

Opinion on whether a trial is required to confirm the efficacy of centoxin. report.

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Opinion

Centoxin is an anti-endotoxin monoclonal antibody type IgM (immunoglobulin M) for therapy of gram-negative bacilli (GNB) sepsis. This human antibody (HA 1A) is to be used to reduce mortality in septic shock induced by GNB infections, by neutralising the effects of the endotoxin. Such infections are frequent and remain an important cause of mortality in spite of ever more active antibiotics.

Genetically engineered by a firm called Centocor, centoxin is a very innovative drug. It was approved for marketing in France (AMM - *autorisation de mise sur le marché*) on 2nd July, 1991, following a pivotal study published in the *New England Journal of Medicine*. However, the methodology of this study gave rise to fierce controversy and, as a result, together with the high price of the product, serious reservations were expressed regarding its use. At this juncture, a group of specialists in resuscitation in the *Assistance Publique des Hôpitaux de Paris* (Paris public hospitals) are proposing a confirmation study. However, there is a problem since this study would include a placebo group for treatment which is already licensed for sale. Since the *Assistance Publique des Hôpitaux de Paris* are to sponsor the trial, their Director General asked the Secretary of State for Health for approval and the latter requested an Opinion from the National Consultative Ethics Committee for Health and Life Sciences (CCNE).

The CCCNE considered the problem and in so doing, broadened its field to review options in order to avoid a similar situation in the future.

Centoxin

In the present state of scientific knowledge, centoxin's efficacy in septic GNB syndromes is plausible, but unproved. Criticism has been levelled at the methodology.

This lack of certitude, together with the high price of the product, has harmful consequences, primarily for patients, because doubt leads to therapeutic hesitation. The consequences are also harmful to public health : on the one hand, use of this medication will lead to expense which is not assuredly justified, to the detriment of other expenditure which might be more useful; on the other hand, the necessity to compare future products to a reference product of unproved efficacy will demand very large trials which will be difficult to interpret, so that evaluation will be compromised. A confirmation test (called "repeat test") of the pivotal study which justified approval for marketing will be necessary.

At this point, such a trial seems hardly feasible. From an ethical point of view to begin with, the presumption that centoxin is effective makes recruitment of a placebo group a difficult operation. This argument could, at a pinch, be ignored, if presumption of efficacy was weak. However, a more potent objection is that since approval for marketing has been given and the drug is available, it would be unacceptable to withhold it from half of the patients, even though due to doubts about efficacy centoxin would not in fact be prescribed to anywhere near one patient in two.

In view of this difficulty, the CCNE had considered several possibilities. However, a new fact arose after the CCNE was asked to give an Opinion : the Food and Drug Administration (FDA) decided not to approve the drug for sale, and at its request, Centocor has started work on a trial with as large a number of patients as in the pivotal trial, placebo-controlled, at an inclusion rate sufficiently high to enable early conclusions.

In the circumstances :

- either trial conclusions are positive, and centoxin is found to be effective
- or else they are negative, and the AMM should logically be withdrawn.

In either case, the "repeat" trial which was planned in France would serve no useful purpose since it has been replaced by a larger scale trial in a shorter time period.

General recommendations

To avoid a repetition of such pitfalls, the Committee offers the following recommendations in the case of serious illness (life-threatening in the short term) :

a) "Repeat" trials of the kind of those which justified an AMM should not be performed after AMM is given, except if new theories or facts arise. The reason for this is that once authorisation is given, there are consequences affecting ethics and possible liability.

b) The only trials which could be carried out after AMM would be of a non-repeat variety on the subject of other indications for instance, or to compare dosage.

c) An AMM should be supported by at least two trials, each of which should be on a sufficient scale. If one of the trials is completed and suggests conclusions before others, the latter's continuation can be an ethical quandary. It is therefore to be recommended that so far as is possible, trials should be simultaneous and conducted according to a timetable which would ensure that when the conclusions of the most advanced are known, recruitment and if possible therapy in the others are completed. If that is not so, their continuation should be submitted to the decision of an independent supervisory committee.

d) Early AMMs or conditional pre-AMMs - i.e. an AMM requiring confirmation efficacy trials to become final - should not be granted.

