A G E N C E
FRANCAISE DE SECURITE SANITAIRE DES
PRODUITS DE SANTE

Analysis of the risk of transmission of the variant Creutzfeldt-Jakob Disease by medicinal products of human origin and labile blood products

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Data update of the *ad hoc* group report dated December 2000

February 2002 report

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- SYNTHESIS -

The scientific data available since the publication in December 2000 of a report by a multidisciplinary and independent group of experts on the risk of transmission of the variant Creutzfeldt-Jakob disease (vCJD) by blood and blood derivatives, have been regularly reviewed. The present report expounds February 2002 expertise update.

There exist no new data on the variant Creutzfeldt-Jakob Disease (vCJD) physiopathology, modes of transmission, distribution and level of infectivity in the various tissues or on the determination of a possible infectious load in blood. The possibility of transmission of the disease by blood remains a hypothesis. There is no new piece of information modifying (upward or downward) the level of risk considered in the report dated December 2000.

On the epidemiological level, no significant increase in the incidence of vCJD was observed. The estimation of the number of people likely to develop vCJD doesn't seem to be modified.
No new risk factor, which could be used a an exclusion criterion on the clinical selection of blood donors, was identified.

No detection test in the present state of development is applicable to humans. However, the donor exclusion criteria, which are implemented at the moment, will remain the most appropriate measure taken for the qualification of blood donations, at least as long as validated detection tests usable on a routine basis and applicable during the whole asymptomatic period remain unavailable.

Leucoreduction remains a precaution to be considered and is a measure which will but contribute to reduce the risk of transmission. It is reminded that there exists no vCJD agent inactivation method applicable to labile blood products.

There is no reason why recommending a measure of exclusion of the donors who stayed in the British Islands, which is more stringent than that currently in place.

The conclusions and recommendations established in the report dated December 2000 remain valid. None of the items dealt with and discussed in the report needs to be modified. There is no new measure to propose which could contribute to further reduce the possible risk of transmission of vCJD by blood and blood derivatives. The measures currently in place are deemed to be effective and proportionate so as to ensure the right benefit-risk ratio for blood and blood derivatives.

Introduction

Within the context of the permanent surveillance by the Afssaps over the risk of transmission of the variant Creutzfeldt-Jakob Disease (vCJD) by blood and blood derivatives, the scientific data available since the publication in December 2000 of a report by a multidisciplinary and independent group of experts have been regularly reviewed. This work was conducted by the same multidisciplinary and independent group of experts all along the year 2001. The present report expounds February 2002 expertise update.

Only the scientific aspects were reviewed. There was new piece of information requiring to reopen the discussion on the other aspects, such as ethic considerations.

The publications referenced in this report were used as a support for reflection. This list of references doesn't intend to be exhaustive on the subject but the articles considered as the most useful in reviewing the risk of transmission of vCJD by blood products were discussed. Considering the recent publication of a report showing evidence of an abnormal form of PrP in urine, the field of expertise was extended to products extracted from human urine, hence the larger acceptation of this report's title.

The experts' objective was to:
- review the data newly published and discuss their results,
- propose, if necessary, measures likely to reduce the risk of transmission and analyse their consequences,
- determine whether the conclusions and the recommendations established in the report dated December 11th, 2000, should be modified.

Note: the same terms and abbreviations as those used in the report dated December 2000 will be used in the present report, and will consequently not be explained. As a reminder, an abbreviation lexicon is included at the end of this report.

1- Infectivity

1.1 Data review

A study relative to the experimental transmission of the BSE agent between primates notably confirmed that the origin of the vCJD cases observed in France, similarly to the British cases, was the BSE agent (*1*). It is reminded that, in the report of December 2000, the BSE risk in France, was essentially attributed to the consumption of contaminated bovine products of British origin, through importation. This risk allowed to determine the number of people likely to develop nvCJD and the theoretical risk presented by blood products.
Two studies on the distribution of infectivity in 4 and 2 subjects with vCJD respectively, were carried out (*2,3*).

