CONSEIL NATIONAL DU SIDA
25-27 RUE D'ASTORG
75008 PARIS
T. 33 [0]1 40 56 68 50
F. 33 [0]1 40 56 68 90
CNS.SANTE.FR

OPINION

ETHICS ON RESEARCH AND CARE

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EARLY ACCESS TO NEW ANTI-HIV DRUGS FOR PATIENTS WITH MULTI-DRUG RESISTANCE

Drafted and submitted by the Standing Committee on Medical Aspects

Standing Committee chaired by Mr Jean-Albert GASTAUT, MD

Committee members :

- Mr Jean-François BLOCH-LAINE, MD
- Ms Françoise BRUN-VEZINET, MD
- Ms Dominique COSTAGLIOLA
- Ms Claudine HERZLICH
- MS Christine KATLAMA, MD
- Ms Catherine LEPORT,
- MD Mr Alain MOLLA, JD
- Mr Philippe URFALINO

Research and editing : Anne MARIJNEN Frédéric DEPETRIS Marc DIXNEUF Mathieu THEVENIN

The present statement, complete with recommendations, was established at the request of the TRT-5 group[1] which referred the issue to the National AIDS Council's chair on February 22nd 2001. The TRT-5 group had observed that it is impossible for people with HIV, to obtain investigational drugs from pharmaceutical firms. The group considered that the public Authorities' intervention would be needed to put an end to this recurrent situation. Another question put to the Council by TRT-5 was : « In the absence of a satisfactory negociated solution, and regardless of specific cases (…), what steps must the public Authorities take in order to make the pharmaceutical firms facilitate early access to unlicensed drugs for all the patients with treatment failure ? »

1 MULTI-DRUG RESISTANCE

Since the implementation of combination therapy, patients in France and other developed countries have access to treatment regimens that control HIV infection in most patients. The general situation for treated patients is a considerable decrease in morbidity and mortality as compared to the first half of the nineties.

However, HIV is characterized by its ability to select antiretroviral drug resistance mutations. Moreover, persons treated can develop intolerance to medication; treatment must then be discontinued and no other drug from the same class can be prescribed. It then becomes necessary to change treatment strategies and initiate new antiretroviral combinations, as often as possible with new drugs.

For some patients who have already received many combined therapies, it is critical to use new drugs, even if the licensing procedures have not yet been completed. In France, the genotypic study of resistances in patients who have already received several therapeutic regimens in each class of antiretroviral drugs, evidences a number of patients with multi-drug resistance. In public health terms, it is therefore essential to continue efforts for the licensing of new antiretroviral drugs.

[1] TRT-5 (Traitements et Recherches thérapeutiques) is an alliance formed by the following associations : Actions Traitements, Act Up-Paris, Aides, Sol En Si, Sida Info Service, Nova Dona and Dessine-moi un mouton.2 The recommendations issued by the group of experts on HIV management, directed by Pf J.-F. Delfraissy state that : « New drugs being clinically developed must concern patients with treatment failure and multi-drug resistance ». p. 72

The issue does not only apply to HIV, but in this particular case the epidemic's history has emphasized the topic. Whilst an effective antriretroviral treatment can achieve prolonged control of HIV infection, multi-drug resistance can cause short-term life-threatening clinical and biological evolution. Moreover, multi-drug resistance is a risk of transmission of resistant strains. Patients' demands for emergency access to salvage therapy through unlicensed drugs are thus consistent with HIV management recommendations[2]. Despite this consistency on therapeutic necessities, the imbalance between supply of medication during its clinical development and demand from patients and clinicians, repeatedly generates antagonistic situations.

The National AIDS Council is aware of the constraints related to pharmaceutical firms' production activities. However, it considers that sufficient quantities of medication must be made available, during the clinical development stage, so as to meet the needs of those persons for whom they are the only short-term hope of survival. In France, there are procedures that enable to meet some of the needs, but various problems remain that cannot be dealt with at national level. Indeed, pharmaceutical product development and licensing are handled within an international framework. A European early access programme limited to the management of multi-drug resistance is therefore necessary. This programme could well be extended to other diseases if a patient is not responding to a treatment.

2 INDUSTRIAL DECISIONS MUST TAKE MULTI-DRUG RESISTANCE INTO ACCOUNT

In the French health care system, multi-drug resistance is characterized by various criteria[3] :

• Biological criteria : percentage of and CD4 cell count/mm^3 ; viral load in number of copies of plasma HIV RNA/mL^4 ; dynamics of these indicators.

• Clinical criteria : severe clinical AIDS-defining occurrences jeopardizing short-term vital prognosis.

• Therapeutic criteria: multi-drug resistance is characterized by viral strains that are resistant to most antiretroviral drugs available in all three classes.

