Presidenza del Consiglio dei Ministri

NATIONAL BIOETHICS COMMITTEE

BIOETHICAL PROBLEMS IN CLINICAL EXPERIMENTATION WITH NON-INFERIORITY PLAN

24th April 2009

PRESENTATION

The National Bioethics Committee in the opinion "Bioethical Problems in clinical experimentation with non-inferiority plan" examines clinical experimentation on medicines which do not present an "added value" in terms of better efficacy or lesser toxicity in comparison to medicines already on the market. These are experimentations which, unlike the "superiority" or "equivalence" plans, present some problems of bioethical relevance.

The document, starting from a definition of "non-inferiority" as "similarities within pre-established boundaries", critically examines the scientific reasons put forward to justify these studies (the possibility of offering patients a useful alternative, better tolerance, lower price), highlighting – even through exemplifications – how only the "superiority" tests have an adequate justification in the interest of the patient, whilst the "non-inferiority" tests mainly answer the needs of the pharmaceutical industry (lower risk, lower cost).

The NBC stresses the inadequacy of the justification, from a scientific and an ethical point of view, of the experimentations of "non-inferiority", recalling the

reduced scientific validity of the research, of the methodological-clinical interest and of the definitive guarantee of efficacy (which is instead assured by medicines which have already been tested and are on the market), the potential "conflict of interest" for the doctor who has the primary obligation to offer patients a therapy which is suitable and of proven efficacy (not guaranteed by the medicines proposed in non-inferiority studies), the lack of transparency regarding the informed agreement of the subject who undergoes the experimentation, who often is not given sufficient information regarding the nature of the study that is being conducted.

The opinion of the NBC stresses the principle, accepted in numerous international documents, according to which the specific interest of the patient must not be subordinate to other interests, including commercial ones or those of the sponsor. In particular, the NBC recommends that the "non- inferiority" studies are presented with more transparency and that the ethical committees carefully examine the methodology with which they are planned, approving only the "superiority" experimentations, which can bring potential advantages to the recruited subjects or to the patients who will use the medicine in the future.

The group undertaking this task is coordinated by Prof. Silvio Garattini and is composed of Prof. Luisella Battaglia, Prof. Adriano Bompiani, Prof. Stefano Canestrari, Prof. Cinzia Caporale, Prof. Maria Luisa Di Pietro, Prof. Laura Guidoni, Prof. Luca Marini, Prof. Assunta Morresi, Prof. Demetrio Neri, Prof. Andrea Nicolussi, Prof. Monica Toraldo di Francia and Prof. Giancarlo Umani Ronchi. The opinion drafted by Prof. Silvio Garattini with the contribution of the other members of the group (in particular of the Prof. Adriano Bompiani and Prof. Demetrio Neri) has been discussed in the plenary meeting of the 24th of April 2009 and unanimously approved.

Rome, 24th April 2009

The President
Prof. Francesco Paolo Casavola

Introduction

The clinical experimentation of the medicines, according to the regulations of all industrialised countries, is possible when it is sustained by an adequate rationale inferred by *in vitro* and *live* studies in various animal species, which can establish a potential therapeutic efficacy and the eventual risk of toxicity. Classically three phases are identified in clinical experimentation: phase 1 or the tolerability phase, which determines the maximum dose that can be administered during a specific period of time; phase 2 or the preliminary efficacy phase and phase 3, which has the fundamental task to establish the relationship benefit-risk and therefore the role of the new medicine in the therapy; this is followed by phase 4, which takes place after the marketing and monitors the toxic effects.

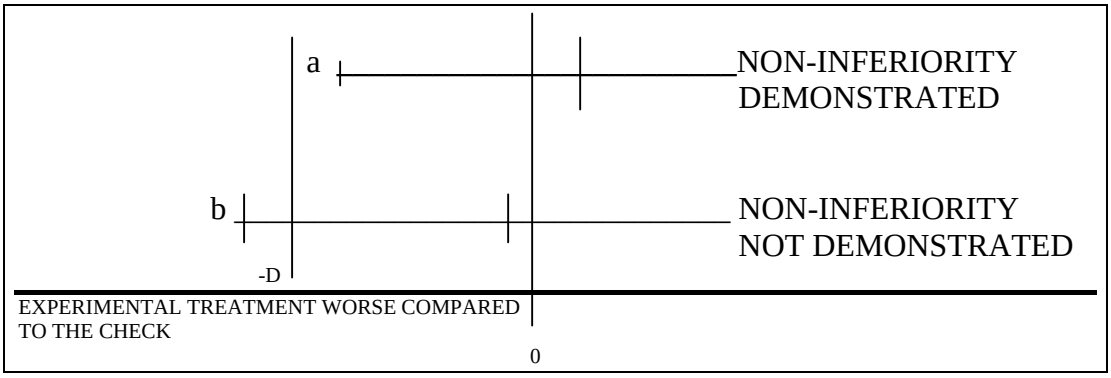
Phase 3 is therefore fundamental for the passing of new medicines and currently consists of two controlled and randomised clinical studies (RCT), in which the medicine can be compared to the placebo or to a medicine of reference with regards to the piece of information which is the object of the study.

