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REPORT: FIRST GENE THERAPY RELATED DEATH

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Chapter I: The clinical case

Introduction

Introduction

During the month of December, we read in the literature (3-5) and learned via the Internet (1-2) of the death of a patient following the injection of an adenoviral vector, within the framework of a gene therapy clinical trial being run at Pennsylvania University. *The Service of Biosafety and Biotechnology (SBB) and the Biosafety Council are obliged to issue expert advice regarding the authorisation of new protocols or amendments to the clinical protocols for gene therapy using this type of vector. The SBB thus addressed a letter to the American Recombinant DNA Advisory Committee (RAC) requesting further information about this death. In the absence of a response from the RAC, and despite the intervention of the American Embassy in Brussels, the SBB managed to gather the information available. The present report is a summary of this information.*

Partial ornithine transcarbamylase deficiency

The pathology treated during the trial was partial ornithine transcarbamylase (OTC) deficiency; this is an enzyme of the mitochondrial matrix intervening in the urea cycle. This genetic pathology is a result of a mutation of the OTC gene, which reduces the hepatic production activities of OTC of 80% to 90% in hemizygotes. This hepatic deficiency in OTC develops in early childhood and leads to an accumulation of ammonia in the blood and the brain, leading to fatal hyper ammoniacal encephalopathy when there is no treatment. An accumulation of glutamin in the blood and an abnormally high excretion of urinary orotic acid also accompany the pathology. The standard treatment for this pathology is the administration of L-Citrulline and a strict protein diet. In some cases, a liver transplant can be considered (27). It should be noted that these patients are particularly vulnerable to all nature of infections (17). Gene therapy has recently become a therapeutic approach.

Clinical protocol

The clinical trial concerned was a phase I trial. It was being carried out at the hospital of Pennsylvania University (General Clinical Research Center) and at the Children's National Medical Center; the principal investigator was Dr Mark L. Batshaw, co- investigators were the

Drs James M. Wilson and Steven Raper. The Recombinant DNA Advisory Committee (RAC) had approved the trial on 4/12/95 under the reference ORDA 9512-139 (28) and ID UPSM-FDR001529. The clinical trial used an adenoviral vector deleted for the gene E1 of the adenovirus (transcription factor necessary for the replication of the adenovirus) and presenting a heat-sensitive mutation for the E2 gene. This vector expresses the human gene of OTC. Doses of $1X10^{8}$ to $3X10^{9}$ units of infectious particles/kg ($2X10^{10}$ to $6X10^{11}$ viral particles/kg) were injected into one of the branches of the hepatic artery using a catheter. The particular criteria for including patients stipulated that the pathology be stable for at least one month, that the concentration of ammonia in the blood be lower than 70µM, and that the titre of anti-adenovirus neutralising antibodies be lower than 1280. It should be noted that among the exclusion criteria, it was recommended that patients do not have a viral hepatitis, AIDS or active tuberculosis (28).

Clinical case

Jesse Gelsinger, a patient aged 18, was the eighteenth patient who was voluntarily presented for inclusion in this clinical trial (14) under the reference OCT.019 (10). The patient received an injection of $3.8X10^{13}$ viral particles ($3X10^{9}$ units of infectious particles/kg) on 13 September 1999 (4). Post-injection, the patient rapidly developed a fever of 40°C (13) together with tachycardia, nausea, vomiting, and muscular pain (13). A hepatic impairment occurred (10), associated with a disseminated intravascular coagulation, which was in the process of improving within 48 hours (11). Unfortunately, after two days, the patient went into a coma (9) and developed respiratory distress (ARDS) requiring artificial ventilation (13). In view of the seriousness of the clinical scenario, which was developing, and the fact that the brain was impaired, the clinicians decided to cease artificial ventilation (18). Death was certified 4 days after having received the injection. At the autopsy, infiltration and inflammation of the lungs were observed (18), as well as anoxia of the kidneys and of the brain, with the spleen and the liver also being affected (16). In the bone marrow, there was also an absence of erythrocyte precursor cells, as well as an abnormality in the maturation of the precursor leukocyte lines (10), which could be linked to a viral infection by a parvovirus type B19 (17). The post mortem investigation led by the investigators excluded human error (8), and the specific analysis of the vector lot administered to this patient did not reveal any particular anomaly (10). In conclusion, and according to Dr James Wilson, the patient died from events occurring subsequent to receiving the injection of the vector (8) which generated a violent immune response (7) and an exaggerated inflammatory response (11) altering several organs and leading to death (5).

