MINI REVIEW

Eight basic considerations on clinical drug development

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ABSTRACT

Therapeutic agents are potentially toxic, for this reason, it is necessary to assess the toxicity of medicine to value the relationship between safety and efficacy. The therapeutic ratio is the relation between potency and toxicity. This relation expresses the parameter to evaluate the efficacy considering the potency, and the toxicity considering the safety. The pharmacokinetic parameters are adsorption, distribution, metabolism, and excretion are related to this criterion. The therapeutic ratio is the ratio between the maximally tolerated and the minimal effective dose of a therapeutic agent and it calculates divining the median lethal dose for the median effective dose. The therapeutic ratio considers the safety of the dose administrated. For instance, in cancer treatment, it represents the minimum tissue damage and the maximum tumour tissue killed. In therapy, the therapeutic ratio determines if a drug can be used on humans. Moreover, it hinges on the use of a drug if it is administrated drug chronically. It has a large therapeutic ratio, but its overall benefits are small. Drugs administrated against an acute disease have a low therapeutic ratio, but they have high therapeutic benefits.

Key Words: *Clinical trial; Safety and efficacy; Basic trial ethics; Biomarkers; Evaluation trial phases; Any sources of trial biases*

INTRODUCTION

Toxicity is an important feature to consider in the phases of the experimentation because it modifies some effects of the medicine.

Safety test

Therapeutic agents can generate carcinogenicity, immune toxicity, genotoxicity, reproductive toxicity, and general toxicity in targeted organs.

Between the ones listed before carcinogenicity, genotoxicity, and reproductive toxicity are modifying variables that can affect a patient during the treatment. Firstly: carcinogenic therapeutic agents can generate a definitive tissue alteration and activate tumour growth. Evidence that emerged in the literature indicates alcohol is responsible for gastroesophageal and hepatic cancer [1,2]. Secondly: genotoxic drugs can produce DNA mutation, break chromosomes, and produce fragmentation. *In vitro* and *in vivo* tests can qualify the entity of the permanent damage. An example of this type of toxicity given by ionizing radiations used in radiotherapy to destroy malignant cells. In the third instance: therapeutic agents can affect fertility and foetal development definitively. An example of this type of toxicity is thalidomide. This medicine has been withdrawn from the market for severe birth defects. Another example of reproductive toxicity is chemotherapy drugs, like cyclophosphamide or procarbazine. The alkylating agents can affect fertility.

Clinical trials in two categories

The word *"pragmaticus"* in the Latin language means about facts. From my point of view, this trial is pragmatic because it deals with the existing problems related to the aggressiveness of advanced pancreatic cancer. It also wants to resolve question marks posed by phase II studies. It is a pragmatic trial also because it wants to explain the impact, and the effect on the pancreatic adenocarcinoma of two therapeutic agents combined against one of these drugs combined with an inert substance. In this way, the effectiveness of the combination is evaluated and the arms, which occurred by assessing this new combination, are considered. It evaluates the condition of the disease during the therapy and survival. The proven facts make this trial a pragmatic trial. "Exploratory trials are clinical trials performed early in Phase I, before dose escalation and safety and tolerability trials. These trials are de facto first-in-man studies but lack a therapeutic or diagnostic goal and do not seek to establish the Maximum Tolerated Dose (MTD) [3-5]."

Biomarkers

The biomarkers are bio-reactive compounds used to detect biological

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patterns. Biomarkers play a key role in drug development improvement. It is important to set clinical trials on personalised therapy to improve effectiveness and reduce cost, risks, and time. Relevance and validity are two features to evaluate a biomarker [6]. Biomarkers are relevant if they can supply relevant information on clinical queries. Their validity refers to the items that they can characterize. In this way, validity represents the spectrum of the tool. For this reason, a good biomarker can determine three parameters and help clinical research. These items are biological features, pathogenic features, or pharmacologic feedback to therapeutic action. Moreover, it is important to connect the biomarker to the clinical endpoint by choosing the appropriate tool. Its use would reduce the uncertainty of the clinical result. In other conditions, biomarkers assess the toxicological profile of a molecule in preclinical research and Phase I and II. In the first instance: selected biomarkers can detect nonclinical safety patterns for human clinical trials such as carcinogenicity, genotoxicity, immune toxicity, and pharmacological and biological safety. In the second instance: selected biomarkers used to find the origin of the arms in a clinical trial. Good biomarkers should be able to also provide information on the patterns that generate these safety characteristics.

Sample collecting ethics

Ethical implications: when the clinician collects the sample, the informed consent must be properly written and very specific because authorization has to fulfil three features:

- The importance of the meaning of the research will be executed on the sample;
- The absence of the consents itself could compromise the aim of the research project;
- The permission to proceed to the research given by the donor, isn't implied in the act of donation so that he could deny the consent to any unwanted use of the sample in question.