Each clinical study should raise an important question, which should be answered conclusively, always keeping in mind that the aim is the benefit of the patient. As the Helsinki Declaration establishes that the placebo cannot be used in case there is a medicine already available (and validated against a placebo) for a specific indication, usually the comparisons are carried out between a new medicine and a medicine of reference, used with optimum dosage. We must however highlight, that the European law founder of the European controlling body, EMEA, does not require comparisons but establishes that a medicine must be evaluated on the basis of three characteristics: quality, efficacy and safety (1). It is therefore not necessary to prove the new medicine has an “added value”.

In the realisation of a RCT three different designs can be used: a superiority design or an equivalence design or a non-inferiority design. The scientific literature reports, in the last decade, a considerable increase of RCTs with non-inferiority plan. It seems therefore important to analyse the bioethical implications of this methodology, used in the experimentation of medicines on humans.

Definition of non-inferiority

Non-inferiority is a kind of similarity within predetermined boundaries. The boundary is represented by the level of inferiority considered tolerable for the new medicine, with regards to the standard of reference. This arbitrary difference in terms of loss of efficacy is defined as “margin of non-inferiority” or “delta”. As illustrated in the picture, non-inferiority is considered established when the interval of confidence at 95% of the efficacy of the new medicine, does not exceed the pre-determined boundary of inferiority.



The zero represents the therapeutic effect of the medicine of reference
-D represents the acceptable loss of efficacy to establish "non-inferiority"
a and b represent the therapeutic effect and the boundary of confidence at 95% of two experimental products.

The experimental medicine for which the non-inferiority is verified, can in fact be less efficient and less safe, but not enough to be recognised as such. So, if the margin of non-inferiority is set at 7.5%, a greater incidence of serious events – for example 7% instead of the 5% which the buyer currently risks, that is generally what happens when the medicine is correctly used in therapy – is not considered sufficient to mark a difference between the new and the old treatment. The new medicine will be considered not inferior to the old one, even if when 1000 patients are treated with the first one 20 more deaths or serious events can occur in comparison with the last one.

Reasons given to justify non-inferiority studies

One of the reasons usually presented, is that there can be patients who do not respond to standard treatments and products with similar activity to those treatments can represent useful alternatives. The aim is reasonable, but the approach is not. What is in fact the logic of establishing the non-inferiority of these products in the general population of patients? If their targets are the non-responders to the available treatments, why not verify the superiority of these products in comparison to the medicines that are little effective in this subgroup of patients? This last approach would take into account the interests of the patients, but not the ones of the pharmaceutical industries, who aspire to a market as wide as possible and not only to a section of it, represented by a subgroup of patients. In other words, once patients who are resistant to a specific medicine are selected, the new medicine should be evaluated only with regards to these patients, instead of carrying on a non-inferiority study.

Another reason put forward is that non-inferior medicines from the point of view of their efficacy can be better from the point of view of their safety.

It must however be observed that generally the RCTs do not have the statistical potency to observe a different profile of toxicity. In case it was possible, given the high number of the patients or the high frequency of the toxic symptoms, to evaluate the toxicity, the study would not be of "non-inferiority" anymore but it would become of superiority with regards to safety.

The "non-inferiority" is in many cases justified when a new medicine has characteristics which facilitate the compliance to the treatment by the patient. For instance a medicine that has to be administered once a week is certainly more

comfortable for the patient than one which has to be administered three times a day. However, if this facilitation requires a truly better adhesion, then the clinical result should also be better (not “not worse”) and therefore a superiority design should be used.

Even in the eventuality – which has never actually occurred – that a non-inferior medicine from a therapeutic point of view was made available at a lower price, it would be difficult to accept. In fact to prove that a possible smaller benefit for individual patients is compensated by the bigger advantage of a more widespread use of the new medicine in the general population, it would be necessary to undertake much more extensive and long term studies compared to the non-inferiority trials. These examples suggest that any question of practical importance for the patients require a superiority test. The superiority test, whether or not the hypothesis proposed takes place, gives information regarding the placing of the new medicine in the context of existing treatments. The non-inferiority test seems instead to answer only the needs of the pharmaceutical industry, ensuring for the new medicine a placing on the market regardless of its value in comparison to medicines already available.