These recommendations should be made known to all concerned, in particular to pharmaceutical firms for which they represent - in particular paragraph c) - a financial effort which may be daunting for innovative products but which does seem to be necessary in the best interests of the community as well as of their own.

Report 14th April, 1992

The problem was put to the CCNE by a letter from the Secretary of State for Health. The Committee designated D. Schwartz rapporteur and he convened a group of experts to deal with the issue. This report sums up the group's thinking as of 14th April, 1992. Events which took place after that date are presented in a complementary report dated 10th June, 1992.

The situation

Statement of the problem

Centoxin is an anti-endotoxin human IgM monoclonal antibody HA 1A designed to reduce mortality in septic shock secondary to gram-negative bacilli (GNB) infection.

GNB infections remain a high cause of mortality, particularly in the event of septicemia. It is estimated that there are about 100,000 cases a year, of which about 30,000 are attributed to GNB. In spite of increasingly active antibiotics, mortality rates for septicemic GNB infection remain high : 20 to 60%, and 50% in cases of severe sepsis, particularly with shock.

Centocor produced by genetic engineering a very innovative drug called centoxin, which is the first of a series of related drugs under study and/or development (anti TNF, anti-interleukin,...)

Centoxin was approved for marketing (AMM) on 2nd July 1991 following a pivotal study by Ziegler et al. the results of which were published in the New England Journal of Medicine on 14th February, 1991. However, the methodology of this study led to fierce controversy and, as a result, together with the high price of the product (more than 21,000 French francs per patient), serious reservations were expressed regarding its use. A particularly serious issue is that new drugs appearing in the future will have to be compared to this reference product of disputable efficacy, which will compromise their evaluation. At this juncture, a group of specialists in resuscitation of the Paris public hospitals, under the direction of Professor Brun-Buisson, proposed a confirmation study. The protocol for this study was approved by the Ethics Committee of the Hopital de la Pitié (5th August 1991) and by the Consultative Committee for the Protection of Subjects in Biomedical Research (CCPPRB) of Créteil on 24th October 1991. However, there is a problem since this trial includes a placebo group for treatment which is already licensed for sale. As the Paris public hospitals are to sponsor the trial, their Director General asked the Secretary of State for Health's approval and the latter requested an Opinion from the National Consultative Ethics Committee.

This report will firstly set out the reservations about this product and will then consider the following questions : Is a confirmation trial desirable ? If so, is it possible ? What other possibilities exist ?

Finally, the report will consider the steps which should be taken to prevent a repetition of

such a situation in the future, and in particular the role of AMM in the evaluation of pharmaceutical drugs.

The first reservation : AMM based on a single trial

The AMM was awarded on the basis of a single pivotal trial performed by Ziegler et al. Generally, an AMM requires several favourable trials. There have been a few exceptions, for instance, AZT in the case of AIDS. In fact at a pinch, a single study would suffice, if it was conclusive, which leads to an examination of scientific reservations in this case.

Scientific reservations

As soon as the article in the New England Journal of Medicine was published, letters sent to the publication expressed reservations. Furthermore, commissions given the task of considering the marketing of centoxin, did not hesitate to criticise certain facets of the pivotal study. The main reservations were the following :

Statistical analysis was essentially done on a sub-group and not on the whole group. The total group, in which there were 543 patients with probable GNB sepsis, was randomly divided into a treated group and a placebo group. The principal analysis was performed on 200 patients with bacteremia, i.e. patients whose blood, drawn before division of the total group and inclusion in the test, later gave rise to positive GNB blood culture. In this sub-group of 200 patients, mortality at 28 days was clearly lower in the treated group than in the control group (30% as against 49%, $p = 0.014$), whereas in the initial group of 543 patients, mortality in the treated and control groups was almost identical (39% and 43%). To make an analysis of a sub-group when there is no significant difference in the whole group, is not considered correct procedure (if only because one could suspect an a posteriori breakdown according to results). The method could be acceptable however if focusing on the sub-group has some logical basis and has been announced in the protocol. These conditions seem to have been verified, if not entirely, at least "approximately".