Regulatory aspect

As stipulated in the appendix M-VII-C of the Guidelines for research involving recombinant DNA molecules: May 1999 (24) published by the National Institute of Health (NIH) of the USA, the investigators of this clinical trial reported the death to the local Institutional Review Board, to the Institutional Biosafety Committee, to the NIH Office of Recombinant DNA Activities (ORDA) and to the Food and Drug Administration (FDA). On 10 October 1999, following the receipt of information about the death, the FDA decided to suspend two clinical trials initiated by Shering-Plough, using adenoviral vectors expressing the gene P53 for the treatment of cancer, injected either directly into the liver, or injected into a branch of the hepatic artery (6). On 5 November 1999, the Department of Health & Human Services of the RAC, reminded sponsors and the principal investigators involved in clinical trials of gene therapy, of their obligation to advise the Center for Biologics Evaluation Research (CBER), of the FDA, as well as the ORDA of the NIH of all serious side effects occurring during clinical trials (24). The RAC also organised a symposium to evaluate the safety problems linked to the use of adenovirus vectors (8 December 1999) (26). Following this symposium[1], the RAC stated that any serious side effects should be reported within 15 days, whether or not these side effects result from the pathology treated or otherwise (19, 23), and the Department of Health & Human Services of the RAC demanded, in a letter dated 13 December 1999, addressed to the various institutions conducting clinical trials in gene therapy, that there be a review of side effects linked to any gene therapy clinical trial (25). What remains particularly controversial is the divergence between the wish of the RAC to distribute information on these side effects and the position of the biotechnology industries which, in the name of the principle of competitiveness, consider that this desire for information is not necessary and is inappropriate (20, 21).

Conclusion

From a clinical point of view, we can firstly discuss the opportuneness of such heavy use (catheterisation in the hepatic artery) of an adenoviral vector for transitory transgenic expression (2 to 4 weeks) in the case of a correction of a congenital enzyme deficiency: the use of this type of vector, of which the considerable inflammatory response is well known, appears to us to be more appropriate in the scenario of local anti-cancer therapy. Furthermore, if the immune reaction to this type of vector can be fatal, it is then important to treat only those patients who present an immunological status able to counteract, or if possible, to minimise the inflammatory effects. In addition, if, as is thought by Dr Wilson, the deleterious effect of the vector has been accentuated by a viral co-infection, it is imperative to verify the viral status of the patient before using a therapy vector and, where applicable, isolation precautions must be taken to protect the

patient from any infection during the therapy. Finally, it appears to us to be urgent to review all deaths occurring during the course of gene therapy trials and, in particular, to verify if other patients have developed a clinical scenario similar to the clinical scenario developed by Jesse Gelsinger.

Finally, from the point of view of the regulatory aspect, faced with globalisation and an increased number of protocols for gene therapy, and because of the slowness of the publication process, it appears important to us that the distribution of information concerning the serious side effects of gene therapy clinical trials be organised in real time, and thus be useful for the authorities providing expert advice regarding safety and ethics.

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Chapter II: Implications

Introduction

Gene therapy is very particular in the history of medicine because it is supposedly the foundation of curative and prophylactic medicine with the goal of correcting the deregulated or defective genes in more than 2,000 cases of genetic diseases, viral infections or functional deficiencies.

Just like other forms of development in medicine, gene therapy comprises complex clinical, scientific and socio-economic elements, but also new ethical aspects.

The development of gene therapy also intervenes at a time when public demands for transparency have been established as an essential component of biotechnology development. Moreover, this report reflects that observation.

The announcement at the end of 1999 of the first death caused by the administration of a third generation adenoviral vector (Chapter I) generated intensive questioning. The purpose of this chapter is to analyse the reactions and implications of the enquiry held into this death.

Clinical case history

The phase I clinical trial at the origin of the death in question was carried out at the Clinical Research Center hospital of Pennsylvania University and at the Children's National Medical Center. The principal investigator was Dr Mark L. Batshaw, and the co-investigators were the Drs James M. Wilson and Steven Raper.

