duration of treatment with lomitapide ranged from 9 months to 3 years. None of the patients were on continuous LDL apheresis. The mean baseline LDL-C at presentation to our facility was 17.2 mmol/L (range, 11.78–21.97 mmol/L), the mean percent drop in LDL-C with lomitapide was 34.1% (range, 0%–87%), gastrointestinal disturbances were documented in 50% of the patients, and no cases of severe liver toxicities or increase in liver enzymes were seen. **Conclusions:** In our cohort of adult patients, lomitapide showed an overall modest reduction in LDL-C, with no cases of increase in liver enzymes and documented intolerance, indicating that most patients were likely noncompliant. This review revealed important considerations when reimbursing expensive medications for rare diseases. Real-world evidence in real-time can support healthcare systems in price negotiations and reaching mutual agreements that can eventually improve patient access to care.

Keywords: lomitapide, homozygous familial hypercholesterolemia, rare disease, pharmacoeconomic, formulary

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disease characterized by an extremely elevated low-density lipoprotein cholesterol (LDL-C) level, usually above 8 mmol/L. These patients have a higher baseline risk of early-onset atherosclerotic cardiovascular disease (ASCVD) than the general population.[1] Diagnosis is typically confirmed by evidence of a functional mutation in one of the three following known genes, which impairs the catabolism of LDL-C: *LDLR*, *PCSK9*, or *APOB*. Clinical features may include tendinous xanthomata and arcus cornealis.

Mutations in the mentioned genes have an additive effect that categorizes patients into heterozygotes and homozygotes. Homozygotes have biallelic pathogenic variants in one of the three genes, with mutations in *LDLR* being the most common, while heterozygotes may exhibit one or more pathogenic variants on different genes. While the prevalence of heterozygous FH is common in the general population, homozygous FH is rare, reported to be

approximately 1:300,000 in a nationwide study in the Netherlands.[2] In Saudi Arabia, the prevalence has been speculated to be higher than the global prevalence due to high rates of consanguineous marriages.[3]

Treatment of homozygous FH aims to lower LDL-C and modify lifestyle to reduce the risk of ASCVD. Patients are initiated on high-intensity statin therapy as early as infancy if diagnosed. Additional lipid-lowering treatments such as ezetimibe, a *PCSK9* inhibitor, lipoprotein apheresis, and lomitapide are also typically added. However, despite these therapies, a global registry of homozygous patients showed that only 12% achieved an LDL-C goal of less than 2.6 mmol/L.[4]

Lomitapide is an oral therapy approved in 2012 and acts by binding and inhibiting microsomal triglyceride transfer protein. Microsomal triglyceride transfer protein inhibition thereby prevents the assembly of apo-B-containing lipoproteins, resulting in reduced production of VLDL and consequently reduces plasma LDL-C.[5] In its pivotal trial, lomitapide was studied in 29 patients and maintained an approximately 40% reduced LDL-C during the trial. Of note, 18 patients underwent regular LDL apheresis during the trial. The most common adverse effects reported with lomitapide were gastrointestinal (GI) symptoms and increased liver aminotransferase levels, for which it carries a black box warning.[6]

Lomitapide is an expensive drug. Its Saudi-FDA listed price is 98,886 SAR/28 tablets (~$26,370 USD/28 tablets), corresponding to an annual cost per patient of approximately 1,285,518 SAR (~$342,813 USD).[7]

At our institution, lomitapide was being used on non-formulary bases for a small number of patients diagnosed with homozygous FH, and its high cost and budgetary constraints were triggering a review for formulary addition. This study aimed to describe our medication use evaluation for lomitapide as it had been used for patients before formulary addition. This MUE was conducted to inform the formulary committee about the current local prevalence of the disease, effectiveness and safety of lomitapide observed in the real world, in addition to other aspects, such as medication compliance and other treatment modalities.

METHODS

This is a retrospective review of patients who were actively prescribed lomitapide at our center from 2019 to 2022. King Abdulaziz Medical City is a 1973-bed tertiary care hospital in Riyadh, Saudi Arabia, under the umbrella of the Ministry of National Guard Health Affairs.[8] The Ministry of National Guard Health Affairs has a unified formulary that is implemented at all its facilities, and recommendations for formulary changes are conducted by a well-organized committee on a corporate level.[9,10] The institutional review board at King Abdullah International Medical Research Center approved this study, with a waiver of informed consent due to the retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Data Collection

Patients prescribed lomitapide were identified through the hospital's electronic medical records. Any patient with at least one lomitapide order was eligible. We excluded pediatric patients on lomitapide as they were enrolled in a randomized trial and were also concurrently on LDL apheresis therapy. Data on demographics, confirmed gene mutation results, duration of lomitapide therapy, baseline, on-treatment, last LDL-C, percent reduction in LDL-C after 1-3 months of therapy (whichever was first available), other LDL-C lowering therapies the patient was on, liver function tests (LFT), physician's documented adverse effects, and compliance were collected.

