Recommandation on making available an antiviral treatment for AIDS.

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Referral to CCNE

In December 1995, the Director-General of the French Medical Drug Agency and the Director-General of the Ministry of Health asked the French National Consultative Ethics Committee to think over firstly, the discrepancy bteween, on the one hand, the restricted availability of products belonging to the new class of drugs which had displayed therapeutic efficacy in the treatment of AIDS (i.e. protease inhibitors) and on the other, the demand that these drugs be supplied on compassionate grounds ; and secondly, the possibility of drawing lots for them.

This question was also referred to the CCNE by the firm of Abbott France, the manufacturers of Ritonavir, one of these products, and by an association of AIDS patients. Note that a similar referral was made to the National AIDS Council by the Secretary of State for Health and that the question was discussed on February 22nd **(1) .**

As the CCNE had to give a reply before March 15, it did not have time to give full consideration to all the problems that the referral raised. The leading figures who testified to the members of its working group were Dr. Vittecoq, President of the Group for the Evaluation of AIDS Treatments at the Medical Drug Agency, Professor Kazatchkine, President of the Centre Interétablissement de Traitement et de Recherche anti-SIDA - CITRAS - (Interestablishment Centre for the Treatment of and Research against AIDS), Dr. Chauvin, Medical Director of Abbott France, and representatives of the interassociation group Traitements et Recherche Thérapeutique - TRT5 - (Treatment and Therapeutic Research). One of the working group's members had an informal talk with Professor Alexandre, the Director of Medical Evaluation, and attended part of the meeting organized on February 15 by the AIDS Committee of the Ministry of Labour and Social Affairs on " methods of allocating medical drugs by temporary authorization of their use, given the small amounts made available by pharmaceuticals manufacturers" . This meeting, which mainly assembled doctors from the Centres d'Information et de Soins de l'Immunodéficience Humaine - CISIH (2) (Information and Treatment Centres for Human Immunodeficiency), was designed to obtain the opinions of practising physicians on this problem. As the situation has been subject to many changes, its history must be briefly outlined.

The facts

The referral concerned the making available of protease inhibitors on compassionate grounds. The latter term is often used ambiguously in connection with drugs. It means, precisely, to make available to patients who have reached a therapeutic " dead end" , drugs which have not yet been completely evaluated but on which justifiable hopes are founded. They are made available by means of an Autorisation Temporaire d'Utilisation - ATU-

(Authorization for Temporary Use) applied for by the manufacturer and granted, if certain conditions are fulfilled, by the Medical Drug Agency before it grants the Autorisation de Mise sur le Marché - AMM- (marketing licence). There are two kinds of ATU : nominative, and for a cohort (the latter is subject to periodical re-examination).

At present, there are three inhibitors of HIV protease : Saquinavir, produced by Roche, Merck's Indinavir, and Abbott's Ritonavir. The present administrative position as regards these three drugs is different in France and the United States : Saquinavir has been given an ATU in the United States and a cohort ATU in France. However, it is not much used and does not seem very promising, and in any case is not concerned by the referral to the CCNE. For Merck's Indinavir, an AMM has been applied for in the USA, and the application should be examined by the Food and Drug Administration (FDA) at the end of February 1997. No application in this connection has yet been made to the European or French authorities. The reason for this delay may be either the present lack of proofs of clinical efficacy required by the European authorities, unlike the FDA, for which proof of biological efficacy is sufficient, or else the marketing policy of the manufacturer, who would rather the American market opened up before turning to the European market. The question of supplying Indinavir is therefore not of immediate importance but will certainly be so in the near future. Lastly, as regards Abbott's Ritonavir, the application for an AMM in the USA is also due to be examined very shortly, and an application for the authorization of its use is due to be made to the European Medical Drug Agency before long **(3) .**

At the end of 1995, the recent scientific results published in the best international journals (4) , (5) showed that the biological efficacy of Ritonavir was excellent because of its remarkable reduction of the viral load, to the point of making the virus undetectable in certain patients by the tests available today. The trials were conducted using a " syrup" that was very badly tolerated by the patients, 35% of whom gave up the treatment ; hence the decision to administer the drug in ule form. At that time, Abbott launched an " international compassionate programme" allowing 800 patients outside the United States to be treated with the syrup. France was " allocated" a hundred of these patients. These are the patients mentioned in the referral to the CCNE of December 1995, in which the Committee was asked to indicate on what ethical basis they should be designated.