The protocol focused on treating young adults suffering from partial ornithine transcarbamylase (OTC) deficiency with an adenoviral vector coding for the human OTC gene by injecting it into one of the branches of the hepatic artery (see Chapter I).

The initialisation procedure of this clinical trial was complex and the initial protocol was subject to a great number of amendments (56).

Initially, the investigators had proposed to treat very young children with a serotype 5 adenoviral vector deleted for the E1 gene of the adenovirus (transcription factor necessary for the replication of the adenovirus) and of which the E2 gene carried a heat-sensitive mutation. The administration protocol stipulated the injection of the vector in one of the branches of the hepatic artery.

For ethical reasons, the control committee of Pennsylvania University refused that the trial be carried out on young children since it emotionally was impossible for the parents to give informed consent (49).

In December 1995, this clinical trial was proposed to the RAC.

At the beginning, the RAC's scientific committee expressed the following criticisms: «Do we have the right to treat patients who are asymptomatic?» and «performing a hepatic catheterisation procedure is risky». The RAC therefore proposed to the investigators to inject the vector intravenously. When this amendment was definite, the RAC approved the clinical trial by 12 votes against one and 4 abstentions. When the project was approved by the RAC, it was submitted to the FDA.

The FDA emphasised that injecting an adenoviral vector by the systemic path risked contaminating germinal cells and, as a consequence, the FDA proposed to the investigators that they verify, by using a murine model, whether in fact there was any risk of vertical transmission of the vector.

In September 1998, J. Wilson published an article in the review «Human Gene Therapy» on the lack of vertical transmission of the vector (96).

Finally, the investigators proposed using a "third generation" adenoviral vector (ΔE1, ΔE3 and ΔE4) in an intra-hepatic injection.

This is the version of the protocol which was approved by the FDA (4, 11).

Reactions of the investigators and the RAC members to the announcement of this death

The announcement of the death in the press immediately generated different reactions in the world of science concerned by the issue, i.e. investigators in American gene therapy.

The investigators (1-3) of the protocol concerned, in addition to Prof. F. Anderson of the University of Southern California, Los Angeles (11) and Prof. L. Market of the paediatrics department of Duke University Medical School (6), presented the death as a tragic but absolutely unforeseeable event, in the light of the phase I clinical trial or pre-clinical data available in the literature (11,17). The investigators then described the patient as a hero who had made a contribution to the advancement of clinical research (6).

In a less emotive tone, other scientists criticised several aspects of the protocol. Prof. R. Erickson of the University of Arizona questioned treating asymptomatic patients (4); Prof. T. Flotte of the University of Florida (19), Prof. M. Seashore of Yale University, like Prof. Erikson (5) expressed doubts regarding the use of an adenoviral vector in this type of pathology (short term expression of the therapeutic transgene necessitating consecutive injections, thus provoking an immune response inhibiting the anticipated curative effect (Chapter I and ref. 5, 22)). Whereas alternative vectors, which are both stable and non-immunogenic, exist and using them was not taken into consideration. Prof. J. Samulski also recalled that hepatic catheterisation was always a risky medical procedure and could be fatal (4). Finally, Prof. I. Verma of the Salk

Institute, California, declared that quality criteria for adenoviral vectors were not sufficiently strict at the present time (Chapter I: ref. 3, 33).

FDA and RAC Actions

Still following the public information of the death, the FDA decided to suspend two clinical trials initiated by the company Shering-Plough, which were using adenoviral vectors injected either into the hepatic artery or directly into the liver (Chapter I and 9,10) although, according to Prof. S. Raper, this type of injection had been used successfully in various studies (6).

The RAC experts organised a meeting on 8 December 1999 to bring together the pre-clinical and clinical information to facilitate clarifying the causes of this death, and to evaluate safety problems linked to the use of adenoviral vectors (Chapter I). At this meeting, Prof. J Wilson related the circumstances of the patient's death (Chapter I). He then added that his team had observed an abnormally high seric concentration of interleukin 6[2] in the patient, following administration of the injection (20). Prof. Wilson also related that at the autopsy, the adenoviral vector and the transgene were found by PCR in all the patient's organs (including the testicles). Prof. Wilson concluded that adenoviral vectors must not be used systemically, nor intra-hepatically, which did Prof. S. Woo, President of the American Society of Gene Therapy (11), confirm.