According to the protocol, the number of patients needed was calculated on the basis of the sub-group with GNB sepsis, which does not entirely coincide with the group with bacteremia. However, from a biological viewpoint, it is logical to accept that treatment should mostly be effective in the presence of bacteremia. On the one hand, endotoxins are much more likely to be found in the blood in cases with bacteremia than cases without (approximately 58 times out of 100 as compared to 20). On the other hand, the antibody is a large molecule which does not leave the blood circulation easily.

As early as 1982, Ziegler had published the results of a trial on a polyclonal in cases of bacteremia, and there have been several studies of this sub-group. Baumgartner published in 1990 a general review called : " Monoclonal anti-endotoxin antibodies for the treatment of gram-negative bacteremia and septic shock" .

By way of conclusion, it can be stated that this objection is not very convincing.

In the sub-group with bacteremia, the control and treatment series are not comparable. The placebo series is from the start slightly worse off than the treatment series. Although there are no prognosis factors which are markedly unfavourable for the placebo series, a multivariate analysis taking account of these factors makes the mortality differential between the two series almost non-significant. The value of p which was initially 0.014, becomes 0.03 or 0.04 depending on the method. As prognosis factors cannot be measured to perfection, and some of them were wrongly not taken into account (e.g. Mac Cabe score), one might well wonder whether a very meticulous equalisation of the two series would not finally lead to an even greater p value, greater than the significance threshold.

This objection that the groups are not comparable is probably the most serious one.

The conclusion drawn from a study depends on the one hand on the degree of significance of p , and on the other hand on whether the hypothesis under study is plausible, the not very convincing level of significance of this study begs a close inspection of the biological and clinical arguments put forward in favour of centoxin.

From the biological viewpoint, the starting hypothesis is logical : it seems to be accepted that complications of the infection are due to the endotoxin and the presence of lipid A. Action of an antibody against this lipid is therefore beneficial. There have always been reservations on this mode of action. In the laboratory, the protective effect of HA-1A in vitro and in animal models was obtained by one team, but other teams have been unable to reproduce the effect.

On the clinical side, there have been experiments with a polyclonal (anti J5) directed against endotoxins of several gram negative bacteria. Four trials were published, two of which reported positive results. The other two were negative.

The first of the positive results, obtained by Ziegler et al., deals with the treatment of GNB infections, as is the pilot study by the same author. Mortality is 22% in the treatment group, and 39% in the control group. The second trial was a prophylactic study in high infection risk surgery. The polyclonal reduced mortality significantly (5% instead of 11%, $p = 0.049$). The third is a prophylactic trial for neutropenia, and the fourth concerned the same kind of subject as the Ziegler pilot study, except that the antibody was a hyperimmune serum and not an IgM, and that the series was small.

As regards monoclonals, apart from the pivotal Ziegler et al. study, only one trial was run. The monoclonal was murine, called E5, whereas Ziegler 's is human. The results of the two trials are curiously dissimilar.

In the E5 test, mortality in the treated and control groups is identical, as is the case with centoxin. But the treatment seems to work only if there is neither shock nor bacteremia, whereas centoxin on the contrary seems to be effective only if shock and bacteremia are present. In fact, the contradiction is perhaps not as flagrant as it might seem because the analysis strategy differs in the two studies. In the E5 test, it was first demonstrated that the effect was significant only when there was no shock and therefore the role played by bacteremia was only studied in patient without shock. In the centoxin text, it was first demonstrated that the effect is only significant if there is bacteremia, and therefore the role of shock was only studied in cases with bacteremia. The importance of shock and bacteremia are therefore not studied in the same groups. Further, definition of shock is not identical in the two studies. In the circumstances, they can hardly be compared.

To end up with, we find on one side, results in favour of the therapy, and on the other, studies which do not contribute confirmation, but do not negate them either. Altogether one gets the impression that these therapies are effective. However, what is not clear is what categories of patients would benefit.

