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Safety and Efficacy of Lomitapide in Treatment of Homozygous Familial Hypercholesterolaemia

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Abstract

Background: *Homozygous Familial Hypercholesterolaemia (HoFH) is a rare genetic disorder characterized by patients suffering from extremely elevated levels of lipid profile parameters despite being on treatment with conventional lipid lowering agents. It can lead to premature death due to cardiovascular disease if left untreated. Lomitapide - a licensed novel lipid-lowering agent may have the potentials to cause a significant reduction in levels of lipid profile parameters and prevent or delay the onset of premature cardiovascular diseases among HoFH patients.*

Aim: *This systematic review aims to evaluate the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH by comparing the changes in lipid profile parameters and percentage of adverse effects experienced by patients before and after addition of Lomitapide as an additional lipid lowering agent among HoFH patients who are currently on conventional lipid lowering medication and yet have an uncontrolled lipid profile.*

Method: *PubMed and the Cochrane library databases were searched for finding relevant randomised placebo-controlled trials and retrospective observational studies published from inception until 1st August 2020 which reported the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH. Therapeutic efficacy assessed by comparing the percentage changes in lipid profile parameters before and after the addition of Lomitapide. Safety profile assessed on the basis of percentage of adverse effects experienced by patients following the addition of Lomitapide.*

Results: *Lomitapide in doses ranging from 10-60mg/day, when added as an additional lipid lowering drug along with conventional lipid lowering medications, produced a significant reduction of up to 96% in LDL-C levels, up to 81.3% in total cholesterol and up to 93.7% in triglyceride level at the maximum tolerated dose. It also proved to be a safe therapeutic option among majority of HoFH patients since mild gastrointestinal disorder was the commonest adverse effect experienced by up to 53 % of HoFH patients following the addition of Lomitapide.*

Conclusion: *Lomitapide significantly lowered the levels of LDL-C, total cholesterol, triglyceride and slightly improved the levels of HDL-C. It was well tolerated and had a satisfactory safety profile among HoFH patients.*

Keywords: *HoFH, MTP inhibitor, LDL-C, HDL-C, Total cholesterol, Triglyceride.*

Introduction

Homozygous Familial Hypercholesterolaemia is a rare, life- threatening autosomal dominant genetic disorder **[**1-3**]** having a prevalence rate of one per 1 million**[**4**]**. It is characterized by the patient suffering from lipid profile parameters, raised way above the recommended target level**[**5, 6**]** despite being on regular conventional lipid-lowering agents like Statins, Ezetimibe Colesevelam, Fenofibrate, Cholestagel, Questran, Modalim and even lipoprotein apheresis**[**7, 8**]**. This is because the normal physiological function of LDL-Receptors in the liver **[**9**]**, which are the essential biological components mandatory for achieving optimum lipid-lowering effects from these conventional lipid-lowering agents are severely impaired by genetic mutation among these patients**[**8**]**. As a consequence, the conventional lipid- lowering agents produces a minimum therapeutic effect on patients of HoFH**[**9, 10**]**. Thus, HoFH patients always remain at constant high risk of developing cardiovascular diseases at an early age due to uncontrolled HoFH**[**4, 5, 8**]**.

Lomitapide is a Microsomal Triglyceride Transfer Protein (MTP) inhibitor - a licensed novel lipid-lowering strategy **[**5**]** which exerts its therapeutic potentials via a mechanism of action **[**9**]** different from that of the conventional lipid-lowering strategies. Thus, it may have the potentials of lowering the ever-increasing lipid parameters in HoFH patients and delay the onset of the premature cardiovascular events **[**5**]** when used in combination with conventional lipid-lowering strategies**[**11**]**. This systematic review aims to evaluate the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH by comparing the changes in lipid profile parameters and percentage of adverse effects experienced by patients before and after addition of Lomitapide as an additional lipid-lowering agent among HoFH patients who are currently on conventional lipid-lowering medication and yet have an uncontrolled lipid profile.

Method

Search strategy

PubMed and the Cochrane library databases were searched for finding relevant randomised placebo-controlled trials and retrospective observational studies which reported the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH. The search was limited to include relevant studies published in the English language from inception until 1st August 2020. The search strategy extracted from PubMed and the Cochrane Library database are as follows:

Cochrane library: Lomitapide in Title Abstract Keyword OR Microsomal Triglyceride Transfer Protein (MTP) inhibitor in Title Abstract Keyword AND Homozygous Familial Hypercholesterolaemia in Title Abstract Keyword OR HoFH in Title Abstract Keyword AND Safety AND Efficacy in Title Abstract Keyword

PubMed: ((((Lomitapide**[**Title/Abstract**]**) AND (Microsomal Triglyceride Transfer Protein (MTP) inhibitor**[**Title/Abstract**]**)) AND (Homozygous Familial Hypercholesterolaemia **[**Title/Abstract**]**)) OR (HoFH**[**Title/Abstract**]**)) AND (Safety**[**Title/Abstract**]** AND Efficacy**[**Title/Abstract**]**)

Inclusion criteria

RCTs and retrospective observational studies which reported the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH were considered eligible for this review. Studies also had to be focused on HoFH patients aged between 20-70 years who are currently on any one of the lipid-lowering medication among Statin, Ezetimibe, Fenofibrate or Lipoprotein apheresis to be considered eligible.

Exclusion criteria

Several research studies retrieved from the search result of both the databases were excluded under specific criteria stated as follows. Randomised control trials and retrospective observational studies which focused on a population beyond the selected age range of 20-70 years and studies that focused on outcomes and interventions irrelevant to the selected PICO of this systematic review were excluded. Unfinished ongoing trials, preliminary reports of ongoing trials, prospective observational studies and pre- prints, published systematic reviews, meta- analyses, literature reviews, newspaper articles, editorials, book reviews focusing on the irrelevant area of research were also excluded.