Yet the pre-clinical and clinical trial data raised many questions within the RAC.

The RAC reproached the investigators for having included this patient when his ammonia seric level was too high (21, 23, 24, 31) and he was not medically stable (29). The investigators responded that at the time of enrolment, the patient presented a seric ammonium concentration compatible with the inclusion criteria described in the protocol (11, 24). The RAC also reproached the investigators that they had not described the cases of two to four monkeys who died during a pre-clinical study using an adenoviral vector with titres 20 times higher than those used in the human clinical trial in question (24, 28). The investigators then stated that the adenoviral vector used in the monkeys was a vector bearing a deletion of the E1 gene and affected by a heat-sensitive mutation of the E2 gene, whereas in the clinical trial, they had used a vector which, in their opinion, presented relatively fewer immune problems, i.e. a third generation adenoviral vector (ΔE1, ΔE3 et ΔE4) (16, 18, 24, 71).

Finally, the RAC declared that the investigators did not report to the FDA in due time the observation that three of the patients being treated had a stage III transitory hepatic impairment (4, 18, 25).

[2] *As a reminder, Interleukin 6 was linked to ARDS and, furthermore, the macrophage cells (cells involved in the production of Interleukin 6) are highly infectable by the adenovirus (20).*

The FDA expert, K. Zoon, concluded that the impact of these deviations from protocol on the death of the patient is not at all evident (24), but that the FDA would have stopped the inclusion of patients had they been advised of the side effects observed during the trial (28, 49).

As a result of the reproaches made against the investigators of the clinical trial for OTC deficiency, the FDA undertook an enquiry at the Institute for Human Gene Therapy (IHGT) of Pennsylvania University (34).

This enquiry revealed 18 violations of protocol in the manner in which the clinical trial was run; the main ones are as follows (72):

1. Patients were not informed of the inherent risks of this clinical trial (72).
2. Patients who had received the highest doses of the vector were not informed that no therapeutic effects had been observed in patients treated with lower doses of the vector (79, 64, 70).
3. Some patients (including the patient who died) had not given their informed consent (72).
4. The patient who died was not eligible according to the protocol of the clinical trial.
5. A conflict of interests exists between the investigators (J. Wilson) and a biotechnology company (Genova) (19)[3].
6. Serious side effects were not reported to the FDA or to the RAC.
7. The dates do not tally for the patient signing the informed consent form and the signature of the witness (40)[4].
8. There was inadequate and insufficient patient monitoring (48, 59).

In practise, the FDA finally decided to suspend any new inclusion of patients in the clinical trials run by the IHGT (34, 35, 42) and called upon Prof. Wilson to justify his actions with regard to these violations of protocol (40).

The President of Pennsylvania University declared that they wish to cooperate with the FDA and the RAC; he demanded that an extra-muros committee of scientific experts be formed to re-evaluate the gene therapy clinical trials run by the IHGT (36, 62).

[3] J. Wilson is the founder and consultant of the Genova company, a firm which provided 20% of the IHGT research budget.
[4] In a clinical trial, when there is informed consent, a witness must confirm that the patient has clearly understood the clinical trial.

Creation of the Public Health Subcommittee of the US Senate

In view of the extent of the enquiry into the gene therapy trials run by the IHGT, a US Senate sub-committee has been set up to assess the protection of patients included in gene therapy trials and to restore public confidence in the national gene therapy programme (45).

One of the first steps taken by this committee has been to demand a list of side effects observed in all the gene therapy clinical trials (36, 42).

A list of 691 side effects was submitted, whereas only 39 side effects were reported to the RAC (NIH) (41, 42, 52, 61). The different deleterious side effects occurring when using adenoviral vectors are:

1. ARDS developed in a patient suffering from cystic fibrosis treated with an adenoviral vector delivered by aerosol (1993) (16)
2. Stage III transitory hepatic impairment (18)
3. Coagulation problems with a reduction of the blood concentration in platelets (14, 20, 40)
4. Hypotension and tachycardia (40).

Several deaths were also reported in the clinical trials held for the treatment of ischemic myocardia, but these deaths were attributed to the pathology itself and not to the treatment (12, 21).

