How is Schering-Plough messing-up?

In « Schering-Plough : le gâchis », JDs n°169, octobre 2004, p 7-9.

The launching in Europe of a trial testing a new anti-HIV molecule causes the indignation of some organizations, who denounce the risk of a "loss of options" for the patients. Convinced that they are doing the right thing, the trial promoters, Schering-Plough laboratory, first refused all negotiations, and then offered a disappointing conciliation.

In June 2004. the US laboratory Schering-Plough was preparing the conduction, in Europe and Canada, of a Phase 2 trial in people living with HIV who have never received any type of treatment (naïve people), to find the optimal dose for its new compound SCH-690.

SCH-690 is an interesting molecule: one of the entry inhibitor class, it blocks the CCR5 co-receptors that allow, with the CD4 receptor, the entry of HIV into the cell. SCH-690 was well tolerated in preliminary studies and showed a significant viral load drop within 14 days of treatment (1.6 log drop with doses of 25 to 50 mg twice a day)(1). It is still not known if the drug's activity will be comparable in a larger number of patients, or maintainable over a long period of time with an acceptable tolerance.

Even though the possibility of a SCH-690 trial in Europe was good news, Schering did not seem to be in a rush to present the trial protocol to patients' organizations (2) (3). After many petitions, the laboratory finally gave in, maybe against its own will and surely overdue.

When the European Aids Treatment Group (EATG) and TRT-5 realized that the protocol was rather unethical and asked for its revision, Schering told them that it was to late: in some European countries, the trial had already been accepted by the local authorities (4) ; any modification to the protocol would considerably delay the development of SCH-690.

The need to restrict entry criteria

The dose trial for SCH-690 will include 80 treatment-naïve people, distributed among 20 clinical centres in Europe (4 in France) and Canada. These patients will be randomised in 4 arms with 3 different doses of SCH-690 (25 mg, 50 mg, 75 mg, once-a-day), or a placebo (5).

During the first two weeks of the study, patients will only receive SCH-690 or the placebo. At the end of week 2, Combivir® (AZT+3TC) will be added to SCH-690. A therapy including Combivir® and Sustiva® (efavirenz) will be given to the patients receiving the placebo. The total duration of the trial is 48 weeks.

The reason why the organization are angered is because of the inclusion criteria defined by Schering (6): as it stands, they would indeed allow extremely immune-suppressed patients (CD4 between 50 and 200/mm^3) with a very high viral load (≥ 100,000 copies/mL), to participate in the study. However, in such patients, "it is precisely recommended to start with a more potent drug combination (four-drug therapy)" (7). Therefore, to prescribe to these people a treatment whose efficacy and optimal dosage and administration have yet to be defined, seems to go against the recommendations and to be unethical.

Specifically, one of the risks these patients are exposed to is of developing resistance to Combivir® and SCH-690. Another is, that blocking the CCR5 co-receptor may contribute to the immune system alteration. This is a particularly deleterious effect in people with a low CD4 count, who are more susceptible to infections. During the Phase 1 trials, one patient actually developed a secondary syphilis and another had to be hospitalised for a long period of time with a high fever of unknown origins. (1). Furthermore, in certain patients, the blockage of the CCR5 causes the emergence of viral strains that use the CXCR4 receptors, which is thought to be associated with a quicker disease progression. Finally, you need to add to that the psychological effect of a first-line treatment failure, which may vary depending on each person.

On the other side, the inclusion criteria used by Schering also allow for the participation in the study of people who, if we refer to the recommendations, are not in need of a treatment (CD4 ≥ 350/mm^3).

The concerns of the associations were equally focused on the protocol criteria defining virological failure and serving as patient stopping rules. Indeed they only take into account the amount of the viral load drop, and with

requirements (-1 log at the 8th week of treatment) below the current recommendations, even though the latter insist on how important it is that the viral drop be rapid ("at least 1 log of the plasmatic viral load after 1 month of treatment"), and that the viral load to be "undetectable after months 3 to 6". (7). The consequences for the patients of that study is that they might continue with a sub-optimal treatment that will give no benefits but cause adverse events and resistance.

Given the excessively wide inclusion criteria and the stopping rules falling short of the current requirements, the Schering study does not have, according to the organizations, any of the scientific rigor which should be expected from an international protocol, and it does not guarantee optimal protection to the patients.

The responsibility of physicians

Acknowledging the legitimacy of the concerns expressed by the associations, the laboratory passed the ball to the investigators: "We believe that the investigators clearly know that they should first consider what is best for their patients before offering them to enter this trial".(...) "The application of national treatment recommendations, either for initiating treatment or defining failure, is the physicians' responsibility" (8). In other terms, it is the only decision of the clinical centres whether or not to apply stricter criteria than those defined by Schering. According to the laboratory it is even more their obligation to apply them if this meets the patients' needs.

This explanation by Schering is quite astounding when you know that physicians involved in clinical studies deal with an obvious conflict of interests, which lies in their double activity as caretakers and investigators. Their duty is indeed to guarantee the best care for patients, but they are also concerned with the competitiveness of their clinical centre at European level. Part of it is the capacity to quickly enrol patients in a protocol. As a consequence, is it reasonable to ask physicians to "take their responsibilities" and at the same time to impose them criteria that in practice do not fit enough to guarantee the patients' security? Wouldn't everybody feel more secure if the criteria applied were in accordance with the experts' recommendations?