From the point of view of the industry, to prove the non-inferiority of new products is less risky than aiming to establish their superiority. If the superiority test fails, it can damage the image of the product, even if that result in reality can provide useful information to doctors and patients. Non-inferiority studies aim instead at not recognising possible differences (which could inhibit access to the market for the new product) rather than highlighting them (in order to better define the so called “place in therapy” of the new product). A documentation of non-inferiority leaves the product in a kind of limbo: its placing within the other available treatments is not defined, but its placing on the market is nonetheless assured.

An example of the use of the “non-inferiority” boundary

As well as being less risky from the point of view of its image, it is also simpler and less costly to prove the non-inferiority than the superiority, as illustrated in the exemplary case, although extreme, of the study COMPASS (2) which recruited 30 times less patients than the superiority trials that had submitted the same hypothesis to verification (3-5).

The larger the non-inferiority boundary set, that is the worse result designated as area of non-inferiority, the more limited is the sample necessary to test the hypothesis. The smaller the sample, the smaller the investment required to conduct the trial and the much bigger the possibility of not highlighting a possible difference and assert the non-inferiority. This has led to the selection of extreme hypothesis: the COMPASS study, for instance, considered the thrombolytic saruplase equivalent to the streptokinase in the treatment of the acute myocardial heart attack even if 50% more deaths would occur in the group with saruplase then in the control group (2). In absolute terms this means considering saruplase as effective and safe as the streptokinase even if there were 35 more deaths compared to the 70 expected deaths every 1000 patients treated. The test of this questionable hypothesis only required 3000 patients, at a time when to verify the superiority of tissue-type plasminogen activators on the streptokinase involved over 90.000 patients in three large and randomised clinical studies (3-5). Besides the paradoxical hypothesis, results of studies like the COMPASS’ arouse perplexity for the width of the confidence intervals. At times the

width of the intervals is such that what is considered non-inferior from a statistical point of view cannot be non-inferior from a clinical point of view, as in the case of the comparison between thrombolitics (6) antidepressants (7), etc.

From what has been said, some criticality profiles for the ethical evaluation of the equivalence or non inferiority protocols emerge, which now are being looked at in more depth in the light of national and international regulations that regulate the biomedical research on human beings (8,9).

Further criticalities in the non-inferiority plans

One objection to the non-inferiority studies concerns the justification for the research. In all national and international documents on the subject of biomedical research on human beings it is recognised as first and necessary (even if not sufficient) condition for the ethical acceptability of a research, its scientific quality. A research lacking from the point of view of its scientific quality is, for this same reason, unacceptable from an ethical point of view, as already stated, from instance, by this Committee in the document on the Experimentation on medicines (1992), where on the contrary is very sharply stated that any research which pursues "marginal or futile aims" must be rejected. The theme has been amply discussed in literature, also because it is certainly not possible to state that only research which pursues scientific aims of great significance or capable of generating new knowledge of universal importance, should be carried out. Scientific quality can be recognised even in research of more limited significance, capable of bringing information limited to a particular area, but precise, not yet part of the scientific knowledge. To use a consolidated terminology, this kind of research can have an inferior "value" in comparison to research of more general importance, but this does not make it inferior in scientific "value".

Many technical problems that are difficult to resolve, still exist when the point of view required is that of the public interest. The margin within which the non-inferiority is accepted is difficult to establish because it is impossible, especially for important illnesses, to accept the idea of relinquishing even only a small part of the benefit given by the medicine of reference. The risk is that the medicine considered "non inferior" will be subsequently used as standard in another non-inferiority study, eroding in this way the progress made by the medicine. It is possible that these transitions would allow the authorisation of medicines that in the end will be indistinguishable from the placebo, a phenomenon known by the term of bio-creep (10). In any case, the apparent loss of efficacy can be higher than what has been hypothesised, as the effect of the standard treatment includes that of the placebo: in fact if the standard treatment forestalls 30% of the expected events and the selected non-inferiority boundary of the new medicine allows the new medicine to forestall only 20%, the apparent loss of efficacy is equal to a third, but can be half if the effect of the placebo guarantees 10% of the total effect. Non-inferiority studies in this way expose the patients to clinical experiments without any guarantee that the experimental medicine is not worse than the standard treatment and without any attempt to verify whether maybe it might be better.