Depending on the criteria adopted, the minimum number of patients with multi-drug resistance is thought to be between 400 and 1000[5] .

Each new drug puts hopes up for patients with multi-drug resistance, but the supply of unlicensed drugs is lower than the demand. For pharmaceutical firms, investing in new antiretroviral drugs is a financial risk, added to which technical manufacturing constraints can sometimes curtail production capacities, especially for new classes of antiretroviral drugs. Their unwillingness to make unlicensed drugs available is also probably related to a concern about not interfering with the enrollment of patients in clinical development trials.

The issue of financial and industrial constraints is not insubstantial. Private pharmaceutical groups' profitability is indispensable for their commitment to research and to the development of new antiretrovirals. It is also critical not to compromise potential development of phase III clinical trials[6]. However, considering patients' health status, the administrative, scientific and industrial procedures for access to potentially effective drugs are often too long.

The National AIDS Council considers that the essential ethical issue is to do every possible thing to save the lives of people infected by HIV. When salvage therapy is possible, its implementation is a collective responsibility shared by the Public Authorities and the pharmaceutical firms. Ideally, drugs for patients with multi-drug resistance should be provided free of charge.

3 THE CURRENT FRAMEWORK OF ACCESS TO UNLICENSED DRUGS

In France, for access to new drugs there are swift procedures that do not exist in the other European countries. Various schemes are thus offered to patients : clinical trials and provisional approvals.

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[2] The current framework of access to unlicensed drugs

[3] For further details, see the 2002 edition of the expert panel on managing HIV infected persons, chapters on « Treatment Failure » pp. 63-74 and « Antiretroviral drug resistance testing » pp. 83-97.

[4] Recent recommendations define virological failure by a plasmatic viral load over 50000 copies of RNA/mL, immunological failure by severe or moderate immunodepression with a CD4 cell count around 200/mm3, and therapeutic failure by previous use of more than fivetherapy regimens in the three available antiretroviral classes.

[5] B. Masquelier et al., « Prevalence of HIV-1 variants with multiple class drug resistance. A French nationwide study », Antiviral Therapy, 2002 ; 7, 5136. 2001 Multivir Study.

[6] Randomized efficiency trials, the results of which determine licensing approval.

3.1 CLINICAL TRIALS

Clinical development trials often have biological and/or clinical eligibility criteria that can exclude those persons most in need of new drugs.

The drawback to clinical trials is that they create geographical disparities related to the limited number of centres. This lack of equality is not compatible with the aim to find a possible therapeutic solution for all the patients in need of the new drugs. The National AIDS Research Agency (ANRS) designs specific trials for patients with treatment failure : PUZZLE trials. In practice, such trials also seem to have come up against an availability obstacle : drug supply during the evaluation stage depends on the willingness of the pharmaceutical companies.

Clinical trials represent an essential means of access to new drugs, but they are only an incomplete solution. The French Authorities subsequently provided other means for patients' access to unmarketed drugs.

3.2 PROVISIONAL APPROVALS

Provisional approvals were explicitly designed to speed up access to unlicensed drugs prior to their full licensing. Regulations have two basic requirements. The cost of drugs bought from the companies is entirely paid for by the national community, i.e. hospitals or health insurance. Also, the scheme is based on firms' voluntary commitment. There are two sorts of provisional approvals.

One is a named-patient scheme and is requested by a clinician for a given patient. Its duration is that of the treatment. It can be used for a drug still in phase II development. Pharmaceutical firms are not overly enthusiastic, particularly as they do not monitor this type of approval and therefore gather very little information on the new drugs involved.

The other provisional approval is a cohort scheme and is based on a protocol between a company and the French Agency for the Safety of Health and Health Products (AFSSaPS), its duration is one year. It concerns medication in phase III development. This provisional approval is of interest to the firms as it enables them to promote a new product and to collect data on tolerance that will be included in the final licensing application. To date, the relatively short period of time between cohort approval and full licensing impedes the scheme's effectiveness.

The National AIDS Council considers it necessary to design a new scheme for early access to new and potentially active drugs. The practical definition of this scheme does however deserve to be elaborated with regard to the firms' international environment. An overly coercive national framework could lead them to displace their activity to other countries.

The institutional response to the issue of early access to new drugs must therefore be considered within a European framework. This would be a substantial breakthrough for greater equality among patients at European Union level, given the disparities of access schemes from one Member State to another.

4 THE NEED TO MODIFY THE EUROPEAN FRAMEWORK

The European Agency for the Evaluation of Medicinal Products (EMEA) considers it beneficial to speed up the approval of drugs liable to be of use to previously treated patients[7]. However, to date there is no European provision designed to facilitate early access to new drugs.

The European institutions[8] are currently revising EU procedures on drug approval, monitoring and safety procedures. In the draft document, two articles could facilitate quicker access to new drugs.