These studies showed that the distribution of infectivity in human tissues corresponds to that which, in the present state of our knowledge on the vCJD agent, could be presumed, that is to say confined to a limited number of organs and tissues (brain, retina, optic nerve, secondary lymphoid organs, i.e. tonsils, spleen, lymphatic ganglions). The relatively high level of infectivity found in the tonsils confirms the potential relevance of this tissue, which is easy to remove, for diagnosis purposes. The infectivity of the adrenal glands noted in one of the studies (*2*) is probably due to the medullo- part of the gland, , as the study didn't include separate measures for the medullo- and the cortico-adrenal hormones. The only further piece of information is the evidence of the presence of PrPres in the thymus and the rectum. As far as the rectum is concerned, these data are still too fragmented (1 positive subject

on three studied patients) to add the history of rectal surgery to the exclusion criteria concerning blood donation. However, the "Comité interministériel sur les ESST" recommended to complete the list of organs considered as potential infectivity vectors established in Administrative Circular DGS/5C/DHOS/E2 n°2001-138 dated March 14, 2001 *relative to the precautions to observe in health care with the view of reducing the risk of transmission of non-conventional transmissible agents*.
So far, all the other studied tissues proved to be negative. In particular, neither abnormal proteins nor infectivity were found in the blood and the buffy coat.
However, these studies are still considered as relatively limited, considering the small number of tested patients and the detection limits of the methods used (human/mouse species barrier for infectivity tests).

Investigational work compared the infectivity kinetics and distribution of the GSS and the vCJD agents respectively, after inoculation to mice. The characteristics of blood infectivity are similar between both agents (*4*).
Here again, it is appropriate to remind that all the results are dealing with experimental transmission of TSSE agents in animal models, while the presence of infectivity in blood has never been demonstrated for naturally occurring TSE to date.
Finally, no new data relating to the experimental transmission study in the sheep model (publication by Houston et al. in the Lancet dated September 16, 2000) are available.

Searching for the BSE agent in the brains of sheep exposed to meat and bone meal proteins during the BSE epidemic in the United Kingdom has failed since sheep brain samples were shown to be contaminated with bovine material. The question of a possible recycling of the BSE agent in the ovine species remains. However, no clinical case evocative of BSE was observed in the sheep so far, even when making the assumption of a clinical expression identical to that of scrapie. Furthermore, the absence of a significant modification in the incidence of scrapie in the British livestock is a point in favour of the absence of massive transmission of the BSE agent in sheep. However, it is necessary to point out that the scrapie epidemiosurveillance systems are still little effective in some countries of the European Union. Thus, this question remains, and considering the possible consequences, it deserves particular attention.

Therefore, there exist no new piece of information relating to the distribution and the infectivity of vCJD in the various tissues, particularly as far as the presence of infectivity in blood is concerned. The existence of temporary or permanent infectivity in the blood of subjects with vCJD hasn't been demonstrated yet. Nevertheless, the results of more relevant studies using primate models are still unavailable. In the meantime, *i)* the presence of the infectious agent in blood during the whole preclinical incubation phase and *ii)* the capability of the infectious agent to be transmitted by blood, are two, *a priori* pessimistic, hypothesis which cannot be formally excluded and which should always be taken as working hypothesis.

1.2 Conclusions

There are no new data likely to modify the determination of a potential infectious load in blood. In the hypothesis of the presence of infectivity in blood, the present state of our knowledge keeps suggesting that the infectious load would be small.

The potential existence of asymptomatic infected subjects remains a plausible hypothesis (*5*). It justifies to eliminate permanently previously transfused subjects from blood donation.

There is no new result concerning the experimental work on the transmission of BSE from sheep to sheep after IV injection, carried out by Houston et al. No other transmission case was observed since the one published in September 2000. So, the remarks on the interpretation of this study remain

unchanged. A similar study with the scrapie agent is on going.

As a conclusion, the possibility of transmission of the disease by blood remains a hypothesis. There is no new piece of information modifying (upwards or downwards) the level of risk considered in the report established in December 2000.

2- Epidemiology

The evolution of the BSE epidemic in the British livestock shows that the decrease in the number of cases continued in 2001 (*6*). In France, the number of cases slightly increased but it is necessary to point out that more than half of the cases registered in 2001 result from the implementation of the screening programme.

The number of cumulated cases of patients developing vCJD goes on increasing in the British Islands (114 cases in February 2002 for 85 cases in November 2000) and in France (5 certain or probable cases on February 1st, 2002 for 3 cases in November 2000) but there has been no significant increase in the incidence (*7,8*). The incidence ratio between both countries was little modified.

