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Hurdles in drug discovery for Gaucher's disease

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ABSTRACT

Metabolic disorders are increasing day by day in current world population. The percentage of the metabolic disorder in US population is less than 20,000 so it has been considered as an orphan disease. For development of drug to an orphan disease is a challenging task for the pharmaceutical industries because of various factors. Among all the metabolic disorder Gaucher's disease is the one rarely seen condition in the people so has been considered as an orphan disease. Medication for the orphan disease is called as orphan drug gauchers disease can be seen in children and adults but, as per the researches the impact of disease is more in children than that of the adult. Another problem with gauchers disease is misdiagnosis of the condition. Main problem in the drug discovery for orphan drug in the EU and FDA is mainly because of lack of harmonization in the orphan drug regulations between FDA and EMA. Another major huddle for the discovery of the medication for the orphan disease like gaucher's disease is lack of synchronization and appropriate guidance from the regulatory industry and this will be burden for the sponsor's to manufacture a medication for orphan disease like Gaucher's disease.

Keywords: Regulatory guidelines, FDA, EMA, Orphan disease.

INTRODUCTION

Gauchers disease is a lysosomal storage disorder. As per European union rules when a disease in population is prone to be 0.6 in 10,000 people which is equivalent to fewer than 23,000 people and Incase of the United states food and drug metrics if disease is affected in the lesser than the 20,000 population is designated as the orphan disease. Finally, as per both US and EU regulatory agencies Gauchers disease falls under the orphan disease category. There is no complete harmony in between the EU and US regulatory it can be seen in the condition when a drug is approved in one agency and if the sponsor wants it to be approved in other agency an additional trial is required. [1] Disease etiology and pathophysiology is similar in both adults and pediatrics. But, the pathology condition in pediatric is slightly different from that of the adult. As per few research studies it was found that occurrence of Gauchers disease is completely depends on age. For suppose the very young age child has the symptomatic condition for Gaucher disease but in case of the adult the diseases condition is asymptomatic it makes much though to cure the disease.

Gauchers Disease is classified into three types based on the presences and absence of the neurological condition in patients. Type-I for the non-neurological form which is the most prevalent situation, Type-II for the acute, infantile neuronopathic form, usually lethal in infancy and Type-III for the chronic, neuronopathic form. Type II and Type III account for 8% and 22% of the cases. [3] Pathophysiology involved in the gauchers disease are glucosylceramide accumulations, sub-population of the Gaucher cells, a specific cell subpopulation, metabolic consequences other than accumulation of glucosylceramide in Gaucher cells, abnormalities in the intracellular trafficking of glucocerebrosidase, casual relationship between GB1 Gene and Parkinson's disease, relationship between Gcase

deficiency and neoplasia, altered iron metabolism. [1, 2]

Involvement of the Gene in disease

Neuronal ceroid lipofusinoses (CLN) is a group of the liposomal storage condition which has been developed by the accumulation of the autofluorescence lipofuscin presented in gauchers disease. As per the Agustine. et al., (2014) Current treatments for all neuronal ceroid lipofuscinoses focus on symptomatic care a therapy for movement impairment disorders and psychotropic medications, antiepileptic for seizures management. In gauchers disease 9 forms of the CLN genes are been identified they are CLN1, CLN2 CLN3, CLN4, CLN5, CLN6, CLN7, CLN8 and CLN10. [5, 6]

Current therapies for the Gaucher disease

Current treatment plan for gaucher disease are enzyme replacement therapy (ERT) and substrate reduction therapy (SRT).

ERT will balance the levels of the Gcase enzyme with an alteration in enzyme which allows the body to break down glucocerebroside. Glucocerebroside enzyme is a substance composed of the fatty chemical builds up in the bone and organs. Subjects who are prone with the gauchers disease are given with the treatment regiment of the ERT via intravenous for the duration of the 2 weeks. There are 3 brands available for it they are Cerezyme (Imiglucerase), vpriv (Velagulcerase alfa) and elelyso (taliglucerase alfa).