The non-inferiority methodology assumes that the patients on which the medicine of reference is evaluated, can be superimposed to those on which such medicine was originally evaluated. Despite the many regulations introduced (11), such uniformity is very difficult to achieve, as recently demonstrated by a study

which conducted two experimentations rigorously equal at the same time, in which the placebo gave rise to results which were difficult to superimpose (12). Finally, in the non-inferiority studies a conduct that is not very rigorous is what seems to give results: in fact the more there's little adherence to the therapy and neglect of the study by the patients, the more the variability increases and therefore the possibility to demonstrate the non-inferiority (13).

In practice an evaluation of non-inferiority studies has demonstrated that on 383 studies that have been examined, in 64% of cases non-inferiority could be established only if the difference was higher than 50% in comparison to the medicine of reference and in 84% of cases only if the difference was more than 25% (14). A more recent evaluation established that only in 4% of non-inferiority studies under consideration a justification had been given for the choice of margin; in addition in 50% of cases inadequate statistical tests had been employed (15).

A further criticality profile sticks to a well-known problem and, even from the Helsinki Declaration, object to more in depth study: the potential "conflict of interest" that can be generated because of the double role of the doctor when he carries out a research within the therapy: it is important to remember that the doctor's primary obligation is to offer the patient the most appropriate therapy between those proved efficient for his/her pathology. Now, in the case of non-inferiority protocols, the doctor plans to give to a part of his patients a treatment that will be, in the best of cases, not inferior to the one it is being compared to.

It is not ethical to involve patients in non-inferiority studies

What kind of ethics legitimates an approach that seems to hide the differences instead of highlighting them? Non-inferiority studies lack ethical justification because they do not offer any advantage to the patients, current or future. They deliberately relinquish to consider the patients' interests in favour of commercial interests. This betrays the substantial agreement that is established between patients and researchers in any correct and informed consent, which presents randomisation as the only ethical solution to answer such clinical uncertainly. Non-inferiority studies aim only to boast of some efficacy, but without giving definitive proof of it. In the informed consent text it is never made clear to patients what a non-inferiority study means. Few patients would agree to participate in the study if the message in the form that asks for their informed consent was put clearly: why would a patient accept a treatment that in the best of cases is not worse, but in reality could be less efficient or safe than the available treatments? Why would patients participate in a randomised test that will offer only doubtful answers, since non-inferiority includes the possibility of a worse outcome? (16) In the current clinical experimentation the patient has the possibility to confide in the action of ethical committees, which have to approve the protocols. It is appropriate that ethical committees are aware of the methodology with which controlled medical studies are planned. Non-inferiority studies should not be approved unless they aim to demonstrate other advantages more relevant to the patients. We should in fact always request that a new medicine is tested only with the "superiority" methodology, to be sure that the study can bring potential advantages to the recruited patients and to the patients who will use the medicine in the future.

It is worth remembering that the DM 18th of March 1998 (reinforced by the DM 12th May 2006), which bears the guidelines for the creation and the functioning of ethical committees, in point 3.7.6 states: "As the informed consent represents an

imperfect form of protection of the subject, obtaining informed consent is not sufficient guarantee of ethical behaviour and does not exempt the Committee from the need to evaluate the experimentation". It is not therefore possible to justify the ethical status of a non-inferiority protocol simply appealing to the fact that the patient has been perfectly informed on the logic, the aims, the risks and the benefits of the experimentation, aspects that the ethical Committee cannot but evaluate in light of the documents attached to the request for authorisation.

Conclusions

Non-inferiority studies disregard both instructions which serve as guidelines to the planning of good clinical studies, or "ask an important question; and give it a methodologically reliable answer" (17). The important question is the one which is real for the patient, therefore the one that tackles a real clinical problem. But a study planned to verify whether a medicine is "not worse" than standard treatments, without any interest in any added value, does not ask any clinically relevant question. This kind of study simply cuts research and development costs, as well as the risks for its commercial image, without a care for the patients' interests. Randomisation should not even be allowed in such circumstances, because it is not ethical to leave to chance the possibility that a patient might receive a treatment which, in the best of cases is similar to the one that he/she would have received anyway, but could also reduce a great number of the advantages that previously had been assured to him/her by current treatment. We hope that the text of informed consent explains the concept of non-inferiority. With regards to the methodological approach and therefore the answer, the uncertainty that surrounds the conclusion of non-inferiority is difficult to accept: however small, the increase of the relative risk inevitably implies an unacceptable excess of negative events in the patients' population. At times the risk can turn out to be significantly higher in the group subjected to the experimental treatment, however all this does not refute the non-inferiority of such treatment (13).

In conclusion, The National Bioethics Committee recommends that non-inferiority studies are illustrated with more transparency and carefully analysed by the ethical Committees, which have to supervise in particular so that the patients' interests are not subordinated to other interests, including the commercial interests of the sponsor.