There exist no new data relative to the estimation of the number of people likely to develop vCJD. So far, when carried out, genotyping could only identify Met-Met subjects at codon 129. Uncertainty on the possibility that vCJD appears later in subjects genotyped Val-Val or Met-Val at the same codon remains, as this was observed in the iatrogenic cases of CJD caused by the administration of an extractive growth hormone, similarly as in Kuru, uncertainty which could modify the present projections of the number of cases.

No risk factor was identified. Only a north-south gradient in the number of vCJD cases was observed in the British Islands, which probably reflects a correlation with the socioeconomic level of the infected subjects (*9*). In any case, no risk factor can be suggested to be used as an exclusion criterion on the clinical selection of blood donors.

However, the last studies published by British teams revise, downwards, the projections of the number of cases expected in the next few years.
The estimation of the number of people likely to develop vCJD was discussed in the report established in December 2000, on the basis of the model published by Ghani et al. The work conducted by Ghani et al (*Nature, 2000*) reached an extremely high estimation of the number of cases (70 to 136 000 cases) for the British Islands as a particularly large number of scenarios were considered. For the record, the modelling published by Cousens et al (*Nature , 1997*) also amounted to a very large estimation of the number of cases (75 to 80 000 cases). By limiting the model given by Ghani et al. to more realistic hypotheses, Dr A. Alpérovitch, in the report dated December 2000, had suggested to retain for the United Kingdom an estimation between 110 and 2 800 cases (for an average incubation period of 20 to 30 years) and between 150 and 6 000 cases (for an average incubation period of 30 to 60 years). Considering the last hypothesis (the most pessimistic one) and a level of exposure to the risk of BSE 20 times inferior in France, the report indicated that 6 to 300 cases in France would predictably develop vCJD in the 40 years to come.
Two new models were published since then.
The model by Huillard d'Aignaux et al. (*10*) produces a number of clinical cumulated cases in the United Kingdom of the order of several hundreds only, according to the various hypotheses included in the model. The current epidemic of vCJD would therefore be very near its peak. However, the relatively low number of clinical cases is compatible with a very long incubation period, in which case the number of infected persons dying before developing the disease can be very high.

The model proposed by Valleron et al (*11*) produces estimations of the same order as far as the number of cumulated cases is concerned, which would be of several hundreds in the United Kingdom with an epidemic peak reached in 2000/2001. The disease incubation period is estimated to be about 16,7 years, which amounts to 80-630 cases and 801 cases when applying it to the models described by Ghani et al. and Cousens et al. respectively.
These studies, as the preceding studies which were more pessimistic, are to be considered with much caution though, given the large number of working hypotheses introduced in the calculation models. Nevertheless, you will note that the stability of the incidence of vCJD in the United Kingdom in 2000 and 2001, with a smaller number of deaths in 2001 than in 2000, is in accordance with one of the conclusions of Huillard d'Aignaux's work on the one hand, and Valleron's on the other, meaning that the epidemic peak could be reached in 2000/2001.
These studies follow the same direction as the less pessimistic hypotheses of the modelling by Ghani et al, as considered as most realistic in the report dated December 2000. However, these more favourable hypotheses concern the total number of (clinical and asymptomatic) cases only in the model by Valleron et al. In fact, the modelling by Huillard d'Aignaux et al. considers a large number of asymptomatic cases.

3 - Tests

It is reminded that the tests now systematically used in France for the detection of BSE in cattle cannot be used in humans for the detection of vCJD, (therefore non applicable to blood donors), even less to the control of blood products.

It has become more difficult to establish a statement of the development of tests for the detection of vCJD in humans considering the industrial stakes. Several publications deserves however to be mentioned.

Soto et al (*12*) proposed a method for the amplification of PrPres in the presence of PrPc. The reaction principle is simple: PrPres aggregates are dissociated by sonication and the PrPsc amplification products induce in turn a change in the conformation of the normal PrP. Several cycles may be performed in the same way according to a principle which reminds of that of a PCR. The method only works with PrP extracted from the brain but not with recombinant PrP, which shows the influence of factors of cerebral origin in the phenomenon of change in the conformation. The method is used in its simple and sensitive principle. It was applied not only to the nervous tissue but also to the lymphoid tissue and it was possible to reproduce it in other laboratories. This work is therefore potentially interesting for the development of a detection test. In fact, the method could be proposed, as a preliminary step to sample preparation, to amplify low quantities of PrPres existing in the samples to be analysed.

