Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

Enrichment Design: Additional Screening Process

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ABSTRACT

Identification of a human subject into a study for a clinical trial involves screening and placebo run in periods. In some cases additional screening process is required as some therapeutic agents will be effective in patients with some disorders as they show changes in response. Hence, an additional screening process called Enrichment design is employed in the clinical trials which includes active treatments as it helps in easy identification of patients in whom test agents are found to be beneficial during early phase of trial. They also helps in identification of patients with better therapeutic response. Thus, this additional screening process restricts the target population into a very small selective group during the clinical trial making the trial process easier and effective.

Keywords- Clinical trial, Screening process, Placebo run in period, Response.

Article Info: Received 12 June 2019; Review Completed 11 August 2019; Accepted 21 August 2019; Available online 30 August 2019

Cite this article as:

R Santosh Kumar R, Shambhavi K, Enrichment Design: Additional Screening Process, Journal of Drug Delivery and Therapeutics. 2019; 9(4-s):803-805 **http://dx.doi.org/10.22270/jddt.v9i4-s.3368**

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INTRODUCTION

In clinical trials, the inclusion and exclusion criteria define the target population. So in order to identify the eligible subjects, a screening period is done before enrolling the subjects into the study. After screening period placebo-run period is performed before the double blind, randomized, active treatment period to know the compliance of patients and also to estimate the potential placebo effect. Thus, screening and placebo run in periods are used as sequential screening processes to select the subjects who meet both inclusion/exclusion and compliance criteria, when active treatment is not given during investigation to patients.

Evaluation of pharmaceuticals or treatments based on hard efficiency endpoints which include death, myocardial infarction, or bone fracture is the main objective of some trials. But these hard end points require a long period follow up for observation. But in contrast short term response for soft end points i.e biomarkers are obtained much more quickly. In some cases, therapeutic agents are found to be effective in patients with underlying disorder that shows responses to the manipulation of dose levels or a single agent or several agents. Therefore, after screening period or placebo run period it is necessary to perform additional screening processes which include active treatments as it helps in easy identification of patients in whom test agents are found beneficial during the early phase of trial. These agents are found beneficial during the early phase of trial. This additional phase of screening process using some therapeutic agent or test or different agents is called enrichment phase which helps in identification of patients with drug efficacy. Such patients showing drug efficacy are then randomised so that they receive either the efficacious dose (reagent) or the matched placebo or the active controls. Thus the enrichment design is defined as a type of design that includes additional screening processes with active treatments that are evaluated in the study[1]. Thus based on the definition the active treatments used to identify the patients are the differences between both screening or placebo run periods and the enrichment designs.

EXAMPLES

Enrichment design consists of 2 phases. The first phase is called enrichment phase in which patients are classified into groups based on the benefits obtained from pharmaceuticals using titration design. The second phase is called randomised double-blind phase conducted with placebo concurrent control so as to investigate formally and rigorously the effectiveness and safety of test agents in patients. During the evaluation of the two phases of an enrichment depending upon the objectives of the trial some or different primary efficacy end points are used. In three clinical trials in the areas of Alzheimer's disease and arrhythmia that is described by Chow and Liu[2] illustrates the enrichment design.

During the early development stage of tacrine, with doses of 40mg and 80mg, 4 times a day that is used in the treatment of Alzheimer's disease, enrichment design is elected for the clinical trial. According to Davis et al[3] all patients with

Alzheimer's disease will respond to any single treatment due to clinical, biochemical and pathological heterogeneity as well as clinical experience. If some patients respond then they show response only within a limited dose range. Thus enrichment design is selected during these situations.

The above clinical trial consists of 4 phases: six-week double-blind dose titration enrichment phase, a two week placebo baseline phase, a six week randomised double blind placebo controlled phase, and a six week sustained phase. Then patients who meet the inclusion and exclusion criteria are then enrolled into enrichment phase trial that consists of 3 two-week dosing periods. The dose in each titration sequence is titrated up from 40-80mg 4 times a day with placebo in dosing periods 1, 2, 3 for titration sequences 1, 2, 3 respectively. The patients are then randomised into one of the three titration sequences conducted in a double blind fashion. The therapeutic responses for each patient at each dose are then accessed at the end of two-week dosing period. The best dose response for a patient was defined in advance in protocol as a reduction of atleast 4 points from the screening value in a total score on the Alzheimer's Disease Assessment Scale (ADAS) [4] and without intolerence side effects. Patients who are identified with "best dose" are then made to enter into a two week placebo baseline period with the hope that this period will be successfully long for tacrine to washout from the body and for the patients to return to screening pretreatment status with outcomes that are comparably effecient.

At the end of two week placebo baseline phase, if the patients points are reduced atleast by 4 in ADAS during enrichment phase then they are entered into subsequent 6 week randomised double-blind, parallel group, placebo controlled phase. Here the patients are randomised either to the active tacrine at their best dose or to the placebo that matches. Then the patients after completing the 6-week double blind phase, then they are entered into the sustained active treatment phase. Thus identification of a group of people who are likely to respond to tacrine at certain dose is done by the selection of an enrichment design with three titration sequences. These identified patients after washout period of 2 weeks are then further randomised to either tacrine at their best dose or to the placebo concurrent control in a double blind phase.

In the development of tacrine the main reason for selection of the enrichment design is to verify whether a short term response to tacrine has predictability for the long term efficacy in the prevention of progression of the patients with probable Alzheimer's disease. The same primary efficacy end points such as ADAS or the Clinical Global Impression of Change were used in both the enrichment and double blind phases for the evaluation of effectiveness of tacrine.