Outcomes

Outcome concerning the therapeutic efficacy assessed in this systematic review was subdivided into individual parameters of lipid profile such as LDL-C, HDL-C, Triglyceride level and Total Cholesterol levels. Readings of these lipid profile parameters on current ongoing lipid- lowering medication and change in the levels of these parameters after adding Lomitapide as an additional lipid-lowering agent were expressed in mg/dL or mmol/L. The difference between the two readings of each parameter was calculated and expressed as the percentage change in each parameter after adding Lomitapide as an additional lipid-lowering agent.

Outcome concerning the safety profile of Lomitapide in treatment of HoFH was determined by analysing the percentages of different adverse effects experienced by HoFH patients in each study following the addition of Lomitapide as an additional lipid-lowering agent along with the ongoing lipid-lowering medication.

Reviewing Process

Only peer-reviewed, full-text RCTs and retrospective observational studies published in scientific journals were selected for the final analysis. Reference lists of each selected studies were inspected and reviewed thoroughly to identify and include any eligible RCTs and retrospective observational studies based on the inclusion and exclusion criteria. The entire reviewing process was solely carried by the author of this review.

Data Extraction

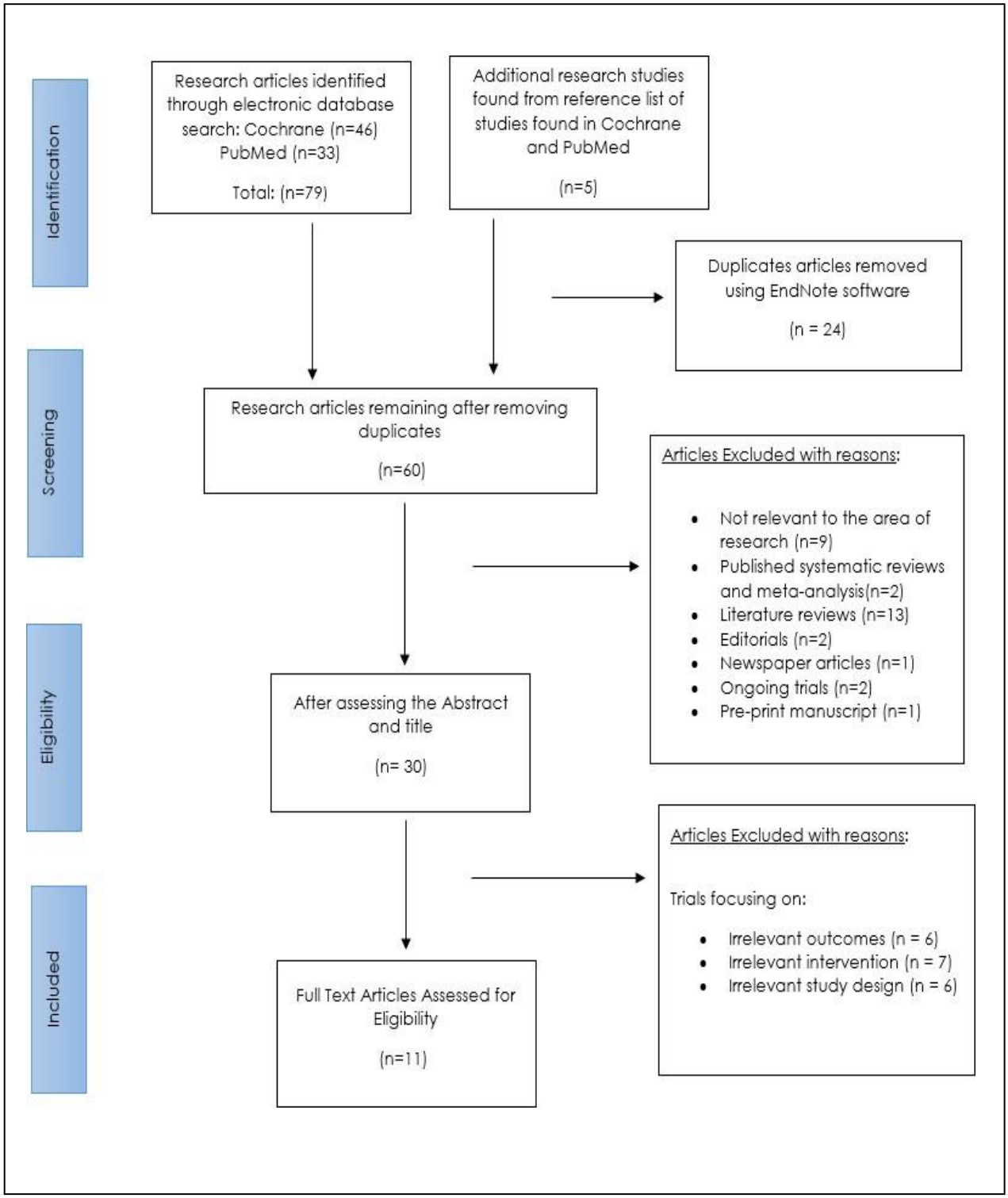
Relevant data concerning the demographics, population, intervention, control and outcomes of each selected study were extracted independently by the author. For instance, data regarding the name of authors along with the year of publication, number of patients in the control/comparator and intervention groups, study design, age and BMI ranges of the participants, ongoing lipid-lowering medication, intervention treatment and study duration were extracted. Data related to the assessments of therapeutic efficacy and safety profile related outcomes were extracted from each selected study as well. Verification of the extracted data was also done solely by the author of this systematic review.