The work conducted by Aguzzi et al identified a specific ligand to PrPsc, which is plasminogen (*13*). Although available when the report was established in December 2000, this work had not been discussed. Identification of this ligand is interesting for the development of a detection test (we could imagine to develop a step consisting in the concentration of the samples to be analysed using the specific ligand) but such work requires a data update in the first place, as no further data was published since then.

Gabizon et al showed the presence in urine of a form of PrP resistant to proteinase K but presenting a molecular weight differing from that of PrPsc, and named «UPrPsc » (*14)*. Such work needs to be confirmed and the physiopathological significance of «UPrPsc » to be explained. If it turns out that this form of PrP specifically appears during the incubation period of certain forms of CJD, this could lead

to the development of a detection test to be carried out on urine.

The publication by Miele et al. shows that PrPsc is not the only usable marker for diagnosis (*15*). The authors identified a gene encoding for a marker specific of the erythrocyte line, the expression of which is diminished in the experimental animal models of TSSE. This work has not been applied to humans and the predictive value of this marker is unknown.

As a conclusion, these articles indicate that research is progressing towards the development of detection tests, although it is impossible to say whether it will lead to the development of tests effectively applicable on a routine basis in humans.

Experts draw the attention on the fact that, unlikely to what happened for HIV, the development of a detection test would probably not be the only most efficacious solution for the qualification of donations and the purification of blood products. The donor exclusion criteria will probably remain the main measure, even when effective routine tests are available. Detection tests will be employed as a complement to the exclusion criteria, in particular to better target and identify risk populations. As a consequence, it is important to point out that the exclusion criteria used are not a default measure on the short and medium terms in the absence of a test but represent the most appropriate measure.

4 - Elimination and inactivation methods

4.1 Elimination/inactivation methods for plasma-derived medicinal products (PDMP)

As far as the elimination methods of the vCJD agent in the preparation processes of PDMP are concerned, the only referenced study, which is relative to nanofiltration, doesn't provide any further piece of information (*16*). It but confirms the efficacy of nanofiltration used to eliminate TSE agents, in particular if the filter porosity is sufficiently small (15 nm). The study also confirms the influence of the agent's aggregation state.

No new specific elimination or inactivation method is being developed at present.

The contribution of PDMP preparation processes to the reduction of the theoretical infectivity relatively to vCJD is now implicitly reckoned by the FDA. In fact, the reinforcement of the exclusion criteria to donors who stayed in the British Islands is more particularly intended for LBP ; by the way, the FDA document mentions « *…plasma derivative products are highly processed, reducing risks of infectious diseases…* ».

Experts wish to point out again that there exists no vCJD agent inactivation method applicable to blood products; the agent inactivation processes (autoclave, oxidation, precipitation with urea) are incompatible with the fragility and the relative stability of the proteins extracted from blood.

4.2 Leucoreduction

The potential relevance of leucoreduction rests on the observation that, in experimental TSE animal models, blood infectivity is essentially associated (90%) with leucocytes. Experts consider that the hypothesis of such a distribution of the vCJD infectivity, used in the report dated December 2000 for the calculation of the residual theoretic infectious load in blood products, remains valid, reminding that the presence of the vCJD agent was demonstrated neither in total blood nor in its fractions. There is no new piece of information as far as the presence of infectivity in platelets is concerned.

Different types of filters are used in the present context of generalizing leucoreduction. There is no existing figure on the proportion and the nature of leucocytes destroyed by the filters used. It is reminded that such an effect could be deleterious, at least if a significant proportion of B lymphocytes and dendritic cells were destroyed; however, infectivity will be less important than in the non-filtered product. Experts recommend to study the effect of the various categories of filters. While waiting for these studies to be completed, nothing indicates that this effect can be such that it calls into question the potential benefit induced by leucoreduction.

As a conclusion, in the context of a precautionary measure, the starting material (cells, plasma for fractionation) leucoreduction remains an approach to be taken into account since it but contributes to reduce the risk of transmission of vCJD by blood products.