RESULTS

At the time of the review, 13 patients were identified to have been prescribed lomitapide during the selected period. Of the 13 patients, 5 were pediatric patients enrolled in an international study funded by the manufacturer and were excluded from this study. The demographics and results for the remaining eight adult patients are presented in Table 1.

Overall, the mean age of the patients was 25.5 years (range, 19–45). Approximately 75% were female, and the duration of treatment with lomitapide ranged from 9 months to 3 years. Of the eight included patients, six had a confirmed genetic test that indicated an *LDLR* gene defect (homozygous).

Regarding other treatment modalities, none of the patients were on continuous LDL-apheresis. Reasons for discontinuing LDL apheresis described included patient refusal, remote living conditions, and, in one patient, catheter complications with multiple admissions for bacteremia. All patients were on maximum statin doses, six of eight (75%) were on evolocumab, and five of eight were on ezetimibe.

Low-Density Lipoprotein Trends

The mean baseline LDL for the eight patients at presentation to our facility was 17.2 mmol/L (range, 11.78–21.97 mmol/L), and the mean baseline LDL just before lomitapide therapy initiation was 14.1 mmol/L (range, 8.7–17.79 mmol/L), as other lipid-lowering drugs were initiated such as statins, ezetimibe, and/or evolocumab. The mean percent drop in LDL-C with lomitapide was 34.1% (range, 0%–87%), and only one patient had an LDL-C below 5 mmol/L. Figure 1 illustrates the LDL-C for each of the eight patients from baseline until the date of this study.

Lomitapide Safety

Gastrointestinal (GI) disturbances, including abdominal pain, nausea, and cramping, were documented in four of eight (50%) patients. For LFT results, no cases of severe liver toxicities were seen, and none of the patients had an increase in liver enzymes, except for one patient

Table 1. Demographics and LDL-C results for the eight adult patients

Patient No.	Age	Sex	Duration on Lomitapide	Baseline LDL-C Level, mmol/L	LDL Just Before Starting	LDL-C 1-3 Mos After Lomitapide	Current LDL-C Level, mmol/L	% Decrease in LDL (from Baseline to Current), mmol/L	Current Total Cholesterol, mmol/L	Other Lipid-Lowering Therapies	Mutated Gene	Patient-Reported Adverse Effect	Liver Function Test	Comorbidities
1	21	F	1.5 y	15	8.7	4	8.4	54%	9.32	Rosuvastatin, evolocumab	Pathogenic variant in the *LDLR* gene (homozygous)	None documented	One elevation during dose escalation, then returned to normal	None
2	21	F	2 y	15.7	13.7	8.8	11.6	15%	12.33	Rosuvastatin, ezetimibe, evolocumab	Pathogenic variant in the *LDLR* gene (homozygous)	Patient reported nausea	No LFT elevation	None
3	20	F	9 M	20.2	13.2	12	12	9%	12.46	Atorvastatin, ezetimibe, omega 3-6-9, evolocumab	Pathogenic variant in the *LDLR* gene (homozygous)	Patient reported GI disturbance	No LFT elevation	None
4	19	F	10 mo	20	16.3	NA	17.8	Increase	18.62	Rosuvastatin, vitamin E, evolocumab	Pathogenic variant in the *LDLR* gene (homozygous)	None documented	No LFT elevation	None
5	19	F	3 y	21.9	12.8	11.56	12.3	10%	14.60	Rosuvastatin, evolocumab	Pathogenic variant in the *LDLR* gene (homozygous)	Patient reported diarrhea and fatigue	Slight increase, but normalized after	None
6	25	F	1 y	11.8	12.9	10.7	6.6	44%	7.94	Atorvastatin, ezetimibe, evolocumab	Pathogenic variant in the *LDLR* gene (homozygous)	None documented	No LFT elevation	None
7	45	M	2.5 y	15	17.8	5.4	0.4	87.40%	3.06	Rosuvastatin, ezetimibe	NA	None documented	No LFT elevation	Diabetes, brain tumor
8	34	M	2 y	17.3	17.3	5.94	8	53.50%	8.63	Rosuvastatin, ezetimibe	NA	Patient reported GI disturbance	No LFT elevation	None

LDL-C: low-density lipoprotein cholesterol; LDLR: low-density lipoprotein receptor; LFT: liver function test; GI: gastrointestinal; NA: not available.

who had a transient increase during dose escalation that normalized thereafter. One patient had moderate to severe diffuse hepatic steatosis.