The situation changed appreciably after the Washington Congress on Retroviruses in January 1996, to which the results of a provisional analysis of the outcome of a phase III international clinical trial were presented. The trial concerned 1000 patients who were divided into a Ritonavir group and a placebo group, for which the results were compared. All patients had fewer than 100 CD4 (the mean figure was in fact around 20 CD4) and in addition to Ritonavir, had been treated for at least a year with a combination of two other drugs that act on reverse transcriptase. In the treated group, the clinical results showed a reduction of the order of 50% in clinical events (criteria of the progression of the disease, or death) and a reduction of the risk of short-term death by a factor of almost two. These results, which have been disclosed to a congress but have not yet been published, should be considered preliminary, because the periods of follow up are as yet short (6 months for the longest) and because of the limited number of events. It is not at all impossible that the trend observed will disappear or even be reversed with time. However, for the first time, AIDS specialists are talking about remission. Consequently, at least the patients defined in the international trial protocol (those with less than 100 CD4 and more than 9 months of antiretroviral treatment) should all benefit from treatment with Ritonavir, i.e. in France, an estimated 18 000 patients. Today, therefore, this is a far cry from the compassionate treatment proposed at the end of 1995, when the question was referred to the CCNE.

According to Abbott France, the difficulties involved in producing Ritonavir on an industrial scale, owing to the complexity of its chemical structure and the need to produce it in its new ule form, mean that it is impossible to make available at once the amounts necessary to treat all the patients who could benefit from the drug, in the light of the results of the clinical trials. Abbott France hopes to reduce this shortage by producing enough to treat

1000 additional patients per month as from April 1996, but for the time being, it cannot or will not commit itself to any precise figures.

It seems certain that preference will be given to the American market, and that this market's size will greatly depend on the next FDA decisions concerning the applications received from both Abbott and Merck. Lastly, it should be stressed that the above figure of 1000 does not include patients participating in current or planned studies, who number about 600.

The initial problem of the 100 patients to be treated with the Ritonavir syrup has therefore expanded into the problem of how to cope with the shortage of ules, which may well last for several months.

Examination by the CCNE of teh questions raised in the referral

As already indicated, the exact question put to the CCNE was the following : when there is a dearth of drugs for treatment, how should they be allocated ? First of all, it should be recalled that this situation is not new. Doctors have often been faced with this difficult problem, sometimes even more dramatically than in the present situation. It is not a question of deciding, as in the case of certain organ grafts, who can be saved and who cannot, but of establishing an order of priority in making treatments available. Once again, AIDS is proving to be a means of bringing to light, and publicly debating, extremely longstanding issues.

One indisputable ethical principle is that of equal access to a product for all patients with an equal need of it. This is why the CCNE straight away rejected a suggestion to take into account criteria such as the responsibilities that the patients might have had in combatting the disease.

This principle must be accompanied by precise rules for action, which are necessary both to ensure the best possible transparency from the point of view of the patients and public opinion, and to avoid deviations which are always possible. Certain deviations concerning the allocation of past treatments have, rightly or wrongly, been denounced, especially unfair geographical allocation ; only transparency can cut short all such accusations, be they justified or slanderous.

The first rule is to define the scientific and medical criteria characterizing the population of patients who are to benefit from the treatment. These initially restrictive criteria may be broadened, as and when the product becomes more easily available.

The second rule - far harder to formulate and apply - is to define a procedure for choosing the patients who are to have priority. The method that has been used in the United States is that of drawing lots on a national level. The CCNE has attempted to establish, without any a priori considerations, a list of the ethical advantages and drawbacks of this method.

One of the first things to notice is that drawing lots, as understood here, has nothing in common with the generally recognized system applied in comparative drug trials. As the latter are designed to compare two treatments about which there is no prior knowledge as to the one that is best, the act of giving the patient one treatment rather than the other involves no ethical problem, and drawing lots, or randomization, is necessitated by the methodological need to test comparable groups. The patient is informed of this randomization and must give prior consent to it before inclusion.