5 - Exclusion of the donors who stayed in the British Islands

The exclusion of the donors who stayed in a prolonged manner in a country highly exposed to the risk of BSE had not been the subject of a consensus by the group of experts in December 2000. On the grounds of precaution, the exclusion measure was nevertheless proposed and enforced in January 2001 (exclusion of the donors who stayed in the British Islands for a period of or longer than 1 year, expressed as a cumulated duration of stay, between 1980 and 1996).
Similar exclusion measures were also taken in several European countries. However, these measures are not harmonized regarding the cumulated duration of the stay, which can be explained with a situation differing from one European country to another in terms of the relative level of exposure to the risk of BSE between each one of these countries and the British Islands, and the distribution of the cumulated durations of stay of the donors native from these countries in the British Islands.
The United States and Canada have reinforced the exclusion measure originally enforced in 1999 (*17,18*). These measures are more stringent than those implemented in the European countries. In particular, the cumulated duration of stay in the British Islands motivating the exclusion of donors changes from 6 months to 3 months. The United States even propose (measures not enforced yet) exclusion criteria to be modulated according to the duration and the country of stay, the period of exposure (1980-1996 or 1980 to date), and finally the type of blood product concerned (product for transfusion or plasma for fractionation).

Experts consider that the reinforcement of the exclusion criteria in the United States and in Canada doesn't rest on any scientific rationale or any new data. These criteria, more stringent, were defined relatively to initial criteria which themselves had not been scientifically evaluated. The measure shall be considered as a mere precautionary measure. There is no reason why recommending a more stringent exclusion measure in France, particularly by lowering the cumulated duration of stay from 1 year to 6 months, reflecting what is proposed in the United States and in Canada. Such a measure would set anyone thinking that there exist new pieces of information showing that the risk seems to have increased compared to what it was in October 2000.

As a result, experts consider that there is no new argument on the epidemiological level, the modes of transmission as well as the infectivity calculations, leading to reconsider the donor exclusion strategy implemented in France. It is useful to remind that, in terms of feasibility, the measure resulted in a very limited reduction in the number of donors (from –1 to –2%), which didn't jeopardize the self-sufficiency in transfusion blood products, especially as the consumption of LBP would have decreased in 2001.

6 - Measures taken in France since December 2000

The following measures were enforced after the recommendations established by the report dated December 2000:

- Exclusion of the donors who stayed in the British Islands:

The exclusion measure intended for the donors who stayed in the British Islands for a period of or longer than 1 year (cumulated duration) between 1980 and 1996 is effective since January 2001. There was no major difficulty relatively to the enforcement of this measure.

- Leucoreduction:

Following the recommendation to apply leucoreduction to the plasma used for the preparation of LBP and PDMP, additional advice was requested from the Afssaps group of experts on viral safety (January 11, 2001). This group of experts confirmed the principle of a maximal leucoreduction for all kinds of plasma products (for direct therapeutic use and for fractionation), even though it was acknowledged that leucoreduction beyond 10^6 residual leucocytes per litre only reduces the potential infectious load in a minimal and non-measurable fashion. However, they proposed this measure of extreme precaution considering the uncertainties on the nature of the cells which carry infectivity in blood and on the efficacy of filters to eliminate them specifically (voir 4.2).
The generalization of plasma leucoreduction (purified FFP, FFP for the preparation of VAP, FFP for the preparation of FDP, PFF) is effective since April 15, 2001, with a target value of approximately < 10^6 residual leucocytes /L (while waiting for the standard to be set).
The residual leucocyte standard is being defined at the moment, on the basis of the dossiers evaluated and the EFS (Etablissement Français du Sang) production quality control results. The standard will be ready by the end of the first quarter 2002. It is reminded that while waiting for the standard to be set, labile blood products, including plasma for fractionation, have been leucoreduced for several months already
Considering the production deadlines, the supply by the LFB (Laboratoire Français du Fractionnement et des Biotechnologies) of PDMP prepared exclusively from leucoreduced plasma at $<10^6$/L has taken place since 2002 for the major part of medicinal products.
The generalization of leucoreduction involved no major difficulty. However, the supply in French PFF was reduced by 8% (plasma loss on filters, EFS data).
It was reminded that there is no harmonized position on the European level, the systematic leucoreduction of cell LBP and/or plasma being enforced in some countries only. There is no European position either on the benefit of plasma leucoreduction for the reduction of the risk.

- Revision of the recommendations on the use of LBP:

The recommendations issued in 1997 by the ANAES are being revised by an *ad hoc* working group from the Afssaps. They will be published during the 2nd quarter 2002 for plasma and red blood cell concentrates and during the 4th quarter 2002 for platelet concentrates and granulocyte concentrates.