Assessment of Risk of Bias

The assessment of the risk of bias and methodological quality of the selected retrospective observational studies will be done using the Newcastle-Ottawa Scale (NOS)[12, 13]. The assessment of the risk of bias and quality of the selected RCT will be done using the Jaded scoring scale[14]. Scores between 0 - 5 will be assigned depending on the actual process of randomisation and blinding applied to participants in each selected study[14]. Scores will also be allocated for the accountability of the fate of each participant involved in the selected trial [14].

Results

Stepwise description of the study selection process is outlined in the PRISMA flow chart shown in Figure 1 below. Sum total of 79 research articles were identified from PubMed and the Cochrane Library after applying the search strategy, as stated in the previous section of the systematic review. Further, five relevant research studies were selected from the reference list of those 79 research articles. Therefore, a total of 84 research articles were identified and inserted in a library of the EndNote software. Twenty-four research studies out of the 84 inserted into the software, were identified as duplicates and removed electronically using the software. After applying the inclusion and exclusion criteria on the remaining 60 research studies, two published systematic reviews with meta-analysis, 13 literature reviews, two editorials, one newspaper article, two ongoing trials, one pre-print manuscript and nine primary research articles focusing on a different area of research were excluded during the screening process. After reading the title and abstract of the remaining 19 primary research studies, six studies were excluded for having irrelevant outcomes; seven for having irrelevant interventions, and six more studies were excluded as they were neither randomised control trials nor retrospective observational studies which were the two specific study designs chosen to conduct this systematic review. Finally, after reading the full text and applying the eligibility criteria, 11 primary research studies were selected for the final analysis of this systematic review because these studies were focused on population, intervention, control and outcomes relevant to the aim of this systematic review. Out of these eleven selected studies, one was a randomised, double-blind placebo- controlled trial and the rest were retrospective observational studies.


Identification
Screening
Eligibility
Included
Research articles identified through electronic database search: Cochrane (n=46) PubMed (n=33)
Total: (n=79)
Additional research studies found from reference list of studies found in Cochrane and PubMed
(n=5)
Duplicates articles removed using EndNote software
(n = 24)
Research articles remaining after removing duplicates
(n=60)
Articles Excluded with reasons:
Not relevant to the area of research (n=9)
Published systematic reviews and meta-analysis(n=2)
Literature reviews (n=13)
Editorials (n=2)
Newspaper articles (n=1)
Ongoing trials (n=2)
Pre-print manuscript (n=1)
After assessing the Abstract and title
(n= 30)
Articles Excluded with reasons:
Trials focusing on:
Irrelevant outcomes (n = 6)
Irrelevant intervention (n = 7)
Irrelevant study design (n = 6)
Full Text Articles Assessed for Eligibility
(n=11)

Study descriptions

Selected studies were focused on a total of 180 diagnosed patients of HoFH aged between 20-70 years who had BMI ranging between 16 - 36 kg/m2, as shown in Table 1 below. These HoFH patients were receiving lipid-lowering treatment with either one or more of the conventional lipid-lowering agents among Statins Ezetimibe, Fenofibrate and lipoprotein apheresis, as shown in Table 1 below. Despite, the

Table 1 Demographics of the studies and baseline clinical characteristics of HoFH patients involved in the studies analysed in this systematic review.

Studies	Study design	Age of Patients	No of patients in Intervention Group	BMI (kg/m2)	Intervention:	Control/Comparator: Ongoing medication/ Placebo	Participant Inclusion Criteria	Treatment duration
Taubel et al., 2016 [5]	Randomised double-blind placebo-controlled trial	32 - 34 years	72	21.8 - 26.5	Lomitapide 10 - 60mg/day	Placebo	HoFH patient	26 weeks
Blom et al., 2018[7]	Retrospective Observational Study	31- 34 years	19	N/R	Lomitapide	Mipomersen, Evolocumab	HoFH patient	26 weeks
Harada-Shiba et al., 2017 [8]	Retrospective Observational Study	40 - 66 years	9	18.8 - 30.6	Lomitapide 5 - 60 mg/day	Standard lipid-lowering therapy ± Lipid apheresis	HoFH patient	26 weeks
Leipold et al., 2017[4]	Retrospective Observational Study	Middle aged	149	N/R	Lomitapide	Statins, Ezetimibe, ± Lipid apheresis	HoFH patient	26 weeks
D'Erasmo et al., 2017[9]	Retrospective Observational Study	Middle aged	15	17.3 - 35.6	Lomitapide 20 mg/day	Standard lipid-lowering therapy, ± Lipid apheresis	HoFH patient	26 weeks
Sperlongano et al., 2018 [2]	Retrospective Observational Study	52 - 62 years	2	N/R	Lomitapide 5 - 30 mg/day	Statins, Ezetimibe, ± Lipid apheresis	HoFH patient	52 weeks
Kolovou et al., 2020[11]	Retrospective Observational Study	8 - 62 years	12	16.7- 28.4	Lomitapide	Statins, Ezetimibe, Colesevelam Lipid apheresis	HoFH patient	3 – 24 months
Averna et al., 2016[3]	Retrospective Observational Study	18 - 45 years	29	19.3 - 28.7	Lomitapide 5 - 60 mg	Lipid apheresis, Statin, Ezetimibe, fenofibrate	HoFH patient	26 weeks
Cuchel et al., 2013[1]	Retrospective Observational Study	18 years or older	29	N/R	Lomitapide 40 mg	N/R	HoFH patient	26 weeks
Yahya et al., 2016[6]	Retrospective Observational Study	20 - 62 years	4	N/R	Lomitapide 10 - 30 mg	Atorvastatin, Ezetimibe, Cholestagel, Questran, Modalim, Lipid apheresis	HoFH patient	9 - 36.5 weeks
Stefanutti et al., 2016[10]	Retrospective Observational Study	28 - 32 years	4	N/R	Lomitapide 10 - 30 mg/d	Statins, Ezetimibe, Lipid apheresis	HoFH patient	12 - 50 weeks

Abbreviations: N/R – Not reported, HoFH- Homozygous Familial Hypercholesterolaemia

Table 2 Results of the outcomes assessing the therapeutic efficacy of Lomitapide in treatment of HoFH reported by each study analysed in this systematic review.