On the other hand for other therapeutic agents, the real efficacy endpoint is mortality that requires along time for observation. So short term efficacy of the agents is accessed by some other objective surrogate end points. Then it is important to know whether the short term efficacy based on surrogate end point is predictive of the hard point such as mortality. Therefore enrichment design is usually employed for the identification of the short term responders at initial stage followed by the main phase of long term study. Examples of this type of trials can be found in the area of Arrhythmia such as Cardiac Arrhythmia Suppression Trial (CAST) [5-7] and Electrophysiologic Study Versus Electrocardiogarhic Monitoring (ESVEM)[8-12].

Cardiac Arrhythmia Suppression Trial is a multi center, randomised, placebo controlled study that is used to test whether the suppression of asymptomatic or mildly symptomatic ventricular arrhythmic agents, ecainide and flecainide and with a placebo concurrent control. The objective of the study is to test the predictability of adequate suppression of ventricular arrhythmia by the active drugs based on Ventricular Premature Contractions (VPC) as recorded by Hotter monitor for mortality. As a result, an open model enrichment design with 2 titration sequences involving only active drugs is selected for this study. Patients with ejection fraction of atleast 30% are randomly assigned to the two titration sequences. (encainide, moricizine, flecainide) or (flecainide,moricizine,ecainide). Morcizine has inferior efficacy in the suppression of VPC in comparison with other 2 agents hence it is inserted in the middle dosing period. Each drug is tested at 2 dose levels. The doses are 35 and 50 mg 3 times a day for ecainide, 100 and 150 mg twice a day for flecainide, 200 and 250mg t.i.d for moricizine. Flecainide is not administered to the patients who have an ejection fraction of less than 30% because it exhibits negative inotropic properties. In patients with ejection fraction of less than 30% the titration sequences are (encainide, moricizine) or (moricizine, ecainide). The prespecified criteria for an adequate suppression of ventricular arrhythmia are

i. Reduction of 80% in VPC

ii. Reduction of atleast 90% runs of unsustained ventricular tachycardia as measured by 24 hour Holter recording for 4-10 days after each dose began. The titration process for a particular patient is stopped as soon a drug and dose are found to yield an adequate supression. Then, the patients whose arrhythmia is adequately suppressed are then randomised to either best drug identified during enrichment phase or to placebo for 3 year long term followup.

The results of CAST indicates the short term efficacy measured as supression of VPC based on Holter non invasive ambulatory electrocardiograhic monitoring might not be a good predictor for the long term hard mortality endpoint. The good independent predictor of recurrence of arrhythmia in the failure to induce ventricular tachycardia or fibrillation by some drug accessed by the invasive electrophysiologic study. The EVSEM trial is the first large prospective, randomised trial conducted to compare the 2 methods as it requires correlating the difference in reccurance rates of arrhythmia with the short term efficacy by both methods, an in patient enrichment phase which is selected to identify a group of patients in whom the test drug exhibits a short term efficacy accessed by either one of the 2 methods. After the patients fulfill their entry criteria and 48 hour Houlter monitoring and electrophysiologic groups for the 2 methods to access the short term drug efficacy.

The first group employed is non invasive ambulatory electrocardiograhic monitoring while the second group applied is the invasive electrophysiologic study. Then in each group the patients receive up to 6 arrhythmia agents in a random order until one drug is predicted to be efficacious or until all drugs have been tried that the patients were eligible to receive. A test drug is identified as effective as accessed by electrocardiograhic monitoring the inpatient enrichment phase which is defined as the failure by the drug to induce a run of ventricular tachycardia longer than 15 seconds with V_2, and V3 stimulation at the right ventricular apex.

If a drug should be proved efficient for a patient during the enrichment phase then that patient is discharged from the hospital for the long term follow-up with the drug and the accuracy of the prediction of efficacy is determined during

the long term follow-up. Patients in whom no drugs are proven to be effective and are not randomized but withdrawn from the study. Enrichment design can also be used for the studies in non responders or in patients intolerant of another agent. Temple provided examples in studies for severe hypertension and psychotropic agents.

The disease targets at molecular level can be identified after completion of Human Genome Project (HGP). Hence treatment modalities that are specific to patients with their identified molecular targets are evaluated in targeted clinical trials. Only the patients who are tested positive for molecular targets are enrolled and randomized into the targeted clinical trials, enrichment design for targeted clinical trials. Examples are ALITO trials [13], TAILORX trials[14] and MINOACT trial[15]. Simon and Maitournam [16] and Maitournam and Simon[17] have discussed requirement of sample sizes between the targeted clinical trials versus untargeted trials.In addition to it Liu and Lin[18] and Liu et al[19] have suggested the use of EM logarithm for statistical inference of treatment effects for targeted clinical trials under enrichment.

CONCLUSION

Screening for possible responders using the active treatments under investigation is the main objective of an enrichment design. However placebo responders will also be identified in the enrichment phase if placebo is also included in the enrichment phase. A dose titration designs with no washout periods is the design employed in the enrichment phase. As a result during the process of identification of responders the treatment effects, carryover effects, and time effects all confound one another. As soon as the first drug is found to yield an adequate suppression of VPC at the first dose the patients are randomized in CAST or ESVEM. Another issue for enrichment design is that whether the response observed is the best drug at optimal dose for the responder or not. on the other hand statistical methods used for analysis which are based on the data from both the enrichment phases and the double blind phase of the trail are not fully developed because of lack of randomization or different methods of randomization for the enrichment design, statistical methods for analysis. In summary, restriction of target population into very small selective groups is done by enrichment design. However distinguishing this small group of patients from rest who are with same alignment in terms of demographic and other prognostic factors for grassroots clinical practice is not possible sometimes. Therefore, the inferences obtained from the trials using enrichment design from statistical analysis remains as a challenge.

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