- Additional expertise on the safety level of the VAP compared to the unit of FFP:

The evaluation of the safety levels of the VAP and the unit of FFP respectively, depended on a validation study of the VAP preparation process with respect to NCTA. This study (recommended by the experts in December 2000) is in progress.

- Improvement of the LFB PDMP preparation processes:

For factor VIII (FACTANE), the 35+15 nm nanofiltered product has been available since January 28, 2001, with the simultaneous withdrawal of the non-nanofiltered factor VIII.
For Polyvalent immunoglobulins IV (TEGELINE), the 75+35 nm nanofiltered product was made available in the course of 2001 for patients with ITP (idiopathic thrombocytopenic purpura),. The demonstration of the NCTA elimination efficacy through this type of filtration (75+35 nm) was not made in the M.A.A. dossier, and the results obtained for some viral families (in particular small-sized viruses) suggest a limited efficacy with respect to TSSE agents.

- Supplying imported PDMP:

Regarding the PDMP which had been identified as presenting the least relevant safety level (factor VIII, antithrombin III, factor VII, fibrinogen and fibrinogen for biological sealant), the Afssaps inquired about the availability of products derived from plasma collected in countries *a priori* with a lower risk of BSE or vCJD, which could be imported in France.
Two out of the three factors VIII for which dossiers were submitted do not meet one or several of the quality, safety and efficacy requirements authorizing their use. It is the same for the antithrombin III studied.
As far as the fibrinogen for biological sealant is concerned, the marketing of the LFB biological sealant (BIOCOL) was stopped.
No medicinal product likely to be imported for factor VII and for the fibrinogen was found.

It is necessary to remind that the group of experts who met in December 2000 had encouraged the supply of PDMP derived from plasma collected in countries *a priori* with a lower risk of BSE or vCJD. However, they had clearly recommended that this precautionary measure couldn't be taken to the detriment of the intrinsic quality of the products offered.

- Consultant, patient and donor information:

An information letter dated January 29, 2001, including a statement of the risk evaluation and a reminder on the necessity to use these products in the strictest respect of their indications, was addressed to physicians, in particular blood product consultants.
On March 30, 2001, the Afssaps received the patient associations and the donor associations who were previously represented at the information meeting organized on November 17, 2000.

7 – Medicinal products extracted from urine

A study (*14*) looked for the presence of PrPres in the urine of animals or human subjects suffering from various types of TSE. A form of PrP resistant to proteinase K but presenting a molecular weight differing from that of PrPsc, named «UPrPSc » by the study authors, was identified. The human subjects studied were suffering from classical forms of CJD, mainly familial diseases.
The origin of «UPrPsc » is unknown and nothing demonstrates that it may be an indirect proof of the presence of PrPsc in blood. «UPrPsc » appears during the second half of the incubation period, before the related clinical signs show up. The infectious nature of UPrPsc is being evaluated.
Experts consider that this is quality work but that it is necessary to reproduce it in other laboratories, previously to any in-depth discussion on the interpretation of the results. The study doesn't give any particular about the physiopathological significance, the origin or the infectivity of such «UPrPsc ».

Regarding blood products, this study doesn't support the presence of PrPsc in blood, neither in the

classical forms of CJD nor in vCJD. However, it provides a possible research direction for the development of a detection test usable on a routine basis.

For medicinal products extracted from urine, gonadotropins and urokinases, it is useful to remind that they are prepared from « donors » who cannot be submitted to any clinical selection considering the particular urine « donation » conditions (high frequency of donations, very large number of « donors »). The clinical selection, particularly in the case of sporadic forms of CJD, wouldn't however defer from « donation » subjects in the final phase of incubation during which «UPrPsc » is present in urine. In the hypothesis of the effective presence of «UPrPsc » and of its infectious nature, transmission cases with gonadotropins would probably already have been observed within the context of pharmacovigilance, all the more as urine comes from menopaused women among other donors, consequently elderly women who are more at risk to be in the final stage of the disease incubation period, and as the recipients are young women who are monitored and have a normal life expectancy, in whom the disease should be detectable. Furthermore, the processes used for the preparation of gonadotropins and urokinases are complex extraction and purification techniques which could include, after a more detailed examination of each one of the preparation processes, various steps capable of eliminating or inactivating the TSE agents, such as high pH treatments, adsorptions and chromatographies. In the case of vCJD, an additional safety criterion requires that «donors » do not originate from countries presenting cases of vCJD or a high incidence of BSE. As a conclusion, the safety of the medicinal products derived from urine with regard to the risk of transmission of human TSE agents doesn't seem to be questionable.