Outcome 1: Therapeutic Efficacy

Studies	LDL-C			Total cholesterol			Triglycerides			HDL-C		
	Control/ Comparator	Intervention		Control/ Comparator	Intervention		Control/ Comparator	Intervention		Control/ Comparator	Intervention	
	LDL-C level on currently ongoing medication	LDL-C level after adding Lomitapide	**Percentage reduction in LDL-C after adding Lomitapide**	Total cholesterol on currently ongoing medication	Total cholesterol after adding Lomitapide	**Percentage reduction in total cholesterol after adding Lomitapide**	Triglyceride level on currently ongoing medication	Triglyceride level after adding Lomitapide	**Percentage reduction in Triglyceride level after adding Lomitapide**	HDL-C level on currently ongoing medication	HDL-C level after adding Lomitapide	**Percentage increase in HDL level after adding Lomitapide**
Taubel et al., 2016 [5]	140.3 mg/dl	5.8-74.9 mg/dl	**49.6 - 96%**	215.8 mg/dl	42.4 -130.2 mg/dl	**39.1 - 81.2 %**	179 mg/dl	9.7 - 80.1 mg/dl	**52.7 - 93.7%**	26 - 57 mg/dl	22 - 41.1 mg/dl	**18 – 38 %**
Blom et al., 2018[7]	324-455 mg/dl	84-233 mg/dl	**26 – 51 %**	N/R	N/R	**N/R**	N/R	N/R	**N/R**	N/R	N/R	**N/R**
Harada-Shiba et al., 2017 [8]	199 mg/dl	115-148 mg/dl	**26 – 42 %**	N/R	N/R	**32 %**	N/R	N/R	**46%**	N/R	N/R	**1%**
Leipold et al., 2017[4]	8.7 mmol/L	4.35 mmol/L	**50 %**	N/R	N/R	**N/R**	N/R	N/R	**N/R**	N/R	N/R	**N/R**
D'Erasmo et al., 2017[9]	426.0 mg/dl	289 mg/dl	**68.2 %**	N/R	N/R	**61.3 %**	N/R	N/R	**52.8 %**	N/R	N/R	**26.5 %**
Sperlongano et al., 2018 [2]	212-295 mg/dl	42-65 mg/dl	**78 – 86 %**	248 - 354 mg/dl	120 -170 mg/dl	**52 %**	80 - 93 mg/dl	34.4 - 40 mg/dl	**57%**	27 - 43 mg/dl	24.3 - 38.7 mg/dl	**10 %**
Kolovou et al., 2020[11]	900 mg/dL	173.5 mg/dL	**57 %**	1000 mg/dL	228.5 mg/dL	**77.1%**	125 mg/dL	83.5 mg/dL	**33.2 %**	34.5 mg/dL	37.5 mg/dL	**8%**
Averna et al., 2016[3]	165.7- 476.8 mg/dL	83.5 - 238 mg/dL	**50.9 %**	N/R	N/R	**32 %**	N/R	N/R	**45 %**	N/R	N/R	**1%**
Cuchel et al., 2013[1]	8.7 mmol/L	4.35 mmol/L	**50 %**	1.0 mmol/L	0.54 mmol/L	**46 %**	11.1 mmol/L	9.44 mmol/L	**15 %**	1.1 mmol/L	1.23 mmol/L	**12%**
Yahya et al., 2016[6]	3.9 -14.5 mmol/L	0.39 - 1.45 mmol/L	**34 – 89 %**	N/R	N/R	**N/R**	N/R	N/R	**N/R**	N/R	N/R	**16 - 34%**
Stefanutti et al., 2016[10]	370 -150 mg/dl	150 - 50 mg/dl	**5 – 83 %**	N/R	N/R	**32 %**	N/R	N/R	**N/R**	**N/R**	N/R	**N/R**

Abbreviations: N/R – Not reported, HoFH- Homozygous Familial Hypercholesterolaemia

Table 3 Results of the outcome assessing the safety profile of Lomitapide in treatment of HoFH reported by each study analysed in this systematic review.