The ethical advantage of drawing lots is that it is the only way of ensuring indisputable equality of chances for the patients, when they cannot be classified according to an order of

priority on the basis of rational criteria. Drawing lots indeed conveys the idea that leaving the verdict to chance is preferable to favouritism. It also allows the expression of a protest against the impossible situation that the shortage creates for doctors (6) .

The ethical drawbacks to drawing lots are the following :

the patients' impression that they are merely indistinguishable numbers ;

the doctors' tacit admission to patients that they are incapable of deciding (even if this is in fact the case) and relinquish their responsibilities, thus undermining patients' confidence in their doctor, with harmful consequences for their health ;

strong but not unanimous opposition from a large majority of practising physicians who say they are used to, and capable of, making choices, even in the most difficult situations ;

practical organizational difficulties, (possibly in relation to bailiffs or to the public, or via live television programmes).

More generally, drawing lots may very conceivably arouse the virtually unanimous opposition of doctors, patients and society. A procedure which to the French way of thinking is so revolutionary is not conceivable without being preceded by a general debate, under conditions far removed from the pressures of emergency and passion.

After weighing up all these arguments, the CCNE makes the following recommendations concerning the question referred to it :

Recommandations

I. The procedure recommended shall comprise the following stages :

1. Precise definition, on a national level and according to medical and scientific criteria, of the patients who are to benefit from the product. These criteria will have to be broadened as and when the product becomes more easily available.

2. Attribution to each CISIH, on a national level, of a number of treatments proportional to the number of their patients fulfilling the above criteria. Patients treated outside the CISIH must also be taken into account.

3. The collective responsibility of the antiviral drug committees of each CISIH for deciding on an order of priority among patients, on the basis of all the pertinent medical, scientific and personal criteria. Drawing lots on a local level may be chosen as a last resort in cases where rational factors of decision do not enable a choice to be made.

II. The CCNE wishes to stress the fact that although very promising, the scientific results obtained are only, as yet, preliminary, and should not be overestimated, because the medium and longterm efficacy of the product, and the types of resistance it is capable of developing, are not yet known. Large numbers of scientifically conducted studies will have to be continued.

Other questions

The CCNE wishes to raise a few questions which go beyond its reflection on the precise problem referred to it.

1. How can the ethical principle of the equality of patients be reconciled with the inequalities inherent in socioeconomic differences ? The preference given to American patients over

European patients has been denounced, but how can help be given to the developing countries which take part in certain drug trials, countries whose patients are far more numerous and do not have the benefit of any treatment at all ?

2. In France, the life of the world of AIDS (7) has, for a month now, been determined by the vague statements, or the silence, of the pharmaceutical multinationals. Is it conceivable to work out clear sound rules for discussion and negotiation between pharmaceutical firms and the French authorities ?

3. The costs of managing patients with AIDS may grow considerably (the estimates proposed for annual treatment range from 60 to 300 000 FF per patient). If the hopes placed in the development of effective treatments proved justified, how could society cope with the cost, without detriment to the efforts made for the benefit of non-AIDS patients and other diseases ?

4. The extremely fast evolution of anti-AIDS treatments, the rapidity with which clinical trials are conducted, and the preliminary results disclosed give grounds for believing that a situation like the one just described will indeed be created. What is the best way of thinking over, calmly but without delay, methods of avoiding further crises ?

5. The problem of AIDS is still often tackled in an irrational way. How can the indispensable rational attitude be achieved ?

These are enormous problems, but they can no longer be eluded. Progress can only be made by holding a vast debate at the national level. The National Consultative Ethics Committee is prepared to contribute actively to this end.

Notes

1. The present report was drafted before this Council published its opinion on February 26, 1996.

2. One of the functions of the CISIH is to " coordinate antiretroviral treatments with case record analyses by clinicians and pharmacists" .

3. The application was submitted on February 26, 1996

4. N Engl J Med 1995: 333 : 1528-1533

5. N Engl J Med 1995: 333 : 1534-1539

6. For the record, drawing lots might be of interest as a complement to product evaluation.

7. And of France as a whole, since the publication of the National AIDS Council's opinion.