Conclusions

The information available since the report established by a multidisciplinary and independent group of experts on the analysis of the risk of transmission of vCJD by blood and blood derivatives doesn't provide any further scientific material or any argument likely to modify the conclusions of the report dated December 2000 (*19*).

Up to date, there exist no new data on the variant Creutzfeldt-Jakob Disease (vCJD) physiopathology, modes of transmission, distribution and level of infectivity in the various tissues or on the estimation of a possible infectious load in blood.. For this reason, the possibility of transmission of the disease by blood remains a hypothesis too. Furthermore, no new piece of information allows to affirm that the level of risk considered in the report dated December 2000 is modified.

On the epidemiological level, no significant increase in the incidence of vCJD was observed in France and in the British Islands. The estimation of the number of people likely to develop vCJD doesn't seem to be modified.
No new risk factor, which could be used a an exclusion criterion on the clinical selection of blood donors, was identified.

Interesting pieces of work were published on methods which could possibly be used for the development of detection tests, in particular methods relative to the cyclic amplification of the change in the conformation of PrP. However, no detection test is applicable to humans at present. Additionally, the donor exclusion criteria, in force at the moment, are and will probably remain, at least on the short term, the most appropriate measure for the qualification of donations, a measure which will be complemented with detection tests usable on a routine basis when the available biotechnological tools allow it.

There is no further piece of information on the capacity of the PDMP preparation processes to eliminate

the vCJD agent. Consequently, the data included in the report dated December 2000 remain unchanged. For LBP, leucoreduction remains a precaution to be considered, a measure which will but contribute to reduce the risk of transmission.
It is reminded that there exists no vCJD agent inactivation method applicable to blood products.

Several countries implemented or reinforced the measure excluding the donors who stayed in a prolonged manner in a country with a high exposure to the risk of BSE. However, these measures were taken without any particular scientific rationale or further data. Therefore, there is no reason why recommending a more stringent exclusion measure in France, which would set anyone thinking wrongly that there exist new pieces of information showing that the level of risk has increased since December 2000.

The conclusions and recommendations of the report established in December 2000 remain valid. None of the items dealt with and discussed in this report needs to be modified. There is no new measure to propose in order to further reduce the possible risk of transmission of vCJD by blood products. The measures in force at present seem to be efficacious and proportionate so as to ensure the right blood product benefit-risk ratio.

Updated figures relative to the number of BSE and vCJD cases appear in the annexe. An *erratum* relative to the calculation of the level of risk bound to factor VIII is also included.

Finally, it is appropriate to follow the possible developments relating to the presence of a resistant form of PrP in urine. In the meantime, there is no reason for anticipating a reevaluation of the safety of medicinal products derived from urine with regard to the risk of transmission of the CJD and vCJD agents.

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Lexicon

BSE:
Bovine Spongiform Encephalopathy

TSE:
Transmissible Subacute Spongiform Encephalopathy

GSS:
Gerstmann-Straüssler-Scheinker Syndrome

Leucoreduction:
Operation consisting in removing, under aseptic condition, the major part of leucocytes in a labile blood product. For technical reasons, the removal is most often incomplete; in such case, the term of "leucoreduction" is preferable to "leucodepletion".

CJD:
Creutzfeldt-Jakob Disease (sporadic, iatrogenic, familial diseases)

FDP:
Frieze-dried Plasma

FFP:
Fresh Frozen Plasma

PFF:
Plasma For Fractionation

PDMP:
Plasma-derived medicinal products

PrPsc:
Abnormal form of the naturally-occurring protein PrP

VAP:
Viro-Attenuated Plasma

LBP:
Labile Blood Products

vCJD:
Variant Creutzfeldt-Jakob Disease

ANNEXE

Update of the numerical data appearing in the report dated December 11, 2000:

- Number of cases of BSE:

- United Kingdom (by 21/11/2001): 181 368 cumulated cases (*179 256 cases in October 2000*) and 526 reported cases for the year 2001 by 30/09/2001 (*1443 cases for the year 2000*).