Another point was raised. Since mortality was lower in the treatment series in the sub-group of 200 patients with bacteremia, whereas it is practically identical in the total group of 543 patients, this means that it is higher in the complementary sub-group of 343 non-bacteremic patients. For the latter, centoxin increases mortality, thus revealing a toxic effect. Indeed, mortality in this sub-group of 343 patients is 45% for the treatment series as against 40% for the placebo series. However, this difference is a long way from being significant and since there is no indication incriminating centoxin toxicity, this assumption may be dropped.

Financial reservations

A dose of centoxin is worth 21,500 French francs. Its effect, according to the pivotal study is restricted to cases with bacteremia, but as the result is not known until it is too late, it must be given whenever probable GNB severe sepsis occurs, which adds up to three times as many cases. This would represent approximately 30,000 patients in France, of which 5,000 would be treated in the Paris public hospitals so that in that sector alone, an expenditure of 100 million francs which would represent 15% of the medication budget of the 50 public hospitals. This drug is distributed through a special hospital pharmacy circuit and is not charged to patients.

A first question must be asked. Can it be said that the expense is unacceptable ? Such an answer was given and accepted for instance for the artificial heart (3 million francs per person). Where is the borderline ? Is 21,000 francs above the limit ? In fact, 5 of the EEC countries out of 12, in spite of a favourable opinion issued by the European Commission, did not approve the drug for marketing, and it is not unreasonable to believe that cost may have influenced their decision.

The cost of centoxin, for hospitals limited by the constraints of a global budget, is bound to reduce possibly more useful expenditure, to the detriment of other patients.

To this difficult question, the answer can never be a categorical yes or no. It all depends on how much confidence there is in the results which brings us back to the question of how sure we are of centoxin's efficacy.

The confirmation test. Is it desirable ? Is it possible ?

Is a confirmation trial desirable ?

We have a product presumed to be effective, but not to an overwhelming degree, for a highly life-threatening disease. There are no drawbacks to this drug, except its cost. This cost-effectiveness ratio is in itself a problem for routine administration. There is a further problem. New products are on the horizon. They cannot be compared to a placebo to test their efficacy, since there is a reference drug to which the AMM was awarded. This is a twofold dilemma. Since centoxin is presumed to be effective, any gain in efficacy contributed by new medication may be weak and to detect the gain, many patients will have to be enrolled. But furthermore, if the new product turns out to be equivalent to centoxin (i.e. a non-significant difference), the only possible conclusion to be drawn is that the new drug is presumed effective, like centoxin but not more so. Doubts on centoxin's efficacy will be a major hindrance for the evaluation of new forms of treatment.

A confirmation test therefore seems essential.

Is such a trial possible ?

In its Opinion on testing of new treatments, the National Ethics Committee postulated that a trial is only allowable in a "situation of equality" where randomising patients is not harmful to them, and the benefits versus drawbacks balance is judged to be equivalent in the two groups for comparison. In this particular case, the situation of equality is not achieved. If centoxin's efficacy is presumed, then the placebo patients may suffer.

There is a further objection : the fact that centoxin was given AMM. Of course, the fact that AMM has been awarded does not compel a doctor to prescribe centoxin either in a trial or in ordinary practice. But AMM does have two consequences. The first is ethical : AMM means that a committee of experts considers the drug is effective. This is a recognition of a presumption of efficacy which reinforces the notion that there is no situation of equality.

The second consequence is a matter of liability. If the trial takes place, a death in the placebo group can lead to legal proceedings in which case the AMM argument would be powerful. For that reason only, physicians may well refuse to participate, and so might patients if they are fully informed when asked to give consent. (In fact, it is more frequently families who will have to decide since the patient is in no state to be consulted). Thus, patients included in the trial will be given placebo, whereas other patients who might be in a neighbouring ward, will be given centoxin which their doctor believes - a belief reinforced by AMM - is the appropriate therapy. Such a situation would be most uncomfortable.

The trial could, stretching a point, be envisaged when it was first submitted to the Créteil CCPPRB because AMM had only just been given and the product's special mode of distribution had not started up and could perhaps be delayed. As matters now stand, it hardly seems possible.