	Outcome 2: Safety profile assessment			
Studies	**Percentage of adverse events experienced by participants**	**New castle Ottawa Scale**	**Jaded Score**	**Conclusion**
Taubel et al., 2016 [5]	Mild gastrointestinal disorders - 46.42% Metabolic Disorder - 5.3% Connective tissue disorder - 7.14% Nervous system disorder - 12.5% Respiratory system disorder - 3.57% Vascular disorder - 5.3%	N/R	5	Lomitapide proved to be effective in reducing LDL-C along with other parameters of lipid profile in a dose-dependent manner and had a satisfactory safety profile among HoFH patients.
Blom et al., 2018[7]	Major adverse cardiovascular events - 21%	******	N/R	Lomitapide lowered LDL-C significantly in patients with HoFH allowing patients to reach the targeted LDL-C level. Incidence of cardiovascular event reduced from 93% to 21% among HoFH patients following the addition of Lomitapide along with the conventional treatment.
Harada-Shiba et al., 2017 [8]	Drug-related adverse effects - 7.5%	*****	N/R	Lomitapide when used as an add on medication, produced a rapid and significant reduction in the levels of LDL-C and other lipid profile parameters in patients with HoFH.
Leipold et al., 2017[4]	Major adverse cardiovascular events - 15%	*******	N/R	Lomitapide, used as an add on medication increased median life expectancy by decreasing the rate of cardiovascular events in HoFH patients.
D'Erasmo et al., 2017[9]	Diarrhoea - 53% Elevated liver transaminase - 0% Liver damage - 0%	******	N/R	Lomitapide proved to be an effective therapeutic strategy in treatment of HoFH and had a satisfactory safety profile.
Sperlongano et al., 2018 [2]	Nausea – 20 % Diarrhoea – 20 % Elevated liver transaminase - 0% Liver damage - 0%	*****	N/R	Lomitapide is an effective and well tolerated agent for the treatment of HoFH . However, it should be prescribed at an early stage of treatment of HoFH among patients with high-risk of developing fatal cardiovascular complications.
Kolovou et al., 2020[11]	Diarrhoea - 16.6% Elevated liver transaminase - 6.67 % Xanthomas - 6.67 % Atheromatic plaque regression - 6.67 % Angina pectoris -13.3 Coronary plaques - 13.3	******	N/R	Lomitapide lowered LDL-C significantly in patients with HoFH allowing patients to reach the targeted LDL-C level and had a satisfactory safety profile as well among HoFH patients.
Averna et al., 2016[3]	Gastrointestinal adverse events - 20.6% Elevated liver transaminases - 16% Elevated Hepatic fat - 24.7%	*******	N/R	The efficacy, safety and tolerability of lomitapide demonstrated in this Italian cohort study indicated the broad applicability of Lomitapide in treatment of HoFH
Cuchel et al., 2013[1]	Gastrointestinal adverse events -17.6% Elevated liver transaminases – 13.04 % Headache - 4.34% Coronary syndrome -10 % Angina pectoris - 10 % Lower respiratory tract infection - 10 %	*******	N/R	Lomitapide lowered LDL-C significantly in patients with HoFH allowing patients to reach the targeted LDL-C level and had a satisfactory safety profile as well among HoFH patients.
Yahya et al., 2016[6]	N/R	*****	N/R	Addition of Lomitapide substantially lowered LDL-C levels and moderately improved HDL-C levels as well. Thus, proving to be an effective therapeutic strategy in treatment of HoFH
Stefanutti et al., 2016[10]	Mild Gastrointestinal adverse events - 25% Transient ALT/AST elevations - 25%	*****	N/R	Lomitapide is an effective and safe add-on lipid lowering therapy to standard lipid-lowering therapy, including lipoprotein apheresis in HoFH. This indicates that addition of Lomitapide decreases the frequency of Lipid Apheresis sessions, reducing cost of treatment and improving the overall quality of life.

Abbreviations: N/R – Not reported, HoFH- Homozygous Familial Hypercholesterolaemia, ALT- Alanine Aminotransferase, AST- Aspartate transaminase

ongoing lipid-lowering medication, these patients had lipid profile parameters like LDL-C, Total Cholesterol and Triglyceride levels well above and HDL-C level well below the recommended target level, as shown in the comparator column in Table 2 above. As an intervention medication, Lomitapide in doses ranging from 5mg/day to 60 mg/day was given to all 180 diagnosed patients of HoFH as an additional lipid-lowering medication along with their ongoing lipid-lowering management as shown in Table 1above.

Selected studies reported outcomes related to the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH. Therapeutic efficacy related outcome was further subdivided into individual lipid profile assessment parameters such as LDL-C, HDL-C, Triglyceride level and Total Cholesterol levels, as shown in Table 2 above. Levels of these lipid profile parameters following the ongoing conventional lipid-lowering medication were expressed in mg/dL or mmol/L and presented as comparator values in Table 2. Levels of these parameters after adding Lomitapide as an additional lipid-lowering agent along with the ongoing lipid-lowering medication were also expressed in mg/dL or mmol/L and presented under the intervention column as shown in Table 2. The difference between the intervention and comparator readings of each lipid profile parameters were calculated and expressed as the percentage change in each parameter after adding Lomitapide as an additional lipid-lowering agent, as shown in Table 2 above.

The outcome related to the safety profile of Lomitapide was determined by analysing the percentages of different adverse effects experienced by HoFH patients in each study following the addition of Lomitapide as an additional lipid-lowering agent along with the ongoing lipid-lowering medication as shown in Table 3 above.

Results of each outcome

Based on the changes in each lipid profile parameter determining the therapeutic efficacy of Lomitapide in treatment of HoFH, it can be deduced that Lomitapide significantly lowered the levels of LDL-C by up to 69%, Total cholesterol up to 81.2%, Triglyceride up to 93.7% and slightly improved the levels of HDL-C up to 38% as shown in Table 2. Findings of the outcome reporting the safety profile of the Lomitapide indicated that the drug was well tolerated and had a satisfactory safety profile among HoFH patients as there were fewer reports of major adverse effects like the elevation of Hepatic transaminase which was observed only among 6.67 -25% patients. Commonest adverse effect experienced by up to 16.6 - 53% of patients were minor ones like gastrointestinal events like diarrhoea, as shown in Table 3.

As for the assessment of the risk of bias, the retrospective observational studies had several limitations and methodological flaws in the selection and comparability process. Thus, were rated with scores ranging between 5 to 7 stars using New castle Ottawa scale as shown in Table 3.

The RCT was assigned a score of 5, since the process of randomisation, blinding and accountability of the fate of each participant was mentioned in the study along with proper reasoning.