Deaths were also observed in the treatment of cancer, but the investigators attributed these deaths to the pathology although, in the majority of the cases, the autopsy did not confirm this diagnosis (41, 44, 47).

As a result, the sub-committee reproached the NIH (RAC) and the FDA for not having tracked these side effects (52, 53) and for not having co-ordinated their efforts (59). On 9 February 2000, President Clinton brought into question the operation of the NIH and the FDA and requested a revaluation of the guidelines for gene therapy (68) and a clarification of the roles of the FDA and the NIH (51), in order to have improved supervision of gene therapy clinical trials (63).

Spontaneous stopping of gene therapy clinical trials

In this context, some clinical and scientific institutions have spontaneously stopped their gene therapy clinical trials.

From December 1999, the Cystic Foundation association stopped two clinical trials using the adenovirus as a therapeutic vector (58).

On 28 January 2000, the Muscular Dystrophy association announced that it was suspending its clinical trials run at the IHGT.

Prof. R. Junghans of Harvard University Medical School, Boston, announced the suspension of clinical trials in order to rewrite the protocols so as to exclude patients presenting cardiac problems (45).

In February 2000, M. Rosenbladt, President of the Beth Israel Deaconess Medical Center announced a provisional stop to the various gene therapy clinical trials treating cancer, haemophilia and coagulation factor genetic defects (65).

Finally, more recently, the University of Florida stopped a clinical trial using a cationic liposome (Allovectin-7) as the therapeutic vector for melanoma, following autopsy results which did not confirm that death occurred as a result of the pathology (81).

Ethical evaluation of gene therapy

Although the bioethical evaluation of clinical protocols in Belgium is the prerogative of local approved ethics committees, it is nonetheless true that the authorisations for gene therapy clinical trials issued by virtue of regional and/or federal regulations of biosafety are issued on condition that the presidents of the afore-mentioned committees certify to the Biosafety Council that the review of the dossiers, from a bioethical point of view, took place in parallel and independently of the biosafety evaluation.

The future GCP directive will propose a European and Belgian legal foundation to this situation and more especially a legal co-responsibility for these committees with regard to decisions to issue an authorisation.

As a result, and in order to avoid that the Biosafety Council be accused of being short-sighted with regard to the gene therapy dossiers, it is useful to present briefly a list of essential references related to the results of the enquiry into the management of protocols for gene therapy in the United States of America.

Given the modest results of the therapeutic effects of gene therapy, as confirmed by Dr A. Paterson, FDA Director (23), and in the light of the concern to preserve patient security (33), some promoters of American medical ethics have raised the problem of misinformation given to patients included in these clinical trials (50).

The ‘marketing’ trend observed in the development of gene therapy has been to minimise the risks and accentuate the therapeutic benefits, probably as a result of pressure from investors (60) and the investigators involved in the projects.

According to Dr A. Shamoo of the University of Maryland, therapeutic trials of gene therapy are not riskier than any other clinical trial (74).

However, as Prof. V. Ramalingaswani states, ethical values must take precedence over the development of new therapeutic technologies (75).

In this climate of reviewing the issues of the sociological aspects of gene therapy, some ethics experts have requested a voluntary moratorium on all gene therapy clinical trials (66).

An American lobby group (Foundation Economic Trends) proposed this moratorium to the NIH, but there has been no response to it at the present time (83, 85).

Consequences in the USA

In order to maximise the security of patients included in gene therapy protocols in the USA, the following decisions and actions have been taken (77, 78, 94, 95):

Information concerning gene therapy clinical trials must remain in the public domain (55).

This public information must also include details of the side effects observed during the trials (55, 57).

The NIH must ensure the distribution of this information, which will be featured on a website (57).

The FDA and the NIH must also verify the adequacy of patient monitoring during the trials (79, 94).

The NIH has strengthened its system of inspecting gene therapy clinical trials (60); there will be random selection of the clinical trials to be inspected (77, 94).

The NIH must ensure that researchers respect the obligation to report all side effects whether related or not to the pathology being treated (95).

Finally, the NIH and the FDA are going to organise Gene Transfer Safety symposiums; these critical forums will analyse the clinical and pre-clinical data of the research into gene therapy.

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