Solutions

It could be thought that feasibility of the study might be more or less re-established if AMM was suspended or the National Ethics Committee issued an Opinion in favour of the trial. It is not the Committee's task to intervene in this manner. The first of these decisions is not within its purview, and the second implies that the National Committee is a court of appeal for a CCPPRB, which is not the case.

The situation being what it is, the Committee is making two kinds of recommendations :

- firstly, aiming to launch similar or complementary studies as compared to the pivotal trial.
- secondly, aiming to avoid a repetition of the problem raised by centoxin (i.e. the role of AMM in therapeutic evaluation).

Similar or complementary studies

Similar studies

The present difficulty is using a placebo in a repeat trial, that is a trial which is very much the equivalent of the pivotal trial. Therefore, what should be attempted is to conduct trials which are close enough to the pivotal trial to serve as confirmation, but different enough to allow the use of a placebo. In other words, it should deal with similar indications for which no pertinent information is available and for which AMM has not been given. The following trials were discussed by the group.

acute fulminating meningococccemia in childhood . There has been a trial for this pathology but it was stopped prematurely for various reasons after 30 subjects had been enrolled. Mortality was comparable in control and treated groups. However, the test was for the anti-J5 polyclonal, and numbers of subjects very small. A new European trial for centoxin is in progress with FDA support. It became operational in October 1991 and requires a great number of subjects (270 are planned). There are now 55 and results are expected in 1993 or 1994, but perhaps earlier with intermediate studies with 90 and 180 subjects now planned. In fact, enrolment is proving difficult and lead times will probably be longer.

Although the situation is not identical to the pilot trial in this respect, both as regards bacteriology and the clinical conditions, it does represent a powerful model as regards the mode of action against the antigen, and if the result were positive, it would be a confirmation of centoxin's efficacy. As a matter of fact, confirmation was requested (following a French initiative) by the Brussels Commission, which granted approval on that condition.

Neonatal GNB septicemia. If one includes necrotising enterocolitis, this represents a large proportion of patients in intensive care units. As regards numbers therefore, a trial seems possible. However, work must start at phase 1 tolerance.

Surgery with a high risk of infection - prophylaxis. As deaths are rare, such a trial would require many subjects. However, it is worth investigating. Ziegler et al. had obtained positive results in their trial for the anti-J5 polyclonal.

GNB infection in cancer. Centoxin might be unhelpful because of neutropenia as has been hypothesised, but not proven. The advisability of such a trial is disputable.

Dosage comparison, or of injection protocols , in GNB infections. Differences may well be minor so that a great number of subjects would be required to obtain results which would be difficult to interpret if differences were non significant. This kind of project was discarded.

Finally, trials on neonatal septicemia and preventive measures in high infection risk surgery would be worth investigating, but as they are not as yet programmed, results will not be forthcoming in the near future. Furthermore, since indications are not those covered by AMM, they would have to be financed by the manufacturer and it seems unlikely that they could accept the financial burden. This leaves only the meningococemia trial which has already begun and should be strongly encouraged.

Complementary studies

Apart from clinical trials, two other types of studies should merit encouragement.

Diagnostic type studies whereby it becomes possible to detect at onset within the group of GNB infections the 30% or so of them which are likely to react favourably to centoxin. So far, the information comes too late. Evidencing the presence of endotoxins should solve the problem. There is ongoing research. If they come up with evidence, the endotoxin patients could not of course be included in a randomised trial in the present situation, since it would be unacceptable to withhold centoxin for half of these patients. But if the drug is effective perhaps the drop in mortality would be sufficient in these patients to be taken into consideration.

Laboratory , in vitro animal studies should make it possible to see whether unconfirmed results obtained by one team of researchers are credible.

Consequence of these studies

Pending results of previous studies, centoxin should be distributed according to existing procedures. It would be possible to verify whether it is much prescribed which does not seem to be the case at the present time, and from reports to the Ministry, there would be information about mortality. It would also be possible to study the results obtained by Centocor on a large cohort of patients of the same kind as those in the pilot study. In both cases, control groups are not available. Results therefore would need to be considered with great caution. However, this might lead to case studies which could at least give some indications.