- France (by 31/01/2002): 258 cases for the year 2001 (by 18/12/2001) distributed as follows: 89 clinical cases, 94 cases resulting from research and 75 cases following systematic screening at the slaughterhouse (*a total of 161 cases for the year 2000*).

- Number of cases of vCJD:

- United Kingdom (by 04/02/2002): 114 certain or probable cumulated cases (*85 cumulated cases in November 2000*), with 20 confirmed cases for the year 2001 and 2 confirmed cases by 4/02/2002 for the year 2002 (*28 confirmed cases for the year 2000*).

- France (by 01/02/2002): 5 certain or probable cumulated cases (*3 certain or probable cumulated cases in November 2000*).

Erratum relative to the calculation of the level of risk bound to factor VIII:

ANALYSIS OF THE RISK OF TRANSMISSION OF THE NEW VARIANT CREUTZFELDT JAKOB DISEASE BY BLOOD AND BLOOD DERIVATIVES

3- Risk analysis and specific recommendations concerning each blood product
3.2 Plasma-derived medicinal products (PDMP)
3.2.1 Factor VIII

Correction of the sentence, p 14 : "In another interpretation, doses would not be fractionable below one iv-Inf.U. It would mean that 2,4 iv-Inf.U. would be distributed in the equivalent of 100 annual doses, allowing the contamination of 2,4 % of the recipients treated annually at the cumulated dose of 500 000 UI of factor VIII, **that is to say of one patient every 42 years**."

1- Determination of the extent of the wrong meaning of the sentence as written in the report

There are two errors in this formulation

a) The clause "that is to say of one patient every 42 years" means that one patient only will be contaminated every 42 years. Over the incubation period lasting 60 years, approximately 1,5 patients suffering from the disease could therefore be observed. This is contradictory with the preceding clause which says: "the contamination of 2,4 % of the recipients treated annually", since one estimation of the above mentioned 2,4 % would be approximately 3000 patients x 0,024 = 72

b) The clause "that is to say of one patient every 42 years" could also be interpreted as each patient has 100% chance to be contaminated after 42 years.

Now, the calculation of the number of chances *not to have been infected after 42 years* can be done by calculating the number of chances not to have been infected each new year, between 1 and infinity.

number of chances not to have been infected the first year = 1 – 0,024 = 0,976
number of chances not to have been infected the second year = $(0,976)^2$ = 0,953
number of chances not to have been infected the third year = $(0,976)^3$ = 0,929
number of chances not to have been infected the fourth year = $(0,976)^4$ = 0,907
….
number of chances no to have been infected the 42nd year = $(0,976)^{42}$ = 0,384 = 38,4%
…
number of chances not to have been infected the hundredth year = $(0,976)^{100}$ = 0,14

Saying that the number of chances not to have been infected the 42nd year is of 38,4% amounts to saying that the number of chances to be infected is of 1- 38,4%, **that is to say 61,6%, not 100%**.

2- Calculation of the contamination expectancy

It is possible to calculate what interests us, that is to say the expectancy of the number of annual treatments before the transmission of the first infectious unit, that is to say the average number of treatments before the transmission of the first infectious unit.

To do so, we have

a- A method which consists in reasoning on a very large finite number of treatments.
We can calculate the average number of treatments between 2 Inf.U. It is the number of treatments divided by the number of U.Inf.
We know that: $\frac{\text{number of treatments}}{\text{2,4 \% of the number of treatments}}$ = 100 / 2,4 that is to say 42.
So, let's assume that the average number of treatments between 2 Inf.U. is of 42 years.

b- Another method is the exact calculation of the average, calculation of the expectancy using the equation: $\sum_{n=0}^{\text{infinity}} n \times p(A_n)$,
where A_n is the following event: there are exactly n treatments before the first Inf.U.

The Law of Large Numbers specifies that when the number of treatments tends towards infinity, the average value for this (finite) number tends towards the average value calculated using the above formula, which means that the use of the intuitive method is correct.

Therefore, we agree that the exact calculation of the average number of annual treatments before the first Inf.U. will also produce the result of 42 years, since the proportion of Inf.U. established previously (from prevalence, reduction, dose values) is independent from the number of treatments (it is still 2,4%) here.

3- So, it is appropriate to correct the clause ", that is to say of one patient every 42 years."

By replacing it with:

", or for each patient, the average annual number of treatments before a contamination is of 42 years."

Or with

", or on average, each patient would receive an Inf.U., every 42 years of annual treatment".