Article 13, pargaraph 6 states that the time-lag in EMEA's response to applications for drug approval can be reduced, at the firms' request, from 210 days to 150, for drugs that « present a major interest from a public health standpoint and particularly in terms of therapeutic innovation ».

Article 73 more specifically concerns those patients whose clinical conditions are of greatest concern: it suggests that a drug could be made available on a « compassionate » basis, and free of charge to the patient (paragraph 6), providing it does potentially have

[7] Committee for Proprietary Medicinal Products (CPMP), Points to consider on the assessment of anti-HIV medicinal products, CPMP/602/95 rev. 3, London, EMEA, May 31st 2001.

[8] The draft was submitted to a legislative resolution vote in Parliament on October 23rd 2001. The drafted proposal from Parliament and the Council will be examined at the Ministers' Meeting on December 2nd 2002.

an « important benefit from a public health standpoint ». The document specifies that this provision will not be detrimental to the specific national early access procedures.

The National AIDS Council acknowledges the cogency of a scheme designed to homogenize procedures within the framework of a revised legislation on drugs in the European Union. However, the Council can but note that the two provisions are not liable to bring France any major progress for patients in need of urgent treatment. The French provisional approval schemes already work and should be put first. Moreover, the term « compassionate » is rather vague and could be detrimental to the effective implementation of article 73.

The major problem is to ensure that firms will be involved in the availability of new drugs for patients with multi-drug resistance. In the documents on applications for approval, the French Authorities (AFSSaPS) recommend that named-patient schemes be implemented as early as possible for certain drugs. The initiative did not reduce the imbalance beteween supply and demand of new antiretrovirals. Even though the procedures do exist, they are insufficiently used for HIV.

Various associations made suggestions to solve this problem. A proposal was issued in 2000 by the European AIDS Treatment Group (EATG)[9]. It was designed to subject, at European level, swift final approval to the implementation of a cohort of patients with multi-drug resistance; the firms were to provide the new drugs free of charge. According to EATG, this cohort would have enabled better evaluation of tolerance and of the drugs' cost-benefit ratio.

Recently, the TRT-5 group suggested to European Members of Parliament that in some cases EMEA recommend open trials. They would be conducted separately from phase III development trials but prior to their completion[10] . They would enable to include patients with no further treatment options and who meet multi-drug resistance criteria. These are called Phase III (a) trials. They would be designed to collect more data on tolerance to the product so as to facilitate improved evaluation of the risk-benefit ratio. TRT-5 nevertheless considers that named-patient provisional approvals should remain the general rule.

5 THE RATIONALE OF THE NATIONAL AIDS COUNCIL'S POSITION

The National AIDS Council's position on early access to developing drugs for patients with multi-drug resistance is based on a set of principles.

Firstly, the Council considers that the availability of a sufficient quantity of free treatments does not have to do with an optional (compassionate) possibility but with an ethical requirement, applicable to all.

The Council therefore considers that the creation of a scheme for early access to developing drugs, limited to patients with multi-drug resistance, is probably the best solution. This Limited Early Acess Programme (LEAP) should be established at European level and apply first and foremost to those patients most evolutional at clinical, immunological and virological levels ; it should also be seen as a last resort.

Secondly, the Council's considered a scheme that was likely to be approved by patients, clinicians, the Health Authorities and also the pharmaceutical firms. Observation of these patients would give companies better data on tolerance well before a drug's final approval. They would thus be less likely to have to face unforeseen adverse effects arising late in the day and causing bad publicity. The firms have a lot to gain from being supplied with early and complete data on possible resistance mutations related to the the use of antiretroviral drugs. An increasing proportion of people with HIV in Europe have taken several treatments and are therefore an ideal target for new licensed products.

Thirdly, as HIV management stands today, patients' hopes regarding access to new drugs (once enrolment in phase III trials is completed) must be kept within reason. Short-term efficiency of « salvage » therapy is only assumed. Probably not all the patients would get any benefit; also, such treatments might cause adverse effects. Moreover, using new drugs as fonctional monotherapies (e.g. when they are not part of a well-tried regimen but just added to previously prescribed treatments that no longer work) may cause new viral resistance mutations which could jeopardize future treatment options. This warrants monitoring the scheme through standard surveillance. The Health Authorities must effectively collect subsequent data.

Lastly, early access to developing drugs limited to patients with multi-drug resistance must not be detrimental to ongoing trials.

[9] See François Houyez, « Egalité devant l'A.T.U. », European AIDS Treatment News, vol. 17 no 1/2, February-March 2000 ; pp. 20-21.

[10] TRT-5 memorandum to the rapporteurs of the draft on the modification of the EU directive on medications 2001/83/CE, Comment améliorer l'accès précoce aux nouveaux médicaments pour les malades en impasse thérapeutique ? June 2002, 6 pages.