More information could become available in the future : results of studies comparing centoxin with new drugs, possibly more effective (or less costly), FDA's decision on centoxin, unforeseen data....

In about a year or two, depending principally on initial results from the meningococcia trial,

the situation could be reviewed taking into account mainly these results and also any other available information.

If conclusions were positive, a confirmation "repeat" trial such as the one suggested by Professor Brun Buisson, or a similar one, would no longer be needed.

If they were negative, such a trial would be needed and upholding the AMM would become a problem.

If they were neither positive nor negative... we would be back to our present state of uncertainty. However, a repeat trial would be even less feasible.

In order to avoid a repetition of such difficulties, the Committee makes the following recommendations.

Role of AMM in therapeutic evaluation

Centoxin : a case in point

A great deal of criticism has been levelled at the slowness of therapeutic trials, mostly, but not only, in connection with AIDS. With that in mind, it has been suggested that for life threatening diseases, AMM should be granted on presumption of efficacy, subject to confirmation. During a probation period, scientifically conducted trials would be not only authorised, but mandatory. It was on the basis of this concept that the Brussels Commission gave conditional acceptance to centoxin. France did not adopt the same attitude because conditional acceptance is not an option in France and authorisation is either granted or is not. However, France shared that opinion and was in fact the originator of the Brussels decision. The AMM commission had to choose between acceptance or refusal and chose to accept on ethical grounds lest further delay bring about deaths which could possibly have been avoided. On the basis of this example, the question arose of creating early AMM, or even pre-AMM.

The events which followed the granting of AMM and the analysis made in this report motivate the following proposed attitudes for serious illness (life-threatening in the short term) :

"Repeat" trials of the kind of those which justified an AMM should not be performed after AMM is given, except if new theories or facts arise.

Early AMMs or conditional pre-AMMs - i.e. an AMM requiring confirmation efficacy trials to become final - should not be granted.

The only trials which could be carried out after AMM would be of a non-repeat variety on the subject of other indications for instance, or to compare dosage.

An AMM should be supported by at least two trials, each of which should be on a sufficient scale. If one of the trials is completed and suggests conclusions before others, the latter's continuation can be an ethical quandary. It is therefore recommended that so far as is possible, trials should be simultaneous and conducted according to a timetable which would ensure that when the conclusions of the most advanced are known, recruitment and if possible therapy in the others are completed. If that is not so, their continuation should be submitted to the decision of an independent supervisory committee.

These recommendations should be made known to all concerned, in particular to pharmaceutical firms for which they represent - in particular the 4th - a financial effort which may be daunting for innovative products but which does seem to be necessary in the best interests of the community as well as of their own.

Complementary Report, 10th June, 1992

On 16th April 1992, FDA sent a fax to the nine member states of the EEC which had approved the sale of centoxin, stating that FDA did not approve the drug for marketing. This decision came as a surprise because FDA's Science Committee had made a positive recommendation in September and FDA generally follows suit. The main reasons given for refusal were the following : on the one hand outcome criteria given by the protocol was mortality at 14 days; intermediate analysis based on that criterion revealed an absence of centoxin efficacy; the criterion then used in the final analysis was mortality at 28 days. Furthermore, the results of the intermediate analysis were known to the Centocor company which had not been planned. FDA concluded that this situation could be a source of potential bias.

A few days later, two articles in the New England Journal of Medicine discussed Ziegler et al. 's pivotal work and drew unfavourable conclusions regarding centoxin.

However, responding to a request by FDA, Centocor started a new placebo controlled trial in June on a considerable number of patients similar to those in the pivotal study and with a sufficiently high rate of inclusion to enable early conclusions.

FDA objections do not seem very convincing. The articles published by the New England Journal of Medicine do not contribute much previously unknown information. All of these arguments add up to a slight, but only slight, weakening of the presumption of efficacy of centoxin and do not modify to any considerable degree the conclusions of this report presented above.

Nevertheless, Centocor's new large scale trial does modify the course to adopt on one major point : it is the result of that trial which must be awaited before a decision is taken, and not the trial on meningococci, as well as some other items of lesser importance listed in our report.