Discussion

A rare autosomal dominant genetic disorder- Homozygous Familial Hypercholesterolaemia

Homozygous familial Hypercholesterolaemia (HoFH) is an extremely rare autosomal dominant genetic disorder[3, 7, 15] having a prevalence rate between 1:160,000 – 1:1000,000[11]. It has a distinct clinical hallmark characterized by elevated levels of lipid profile parameters like LDL-C, Total Cholesterol and Triglyceride levels[2, 7]. Markedly elevated LDL-C levels being the commonest laboratory finding among the majority of HoFH patients[2, 7].HoFH patients are almost always found resistant to the therapeutic effects of conventional lipid-lowering agents with which they are commonly treated[2] such as Statins, Fenofibrate and Ezetimibe[16]. Therefore, these patients barely respond to their ongoing lipid-lowering medication and remain exposed at constant risk of developing atherosclerotic cardiovascular events throughout their life [2, 7, 17]. Thus, at the earliest stage of the diagnosis, HoFH patients need to be treated with appropriate lipid-lowering medications which have the potentials to cause a significant reduction of all lipid profile parameters and minimize the risk of the early development of cardiovascular diseases[18] which is absolutely crucial to prevent early mortality among HoFH patients.

Shortcomings of the conventional lipid- lowering strategies

Similar to patients suffering from any clinical subtypes of Hypercholesterolaemia, patients suffering from HoFH is also recommended to maintain an optimum level of lipid profile parameters by The European Atherosclerosis Society (EAS)[2] and The American Heart Association[8]. As per recommendation, a HoFH patient, in the absence of existing chronic comorbidities, should maintain an LDL-C level below 100 mg/dL or 2.6 mmol/L, and in the presence of existing chronic comorbidities and other cardiovascular risk factors, the level should be maintained below 70 mg/dL or 1.8 mmol/L to avoid the risks of sudden cardiac death [2, 8, 19]. However, HoFH patients under the current ongoing treatment with conventional lipid- lowering agents are not able to meet either of these

recommendations or targets set by The European Atherosclerosis Society (EAS) and The American Heart Association[7]. The solution to this dilemma and the actual aetiology behind the therapeutic failure of these conventional lipid-lowering agents among HoFH patients lies deep within the pathophysiology[20] of the disease itself and its co-relationship with the mechanism of action of these conventional lipid- lowering agents[15, 21].

Relevant literature [1, 22] focusing on the pathophysiology of HoFH states that HoFH occurs due to mutations in LDL- Receptor genes. These genetic mutations heavily impair the normal functioning process of the LDL- receptors present in the liver cells[5]. Conventional lipid-lowering agents like Statin, Ezetimibe, Fenofibrate and others works by binding to LDL- receptors in liver cells and produce their lipid-lowering effects[4]. Thus, in a HoFH patient with non-functioning LDL-receptors, the conventional lipid-lowering agents can do little in reducing the severely elevated levels of lipid profile parameters[9]. Thereby exposing HoFH patients at constant risk of sudden cardiac death [8].

As a solution to this dilemma, clinicians turned towards Lipid apheresis procedure as an alternative lipid-lowering strategy which could temporarily reduce the levels of lipid profile parameters by 50% - 70% among HoFH patients[2, 7]. Such reduction was possible as the procedure does not require functional LDL-receptors for lowering lipid levels[23, 24]. However, even Lipid apheresis, in combination with the conventional lipid-lowering strategies like Statin, Ezetimibe, Fenofibrate, could do little in maintaining the target level of lipid profile parameters[23, 24]. Since Lipid apheresis had its own distinct shortcomings[3]. Lipid apheresis being an invasive procedure[25], meant that it could only be given in specific scheduled sessions with a certain time gap in between scheduled sessions [6]. As a consequence, the lipid levels returned back to being severely elevated soon after the effects of Lipid apheresis subsided and remained elevated throughout the interval periods between consecutive sessions [10, 25]. This indicates that HoFH patients are living at constant risk of sudden cardiac death between consecutive Lipid apheresis sessions[25]. However, HoFH patients with rapidly increasing lipid profile parameters could only benefit from Lipid apheresis, if it could be given at a frequency of once every week[8]. Application of Lipid apheresis at such high frequency is an inevitable limitation for HoFH patients around the world since it is an expensive lipid-lowering strategy available only at specialized cardiac centres[8]. Nevertheless, there is contradicting evidence in relevant literature[26, 27] which shows that HoFH patients, despite undergoing frequent Lipid apheresis in combination with conventional lipid- lowering agents, still developed cardiovascular diseases like aortic valve stenosis and Myocardial infarction at an early age [1, 26, 27].

This suggests that there is an absolute need for a newer lipid-lowering agent which could aggressively act to lower the elevated lipid profile parameters and maintain the optimum recommended levels of these parameters [2, 8, 19] via a mechanism of action which does not rely on the proper functioning of LDL receptors in the body. Lomitapide – a novel lipid- lowering agent which exerts its therapeutic lipid-lowering potentials via the inhibition of microsomal triglyceride transfer protein [1] without requiring the need of functional- LDL-receptor in the body [28]. May have the potentials to be a promising therapeutic strategy for lipid management among HoFH patients when used as adjunctive therapy with the maximum tolerated dose of conventional lipid-lowering agents [2, 3, 7, 11]. This systematic review aims to evaluate the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH by comparing the changes in lipid profile parameters and percentage of adverse effects experienced by patients before and after addition of Lomitapide as an additional lipid-lowering agent among HoFH patients who are currently on conventional lipid-lowering medication and yet have an uncontrolled lipid profile.