Said this, the donors could retire the consent to obtain the sample at any moment if she or he is not in agreement with the scope of the research project. This matter is set on the autonomy of the donor. The sample must treat with the best discretion and privacy in a way to respect the patients' respect. It is a statement that defines the roles to legally respect human tissues involved in research [7]. The main legal consideration is the ownership based on a principle, "every man has a property in his person." according to the philosopher John Locke. The informed consent to collect a sample gives legal authority to the treatment of the donated tissue and it can be given also by the person who exercises tutorial authority. Therefore, the tissue uses under the mentioned legal conditions and in respect of privacy [8-11].

Ethical principles

If I would be invited to take part in a clinical trial, I would consider three items to be informed properly and make the appropriate decision. These are: firstly, informed consent to know arms and benefits, secondly care and protection of research participants and third instance protection of research participants' privacy. Personal autonomy is traced by the philosopher Emanuel Kant; he established that anybody could decide by himself to do an action. For this reason, the informed consent provides me with information about the standard adopted during the trial and it makes me aware of the risks that I occur. In this way, I could voluntarily subscribe to the informed consent [7]. My protection should be set on the consideration of three items. They could let me take the appropriate decision. These are:

- Non-maleficence: harms must be avoided to respect the person,
- Beneficence: by balancing benefits and risks I can evaluate my prognosis
- Justice assesses how risks and benefits are distributed [8].

So, remembering the motto of Hippocrates" *primum non nocere*" first do not harm, I could decide properly if these three roles are respected. If I want to take part in a trial, I should also consider how personal data and samples of tissue are treated. I should evaluate if respect the criterion dictated by the human tissue act and data protection act to consider the level of confidentiality [8]. Nevertheless, I should consider if GCP (good clinical practice) standards are attempted to evaluate the clinical practice standard that set the trial. It ensures safety, quality, efficacy, and multidisciplinary guideline for overall rules, like non-clinical safety and genotoxicity studies [9].

Clinical drug development

Clinical Drug development is composed of four phases, and they are represented by the progressive testing of molecules.

Phase 0

Phase 0 is comprehensive of *in vivo*, *in vitro*, and in silicio testing to assess the pharmacological target, bioavailability, and pharmacokinetics *in vivo*. It also aims to develop biomarkers and to esteem the toxicity. Preclinical drug development is characterized by three stages: early, mid, and late.

During early-stage *in vitro* tests set pharmacokinetic/ pharmacodynamical characterization, the mild stage is used to assess toxicity, and, in this way, the safety and the late stage sets chronic toxicity [10]. Considering the previous description phase 0 is a testing period to set the molecule to be assessed on human beings.

Phase I

Phase I trials are the earliest studies conducted on human beings they are used to set the dose of medicine by using the dose expiation to find the right dosage. Two parameters are considered to do it; they are the MTD (Maximally Tolerated Dose) and DLT (limiting toxicity dose). This phase is also used to assess the tolerance of human beings, as shown in the literature.

Phase II

Phase II trials esteem the therapeutic activity, decide how to set Phase III and detect the risks for serious toxicity monitoring, and assess the dose and side effects. Phase II trials have a larger sample size than phase I and they were randomized to compare the new treatment with a placebo, no treatment at all, and standard care. Phase III trials compare new treatments with standard care, and/or placebo for instance. They have randomized two or more groups (1:1), (1:2), and (1:3) to control the effectiveness of the new therapeutic agent even under giving different doses of the standard treatment. They need the largest number of participants to be realised. During this phase, the investigator controls the side effects to balance risks and benefits. Randomization is important, in a phase III trial, because this phase aims to control the efficacy and the safety of new treatments against a control. The groups of participants treat based on the treatment;

patients are assessed by the allocation. The investigators can compare the presence or the absence of disease. The evaluation is based on the difference in the outcomes between the groups. Another safety measure to protect the outcomes is the masking procedure, in which the patient, investigator, or monitoring committee is not aware of the administrated treatment (in a single, double, or triple-blind trial).

Phase III

Phase III trials are large-scale tests, and they are set on the largest population of participants. Reducing allocation problems, give a higher statistical safety, and produces meaningful and powerful results for each group [12].

Phase IV

Phase 4 consist in all the operation that aims to assess the product during the post-marketing AND pharmacovigilance review phase.

Data evaluation damage

The randomized trial has two types of biases:

- A selection bias is caused by a mistake in choosing the participants or groups that participate in the trial. In the recruited group of patients, there should not be hardly any differences between the patients, even if the population is composed of many patients. They are allocated for the same disease or conditions. If there are meaningful differences, the outcome of the study is compromised. An example of selection bias is the ineligibility of randomized patients due to inclusion/exclusion criteria.
- Accidental bias is by definition: a bias that can damage the follow-up to reduce the balance of risk factors or jeopardise the diagnostic variables in the groups of randomized patients. For example, the death of a patient, the withdrawal of a participant, and the alteration of the therapy, could modify the follow-up and it would jeopardise the randomization [12,13].

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