SRT mechanism of action is completely differing from that of the ERT. In case of the SRT it deteriorates glucocerebroside levels. SRT are the oral medications and currently there are only two SRT medications which are approved by the FDA but not in the EU region. Usually SRT are not recommended for the few people but not for all the people because of the adverse life-threatening conditions of the SRT. [3, 4, 5]

Legal issues involved in gene therapy development

Issues will rise due to lack of harmonization in the gene therapy trials, spiraling costs, patient access, technology used for the identification of the disease and specific surrogate markers of the trials. As per Cox, (2010) In Gaucher disease trials identification of the subjects with disease and keeping them into the trial is a complex process because of the stringent informed consent form and improper insurance packages for the orphan drug.

Ethical parameters

For conduction of trials there are few ethical requirements they are social values, scientific validity, fair subject selection, Risk- benefit ratio, independent review, respect for the human subjects, fair subject selection and collaborative partnership. [2]

Importance of the validity are to have to social value; research studies must have a valid scientific design, so a valid design is an ethical requirement on the human subjects research. Presence of the enough population n in the trials are important to obtain the valid data for the approval of the treatment for the disease. In case of the diseases like the Gaucher's disease the availability of the subjects is a complex because of the lack of the large prone population.

Social values that are woman of child baring potential and breast feeding women need to identify before administration of the medication.

Ethical challenges in the Gaucher's disease

As it was mentioned earlier the occurrence of the gaucher disease is mainly due to the presence of the glucocerebrosidase even though the occurrence of the disease is not limited to only one pathology condition, but it can be of various ways. Such complexities have led to challenges in defining the appropriate criteria for enrollment of patients in clinical studies of rare disease. As per the Bhattacharya, S. Numerous factors which add complexity to find the appropriate clinical end points in rare disease and need of the high degree of the transparency between industry and regulatory authorities to define an appropriate regulatory path. [6, 3]

Influence of the R&D in the rare disease drug development

R&D of the organizations from past few years has significant chance to help in the development of the medicine for the rare diseases in addition with the help of the Critical quality attributes the moiety whatever has been identified is carefully developed and protected from the uneven circumstance which will be raised in the development process. [4, 1]

