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Letter to the Editor

THE CURIOUS CASE OF LOMITAPIDE

Lomitapide is a new microsomal transfer protein inhibitor. It has been approved as an orphan drug for treating homozygous familial hypercholetelemia. The drug went through various see-saw phases in its brief life. Understanding the life history of Lomitapide gives a unique opportunity to analyze diverse case scenarios during clinical trials and their rectification by using scientific methodology.

Like a human being, drugs do have their own stories. Each story is worth telling. But, what differentiates the story of lomitapide from others is the innovative thinking and lessons to be learned for the doctors actively involved in clinical research.

Lomitapide was discovered in early 1990s by Bristol-Myers-Squibb (BMS) as the first microsomal transport protein (MTP) inhibitor. MTP is present in enterocytes and hepatocytes. Its main function is to transport triglycerides from endoplasmic retinaculum to Golgi bodies. In Golgi bodies of enterocytes, they are combined with Apo B 48 to form chylomicron, while in hepatocytes they combine with Apo B-100 to form very low density lipoprotein (VLDL) [1]. So, the MTP inhibitor decreases the synthesis of VLDL and hence, reduces the LDL levels in the blood. BMS started clinical trials in 1996 with the fixed dose of 25-100 mg/day. The drug was a huge success in bringing down the LDL cholesterol levels (primary outcome parameter). Unfortunately, BMS decided to discontinue the development citing excessive adverse drug reactions (ADRs), including the gastrointestinal tract (GIT) disturbances (diarrhea) and increased hepatic fat content. In 2001, BMS donated the rights of the drug to Dr. Daniel Raderof University of Pennsylvania (UOP).

The investigators at UOP demonstrated reasonable safety of lomitapide using regimen involving careful escalation of the doses in each patient coupled with rigorous low-fat diet. With new safety data, they managed to get an orphan drug status and funding needed for further clinical trials of lomitapide in patients of homozygous familial hypercholestelmia. In December 2012, US-FDA gave the approval of the drug for using in patients of hereditary hemochromatosis (HH) [2].

There are three important points to be learned for clinical investigators. A vast number of the new entities which come to clinical trial phase are withdrawn due to adverse effects profile. It is time to revisit one of the basic concepts of pharmacology regarding a drug and a poison. The concept was well-acknowledged by Paracelsus in these words - "All things are poison, and nothing is without poison, only the dose permits something not to be poison" [3]. Lomitapide was in trials in late 1990s, but in spite of being efficacious was withdrawn by the company due to deranged hepatic transaminase levels and fatty deposition. The most interesting point to note was the regimen chosen by the investigators at UOP. They used dose escalation in each patient, starting with least dose and increasing it at fixed intervals to reach a stable level. Careful dose escalation in each patient led to a marked decrease in the incidence of GIT and hepatic adverse drug effects.

The investigators knew that such a tight dose regimen would be a detrimental factor in market success where already drugs with similar efficacy, and better safety profile were present. So they identified the unmet need of a drug for a rare genetic disorder - HH. The therapeutic goals achieved in patients of HH are usually unsatisfactory with standard medications like statins due to the absence of LDL receptors. The mechanism of MTP inhibitors is independent of functionality of LDL receptor that gives them a unique advantage in patients of HH. Orphan drug status for developing a drug, is important since it secure funding as well as much required help in drug development.

However, as an orphan drug is used clinically, and more information regarding its efficacy and safety is made available, these orphan drugs can also be repositioned for other diseases. As far as lomitapide is concerned, its therapeutic efficacy has already been established in patients of hypercholestrelemia and hypertriglyceredemia (in phase II trials in late 1990). Hence, once the lomitapide is approved for HH, than it is reasonably easy to reposition it for treatment-resistant hypercholestrelemia or even be supplemented to primary therapy of uncomplicated hypercholestrelemia.

So, it can be inferred that drugs or new therapeutic entities are too valuable a resource to discard on the basis of a few parameters. These parameters are no doubt important to all stakeholders in healthcare, but innovative thinking such as regimen alteration, changing patient pool or modification in clinical trial outcome parameters can save the drug from going into the abyss.

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