Lomitapide Direct Cost

The total estimated cost for the treatment durations for the eight patients, which ranged from 9 months to 3 years, was 16,830,768 SAR ($4,488,205 USD). Treating the same cohort of patients for another 5 years would have a budget impact of approximately 37 million SAR ($10 million USD). Note that the cost of various strengths of lomitapide capsules are equal, as per the Saudi-FDA registered price.

DISCUSSION

In our cohort of adult patients, lomitapide showed a very modest overall reduction in LDL-C, with some patients showing almost no reduction whatsoever. This is contrary to other real-world studies that reported a much higher percentage of LDL-C lowering; a study in Italy reported a reduction reaching 60%, and similar findings were reported in the Pan-European Project, which included 75 patients with homozygous familial hypercholesterolemia.[11,12]

In addition, no cases of liver enzyme increase or liver toxicity were observed. Documented patient complaints of GI symptoms suggest that most patients may have been noncompliant with treatment. Therefore, efforts to provide patient support services that incorporate compliance assurance for such expensive therapies are needed. One patient with an extremely low LDL-C (patient 7 in Fig. 1) did not have a confirmed genetic test, highlighting the importance of implementing strict prescribing criteria based on a confirmed diagnosis.

The cost of patient self-administered expensive drugs should be factored into decisions regarding formulary addition, and methods to minimize wastage of such drugs should be carefully monitored by healthcare systems. For instance, evinacumab, a newly approved drug for homozygous FH, unlike lomitapide, is administered as an intravenous infusion once monthly, which offers an alternative with at least a guaranteed compliance and control over wastage, despite the oral route typically being a preferred route by patients.

Health technology assessment agencies are in disagreement regarding decisions to reimburse lomitapide. The National Institute for Health and Care Excellence (NICE) has agreed to fund the drug while commissioning is managed through specialized commissioning teams, with strict audit requirements, including the formation of a registry for all patients on lomitapide.[13]

On the other hand, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended against listing lomitapide, citing that the efficacy data were limited to surrogate endpoints and the significant risk of hepatic adverse events.[14]

Although CADTH points are valid, patients with barriers to LDL apheresis and an extremely high risk of

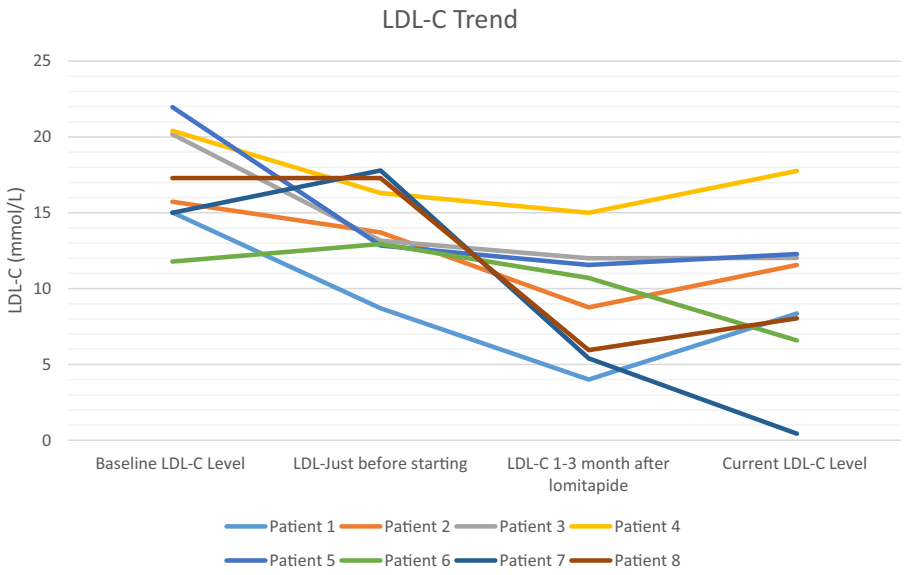

Figure 1. LDL-C trend for each of the eight patients, from baseline until the date of this study. LDL-C: low-density lipoprotein cholesterol.

ASCVD may have no other option, and denying treatment would be challenging for formulary decision-makers. Therefore, the responsibility of the decision-makers goes beyond approving funding and must align with implementing close monitoring plans, patient selection criteria, and a discontinuation criterion.

Limitations of this medication use evaluation are the limited number of patients, variation in duration of administration, and probable therapy interruption in some of the patients due to the non-formulary status of lomitapide.

CONCLUSIONS

This study highlights important considerations for the reimbursement of expensive medications for rare diseases. First, the importance of continuous monitoring of effectiveness and safety should be considered to determine the value of ongoing utilization. Second, the possibility of noncompliance should be factored into the decision-making process. Third, real-world evidence in real-time can support healthcare systems in price negotiations and reaching mutual agreements, ultimately improving patient access to care.

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