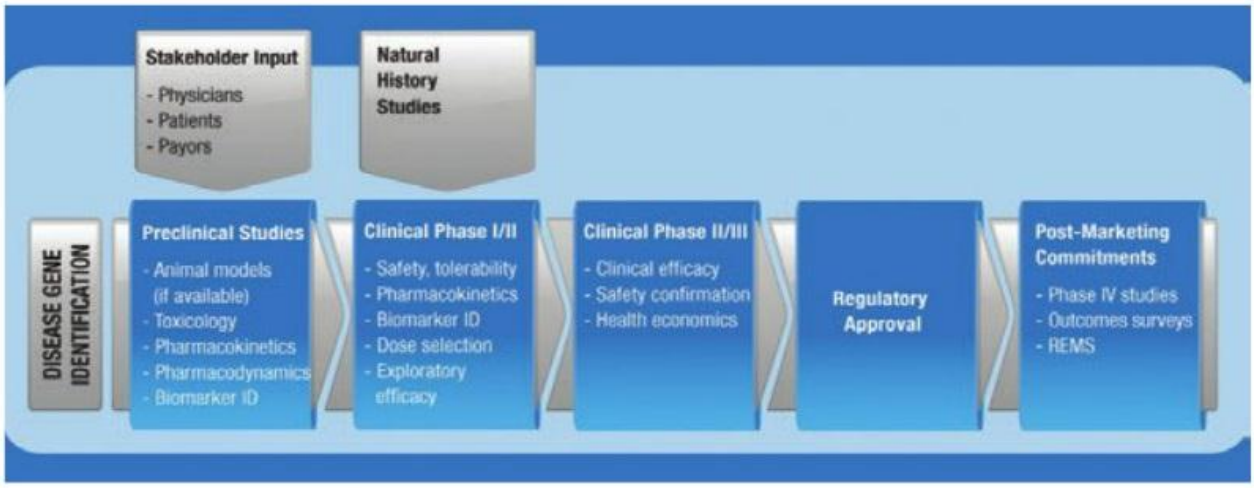

Figure I The R&D paradigm in rare diseases

Cost of production

According to the few research studies it took nearly 30 millions of euros for development of gene therapy of the rare diseases and all the budget what has been invested by the companies is directly or indirectly imposed on patients who are about to take the treatment for disease. In few cases there is a fear about the bankruptcy and the financial ruin not only for the company but also for the patients who uses it. As per the Minstry et al certain groups such as rare disease umbrella organization, including global genes, National organization for rare disorders (NORD) and (CORD) Canadian organization for rare disorder also serve some of these functions for the data identification and fund raising for the gauchers disease. [7]

Challenges in the Clinical trials of Gauchers disease

Randomized controlled trial is considered as one of the best and the pioneer standard in the clinical trial design. But, in the rare disease's condition it is completely different because of the lack of the viability of the subjects for administration of drug which has been discovered. because a small, uncontrolled trial can be the best way in some cases, but it is not appropriate for few rare disease conditions. Patient registries of the gaucher disease is very complex because of the rare availability of the venerable subjects. Geographic dispersion is also one of the major problems so having the multicenter or even multinational collaboration with the groups will helps a lot in success of the trials. [7, 8]

Regulatory environment for Gaucher disease

After the drug discovery and development of the medicine next step is the regulatory approval of the medication into the market. Companies invest billions of money and dreams for the success of the medication in the market not only companies, subject who are suffering with the disease will also wait for the new innovative medication for the treatment of their disease. Inspite of all work, dreams and hope of the medication regulatory decision about the medication into the market is an important factor.[6,7] But, in case of the disease like the gaucher is completely different because for development of the drugs to such disease is not only risk but also cost of development will be 5 times more than that of the normal disease condition in drug development. For instance, lack of the data about the efficiency data from the animal data leads to problem in approval of the oral gauchers disease which comes under SRT class.

Regulatory environment and challenges in EMA

In EU region Committee for advance medicine therapy plays a significant and gives advices to EMA for the scientific advices and EC gives approval of the medication. Rules for the orphan medication are laid down in the regulation (EC) 141/2000. Challenges are due to the high un-met medical need and short development timelines. Compared to biopharmaceuticals comparability exercises are required more frequently for ATMS, they are usually more complex and analytical data might not suffice to

demonstrate comparability about the diseases like gauchers disease. [3, 4]

Regulatory environment and challenges in FDA

In FDA region rare disease are approval under orphan drug act (21 CRF 316) drugs are approved. US potential incentives comprise of financial incentives and increase assistance from the FDA's office of orphan product development. All orphan drugs in the FDA province are revised under the fast-track regulatory review and slighter safety data customary necessities and for the approval of it emanates with the laborious risk evaluation and mitigation strategies requirements which is complex for the gauchers disease. [3, 4, 5]

Collaborative approach from EMA and FDA for challenges

The collaborative approach document helps in the rapid and smoothen the Pediatric investigation plan/ pediatric study plan. It has suggested the two best complementary approaches they are extrapolation of efficacy and modelling based approaches and a multi-arm, multi-company development programmed, to Identify the safety and efficacy of each emerging product. [2, 4]

CONCLUSION

The rarity expressed by the guacher disease has made misdiagnosis and mistreatment of the disease and lack of subjects for the clinical trials leads to the complex in the development of the drug. Priorities need to be taken for the development of the sustainable animal model phenotypes, identification of the exact pathophysiology involved in the disease occurrence. Continued efforts need to be built for the design of the clinical trial models which suits for the best outcome of the product.

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