6 ADVOCATING A LIMITED EARLY ACCESS TO DEVELOPING DRUGS PROGRAMME FOR PATIENTS WITH MULTI-DRUG RESISTANCE (LEAP)

Articles 13 and 73 of the drafted modification of drug regulation may offer a promising framework for early access to developing antiretroviral drugs. However, they will not guarantee that access will be effective.

The Council therefore advocates that to the draft, by way of a European Parliamentary amendment or through the Health Ministers' initiative, be added a clause whereby developing drugs with a potential benefit to patients with multi-drug resistance would be made available free of charge.

Availability should be planned within a European LEAP if the national regulations are not used to meet the needs expressed by the Health Authorities, clinicians and patients of the countries concerned; the required quantities should be provided. At European level, the LEAP should be evaluated by the EMEA[11] once the Committee for Proprietary Medicinal Products (CPMP) has been consulted. The CPMP's opinion would partly be based on possible evaluations conducted by national agencies.

Clinicians would be responsible for drug prescription. The National AIDS Council considers that new drugs, about which knowledge is incomplete, cannot be used without systematic observation of patients involved. Patient follow-up would have to be patterned in the same way as observational cohort follow-up. The Health Authorities should collect and analyse data jointly with the firms. A LEAP for patients with multi-drug resistance should be discontinued once provisional cohort approval or full approval is obtained.

Once initial data enabling to assume the product's potential benefit are communicated, the Health Authorities, jointly with the national and European clinicians and epidemiologists, should organize registration of patients potentially concerned by the LEAP. For the initiation of patient follow up, the EMEA should also promptly ensure consultation with the firms involved. Whatever the case, access to the programme should be coordinated with patient enrolment in clinical development trials.

Such a programme implies that firms should make provisions, prior to production, for the required financial and technical means. The limited early access programme nonetheless presents a three-fold advantage :

• Using national schemes increases overhead costs and procedures which are detrimental to speedy implementation in all the European countries. A European LEAP and the possibility for the CPMP to give its opinion on provisional data on results from phases I and II of drug development could give the approval mechanisms some flexibility (one single opinion).

• When national measures, particularly French programmes, are shown to be technically more favourable, their utilization should remain the general rule. The European LEAP must not replace existing schemes, but complete them.

• Data on tolerance and on resistance selection for patients with multi-drug resistance benefitting from the early access scheme devised for them, will be included in the documents for drug approval applications. Data will provide precisions on drug effects liable to warrant a modification in the information given to prescribers.

RECOMMENDATIONS

At the request of the TRT-5 Group, the National AIDS Council reappraised the issue of access for patients with multi-drug resistance to new drugs whose antiretroviral efficiency can be assumed, but that do not yet have full approval.

The French Health Authorities and legislators have produced remarkable provisional approval schemes. They have reduced access delays to new drugs for patients with advanced infection for whom they are the only hope. Despite mobilization of patients, clinicians and the AFSSaPS, they do not however meet the needs of patients with multi-drug resistance.

The National AIDS Council subsequently adopted the following recommendations.

1. The National AIDS Council considers that availability of antiretroviral drugs liable to be a therapeutic contribution for all patients with multi-drug resistance whose short-term vital prognosis is at stake, is an ethical obligation. This obligation must be taken into account as such by the pharmaceutical firms.

[11] The basis could be Amendment no 34 of Parliament's legislative resolution on the EU's procedures. Its article 10, par. 6 (a) enables the Drug Agency to adopt a speeded procedure to « make available new effective drugs for the treatment of incurable diseases ».

2. To supplement the texts currently being debated in European institutions, the National AIDS Council recommends that the French Authorities advocate not only the extension of provisional approvals to each Member State, but also that they promote the implementation of a Limited Early Access to new drugs Programme for patients with multi-drug resistance (LEAP). This scheme would in no way replace national systems that might be as good or better, nor would it reduce access to existing procedures. For the time being, the scheme must be set up in France.

3. Due to limited knowledge on the developing drugs which will be used, the National AIDS Council recommends that LEAP beneficiaries be very strictly monitored. Follow up must yield data on tolerance and viral resistance to these new drugs, and thus complete data from companies.

4. The National AIDS Council suggests that patient follow up be organized along the lines of a clinical trial cohort. The Council recommends that the Health Authorities monitor both patient follow up and data collection. Data could be used for drug approval applications.

5. The National AIDS Council recommends that the Health Authorities and clinicians ensure that both patient registration and allocation schemes cause no discrimination. It is also necessary that enrolment in this cohort be planned jointly with clinical development trials so as to cause no inconvenience.

6. The National AIDS Council recommends that the national and European Health Authorities guarantee the financial, material and human resources so as to ensure coordinated data collection, observation validation and analysis.

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