Outcome 1: Therapeutic efficacy of Lomitapide in treatment of HoFH

According to the reports of the only known randomised, double-blind placebo- controlled trial [5] published during the time of conducting this review, by Taubel et al.,2016 [5] which consisted of 72 HoFH patients. Lomitapide in doses ranging from 10-60mg/day given as an additional drug along with other conventional lipid- lowering agents, produced a significant reduction of up to 96% in LDL-C levels at the maximum tolerated dose. Other than LDL- C, it also reduced Total Cholesterol and Triglyceride levels up to 81.2% and 93.7 % respectively and improved the level of the "Good Cholesterol" HDL-C by up to 38%, as shown in Table 2. Such drastic improvement in lipid profile parameters of HoFH patients can be no less than a life-saving therapeutic response.

The results of the RCT [5] can be considered as a reliable and a strong source of information since it was based on a well-structured methodology and had a fairly large population size of 72 HoFH patients considering the low incidence rate of the disease. The overall results of the RCT

[5] were consistent with the results of identical outcomes assessed and reported by other observation retrospective studies [1, 4, 6, 9-11] analysed in this review as shown in Table 2, except the study conducted by Harada-Shiba et al.,2017[8] and Averna et al.,2016[3]. Despite reporting consistent results regarding the reduction in levels of LDL-C, Total cholesterol and Triglyceride, Harada-Shiba et al.,2017[8] and Averna et al.,2016[3] reported an insignificant improvement of only 1% in HDL-C levels following Lomitapide intervention. However, both studies [3, 8] had several methodological

limitations, including small sample sizes. Thus, the contradicting evidence from these two studies [3, 8] were much weaker compared to the evidence in favour of Lomitapide provided by other studies [1, 4, 6, 9-11] analysed in the review.

Such a drastic reduction of highly elevated lipid profile parameters among HoFH patients with endogenous non- functional LDL-receptors could only be achieved by Lomitapide. As unlike any other conventional lipid-lowering strategies [29] Lomitapide inhibits the assembly of Apolipoprotein -B [29, 30] which is an essential component for the synthesis of LDL and VLDL in the liver[31]. Thus, Lomitapide lowers LDL concentration in blood circulation simply by inhibiting the synthesis of LDL [31] without requiring the use of functioning LDL-receptors in the body.

As a result of such significant improvements in lipid profile parameters following the addition of Lomitapide as an adjunct therapy, HoFH patients involved in these studies [1, 4, 6, 9-11] could either permanently discontinue or markedly reduce the frequency of undergoing the invasive procedure of Lipid apheresis as their lipid profile parameters were well under control following the addition of Lomitapide.

Outcome 2: Safety Profile of Lomitapide in treatment of HoFH

In order to evaluate the tolerability and safety profile of Lomitapide, it was administered in a minimum dose of 5mg/days and increased up to the maximum tolerated dose of 60mg/day in studies [1, 4, 6, 9-11] analysed in this review. Considering the findings of the safety profile related outcomes of Lomitapide in treatment of HoFH, assessed in the RCT [5] as well as all the retrospective observational studies [1, 4, 6, 9-11]analysed in this systematic review as outlined in Table 3, Lomitapide was found to be well- tolerated and safe among the majority of HoFH patients. Mild gastrointestinal disorders like diarrhoea, nausea, vomiting dyspepsia and abdominal pain were the commonest side effects observed among 17% - 53% HoFH patients following the addition of Lomitapide alongside the conventional lipid-lowering agents. However, data from the follow-up period of these studies [1, 4, 6, 9-11]stated that these gastrointestinal symptoms were manageable with dose reductions or temporary discontinuation of treatment with Lomitapide followed by a short course of Antidiarrheal medication and maintenance of low-fat diet[4, 8, 9, 32].

An elevated level of liver transaminase and hepatic fat accumulation indicating liver damage in the form of hepatic steatosis was the second commonest adverse effect reported among 6.67 - 25% HoFH patients in four[1, 3, 10, 11] out of the ten observational studies after addition of Lomitapide. However, the RCT [5] did not report such elevation of liver enzymes among the participants following

Lomitapide intervention. Two other observational studies[2, 9] also investigated the level of hepatic transaminase among HoFH patients. However, in contrast to the findings of the other four observational studies[1, 3, 10, 11], these two studies [2, 9] also reported no significant elevation of hepatic transaminase among the patients, similar to results of the RCT. However, these two observational studies [2, 9] reporting no significant elevation of liver enzymes among HoFH patients had major methodological limitations and a very small sample size comprising a total of eight HoFH patients compared to other four observational studies [1, 3, 10, 11]which comprised of a total of 74 HoFH patients as shown in Table 1. Nevertheless, the elevation of hepatic transaminase subsided following dose alteration or temporary discontinuation of the treatment with Lomitapide. Moreover, none of the studies reported any drop out of participants due to any severe adverse effects following treatment with Lomitapide.

Based on the evidence and considering the overall possibilities of severe liver damage in the form of hepatic steatosis from long term usage of Lomitapide among HoFH patients, Food and Drug Administration (FDA)[30] and European Medicines Agency (EMA)[33] recommended clinicians to thoroughly investigate all HoFH patients on a regular interval through frequently scheduled follow-ups sessions throughout the course of treatment for identifying any early signs of developing hepatotoxicity [7]. However, a small percentage of HoFH patients are still found to limit or discontinue the regular intake of Lomitapide due to the fear of developing chronic liver disease in the long run[34]. Despite not having any strong evidence supporting their negative approach towards being treated with Lomitapide[34].