A competitive environment

It is difficult at first to understand Schering's reasons for being so inflexible. Is it that the company despises the patients' ethical requirements and takes them as trivialities? Maybe. Despite their apparent desire to collaborate with organizations, some companies have a hard time to accept that some collaborative groups dare disapproving of their development strategies. In France, the discussions that took place within the Parliament to review the Huriet Act were a good example (9). Only on a very few occasions so much energy has been spent to oppose the right to access protocols that the organizations claimed for.

However there might be another reason for Schering's attitude, which has become clear today. Another pharmaceutical company, Pfizer, has planned to launch their Phase II/III study to test their own anti-CCR5 compound, UK 427-857, no later than by the end of 2004 (10). According to some sources, these trials should enrol more than one thousand people in Europe, in North America and in South Africa. If all goes well, Pfizer's anti-CCR5 could therefore covet its share on the market and come out before Schering's SCH-690! This would be economically prejudicial for Schering and would not be of the taste of their stakeholders. This extremely competitive environment could therefore explain why Schering is so apprehensive to deal with the organizations, with which they might consider that they do not have time to lose.

A promise for amendments

At the time this article is being written, that is one month and a half after the start of the discussion between the laboratory and the organizations, and given the persistent dissatisfaction of the organizations in the countries involved (France, Italy, Portugal, etc.), Schering seem to be altering their position. In a letter to the investigators, they "recommended" new inclusion and failure criteria that are more in line with the demands of the organizations, which are still not fully satisfied (see box), in particular by the fact that waiting for an undetectable viral load between the 3rd and 4th month of the treatment is still not considered to be a necessity by the laboratory. Furthermore, Schering promised to amend the protocol in the shortest delay in order to include these new entry and failure criteria, but without giving any precise date. This is why the organisations wonder whether or not they should trust this promise which come slate, is still not effective, will not be retroactive and is probably guided by the will to avoid conflicts (11)? All the more that Schering persist in refusing to publish the list of the investigators involved in the trial. Such persistence is not quite reassuring, above all coming from a company whose recent activities show an obvious lack of deontology (12).

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Notes

(1) "SCH D: Antiviral Activity of a CCR5 Receptor Antagonist" (A 140LB), Schurmann DS, 11th CROI, 8-11.02.04.

(2) EATG (http://www.eatg.org) and TRT-5. TRT-5 gathers members of the organizations Aides, Arcat, Act Up, Actions Traitements, Sida Info Service, Dessine moi un mouton, Nova Dona, Sol En Si.

(3) To be exact, Schering did agree to meet with the organizations, but refused to share the study protocol. It was until the groups threatened to cancel the meeting that they agreed to defuse the documents.

(4) At the time this article is being written, the French Committee of Protection for the People had not yet given its advise on the protocol.

(5) "Update on Schering-Plough's entry inhibitor in phase II clinical development", Levin J., XV International AIDS Conference, July 11-16, 2004, Bangkok, http://www.natap.org/2004/Bangkok/bangkok_07.htm

(6) Letters from the EATG to Schering-Plough and from the TRT-5 to Schering-Plough, relevant dates the 6.07.04 and the 08.07.04.

(7) "VIH Edition 2004", Girard P-M., Katlama C., Pialoux G., Doin, 2004.

(8) Schering-Plough's response to the EATG, by Dunkle L, 12.07.04.

(9) Art. 42, Public Health law. See the reports in the French Senate (http://www.senat.fr/dossierleg/pjl03-019.html) and the National Assembly (http://www.assemblee-nat.fr/debats/index.asp).

(10) http://www.natap.org

(11) The laboratory insisted that the investigators should not delay the enrolment of patients while amendments were being made to the protocol.

(12) Although it is not restricted to this company in particular, Schering tends to collect heavy penalties: in 2002, for the delivery of ineffective anti-asthmatic drugs, which was related to the death f 17 asthmatic people; and this year, for a fraud case affecting Medicaid, the US programme for people with few resources. The company is also being investigated for questionable marketing practices.

Inclusion criteria for protocol P03802 which evaluates the optimal dose for SCH-690 in naïve people:

Age ≥ 18 years old
Not to have taken antiretroviral drugs
CD4 ≥ 50
HIV RNA ≥ 5000
Phenotype testing showing only CCR5-tropic strains
No antecedent of neuropsychological diseases

In a letter to the investigators, Schering recommended to exclude patients with less than 150 CD4/mm^3 and not to "systematically include" patients with more than 400 CD4/mm^3 or viral loads above 100,000 copies/mL.

Failure criteria conducting to patient's stopping:

Not to obtain a viral load drop of 1 log by week 8 of the trial
Intolerance to Combivir®
Development of CXCR4-tropic viral strain
Growth in the QT interval
Convulsion attacks

The modification agreed to by the laboratory in a letter to the investigators concerning the viral load drop was that it should be at least 1 log by the 4th week of treatment.