Besides, gastrointestinal disorders and elevated liver enzymes, there were few reports of metabolic disorders, connective tissue disorders, respiratory disorders and cardiovascular diseases[1, 5, 11] among HoFH patients following the addition of Lomitapide. However, it is yet unclear whether any of these side effects originated following the addition of Lomitapide or whether these adverse effects were due to the side effects of the ongoing treatment with conventional lipid- lowering agents[22, 29, 35]. However, it quite unlikely for Lomitapide to contribute to the development of adverse effects related to the cardiovascular system [1, 4, 7, 11] There is no clear explanation behind such reports. Moreover, the adverse effects related to the cardiovascular system are more likely to occur as a result of the worsening prognosis of the existing comorbidities rather than as a potential adverse effect of a lipid-lowering drug-like Lomitapide. In addition, Lomitapide has even proved to be a safer lipid-lowering option in the long run as according to the reports of two observation studies [2, 10]having an extended follow-up period of over 52 weeks, there were very few reports of minor Lomitapide induced

adverse effects even during the extended follow-up phases. Thus, proving Lomitapide to be a safe and well-tolerated lipid-lowering strategy among HoFH patients.

Comparison with other published systematic review

Until now, one systematic review has been published in 2nd March 2017 by Liu et al., 2017 [32] which evaluated the efficacy and safety of Lomitapide in treatment of different subtypes and severity of Hypercholesterolaemia. The published systematic review[32] was based on studies focusing on patients suffering from either Heterozygous or Homozygous Hypercholesterolaemia of severity ranging from mild to severe. However, the evidence from the published systematic review[32] is weak as it had major methodological limitations. It was conducted with evidence extracted from weak sources like case reports done on individual patients rather than a group of patients. Also, the systematic review[32] analysed data extracted from a single outdated randomised control trial published by Samaha et al., 2008 [35] focusing on all subtypes of Hypercholesterolaemia patients in general. Despite being outdated, the RCT also had a small sample size along with several other methodological flaws and a high risk of bias. Thus, findings from the previously published systematic review[32] cannot be generalized and applied to a mass population. As a conclusion, the authors of the review [32]stated that the information regarding the safety profile of Lomitapide in treatment of HoFH was unclear from the evidence reviewed and needs to be addressed in future research studies.

Unlike the previously published systematic review[32], this current systematic review is focused specifically on patients suffering from Homozygous Familial Hypercholesterolaemia(HoFH). It is based on analysis of evidence regarding the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH extracted from the latest known RCT and observational studies published until the time of conducting this systematic review. The studies analysed had much larger sample sizes compared to the case reports analysed in the previously published systematic review [32]. Therefore, the evidence from this current systematic review is more reliable and carries substantially higher strength compared to the evidence from the previously published systematic review [32]. Thus, making its findings more applicable to a mass population. Furthermore, this current systematic review resolved the gaps in research regarding the safety profile of Lomitapide in treatment of HoFH, which were addressed in the previously published systematic review [32].

Limitations

Since HoFH is an extremely rare genetic disease, a reasonable evaluation and analysis of the therapeutic efficacy and safety profile of Lomitapide in treatment of HoFH is challenging as the sample size in each study analysed in the review were small. Except one, all the studies analysed in this review are based on retrospective observational study design without having a placebo-based comparator which makes the report from each study subjected to the risk of bias due to the lack of an appropriate comparison of results. The data reporting each outcome in these studies were mostly extracted from previous medical records of HoFH patients instead of being recorded and monitored actively as it is done on RCTs which increases the chance of human error affecting the results. Moreover, several confounding variables like age of participants; existing comorbidities and treatment duration varied widely between each study. Such variation may have a potential effect on the results obtained from this review as well. Furthermore, most of the studies conducted on Lomitapide were funded by pharmaceutical companies involved in mass production of the drug. Therefore, there is an increased chance of publication bias which should be considered while interpreting the results of this review.

Conclusion

To conclude based on the evidence from studies analysed in this systematic review, the addition of Lomitapide along with conventional lipid-lowering agents in the treatment of HoFH has significantly lowered the level of LDL-C and other parameters of lipid profile like total cholesterol and Triglyceride. Lomitapide has also improved HDL -C levels to a moderate extent, allowing HoFH patients to reach and maintain the recommended lipid profile parameter targets set by The European Atherosclerosis Society (EAS) and The American Heart Association. Therefore, considering such therapeutic potentials and the satisfactory safety profile of Lomitapide, it can be considered as a valid therapeutic option for the treatment of HoFH patients which lowers life-threatening cardiovascular risks. As a sign of positive hope for HoFH patients worldwide, Lomitapide has received FDA approval, and it is indicated for the treatment of HoFH in many countries which includes the United States of America, Canada, Taiwan, Korea and many countries in the European Union.

Nevertheless, due to the rare incidence of HoFH worldwide and lack of acceptance and usage of Lomitapide as an add-on medication, there is a lack of strong evidence regarding the safety of Lomitapide in treatment of HoFH. Specifically, the long-term impact of Lomitapide intervention on the liver, potentially leading to Lomitapide induced hepatic steatosis. Little is also known about the therapeutic efficacy of Lomitapide as a monotherapy in the treatment of HoFH due to the lack of

randomized placebo- controlled trials using Lomitapide as the only lipid-lowering agents instead of using it as an add on lipid-lowering medication. Lastly, although the exact mechanism of Lomitapide responsible for reducing LDL-C is known, the exact mechanism behind the reduction of total cholesterol, Triglyceride and an increase in HDL-C levels is far from being clearly understood. These gaps in research need to be addressed in future through large randomized, double-blind placebo-controlled trials. Strong evidence from such RCTs may fill in these existing gaps in research regarding the use of Lomitapide in treatment of HoFH and keep the hopes alive among HoFH patients for a risk-free healthier tomorrow.

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