BELGIAN ADVISORY COMMITTEE ON
Bioethics

Opinion no. 60 of 27 January 2014 on the ethical aspects of liver transplantation in patients suffering from acute alcoholic hepatitis (AAH) who do not respond to traditional medical treatments

Content of the opinion

Introduction

On 7 October 2011 Professor Jean-Paul Van Vooren, Senior Consultant at the Erasmus Hospital in Brussels, sent a request for an opinion to the Advisory Committee on Bioethics.
The question related to the treatment of acute alcoholic hepatitis (AAH) by means of transplantation in patients who do not respond to traditional medical treatment[1] and have been abstinent for less than six months.
Its terms are as follows: "Is it acceptable to envisage performing a transplant in the knowledge that:

- This strategy does not respect the tacit rule of six months' abstinence from alcohol before a patient is placed on the list for a liver transplant.
- 75% of these patients will die during this six-month period.
- This position is not shared by other Belgian transplantation centres.
- This six-month rule is not laid down in writing anywhere, and in particular does not figure among the Eurotransplant criteria.
- The predictive value of six months' abstinence with regard to the long-term survival of the transplanted organ has not been demonstrated (utilitarian view of organs in relation to the shortage thereof).
- The first experiment carried out in conjunction with other French centres yields very encouraging results with a low risk of relapse into alcoholism, comparable to that reported in the literature after observance of a six-month period of abstinence, and this experiment has been accepted for publication[2] in the *New England Journal of Medicine*."

In its meeting of 12 March 2012, the Committee decided to examine the question from the point of view of its medical, social, legal and ethical aspects, and entrusted the preparatory assignment to a "Patient's own Responsibility" select committee (CR 2012-2), which began its work on 29 October 2012.

I. Subject of the opinion

In Belgium the liver is the second most transplanted organ, after the kidney. There are many medical indications for liver transplantation (LT), but patients suffering from very severe liver failure owing to chronic alcohol abuse (alcoholic cirrhosis) are currently the most numerous. With a view to his inclusion in the liver transplantation programme, a patient presenting chronic and terminal[3] alcoholic cirrhosis must have been abstinent for at least six months. For the medical world the cause of the pathology, in this case chronic alcohol abuse, may not

[1] That is to say patients for whom no therapeutic alternative is possible, for example in the form of drug treatment.
[2] Mathurin Ph., Moreno Ch., Samuel D., Dumortier J., Salleron J., Durand F., Castel H., Duhamel A., Pageaux G-Ph., Leroy V., Dharancy S., Louvet A., Boleslawski E., Lucidi V., Gustot T., Francoz C., Letoublon C., Castaing D., Belghiti J., Donckier V., Pruvot F-R., and Duclos-Vallée J-C., *Early Liver Transplantation for Severe Alcoholic Hepatitis*, N Engl J Med, 365; 19; pp. 1790-1800, November 10, 2011.

[3] This adjective denotes the state of the organ and not the patient; it indicates that there is no therapeutic alternative to a liver transplant.

constitute a criterion for exclusion *a priori* from the benefits of health care meeting the patient's needs. The party requesting the opinion highlights this criterion of six months' abstinence, the purpose of which is to guarantee, as far as possible, the patient's future abstinence after he has received a transplant.

The current request for an opinion can be placed in the context of recent clinical research on the treatment of certain serious forms of alcoholic hepatitis: acute alcoholic hepatitis (AAH)[4]. Indeed, scientific advances in the diagnostic and therapeutic fields have made it possible to target a new group of patients likely to be able to successfully undergo a liver transplant. It can reasonably be reckoned that the inclusion of this group of patients among the potential beneficiaries of a liver transplant is medically justified, since transplantation is likely to improve their survival rate.

However, these results mean that if AAH were to be retained as a new recognised indication for liver transplantation, an additional group of patients would be added to the transplant waiting list – and what's more, in a position of priority – in a situation characterised by a chronic shortage of available organs. The effect would be to increase the mortality rate among patients on the waiting list.

There is currently no consensus either among the Belgian transplantation centres or at international level, as to whether or not AAH should constitute a new indication for liver transplantation. The answer to this question encompasses both ethical and medical considerations; hence the submission of this request for an opinion to the Committee.

Indeed, the Committee considers that the question put to it, which stems from medical advances in a situation of shortage, basically affects the dual ethical problem of *delimitation* of those groups regarded as having priority in accessing this kind of treatment, and thus the subsequent problem of the *criteria adopted* to put this delimitation into practice.

Moreover, in this context the problem of the transposition of surgical innovations into everyday clinical practice is again raised[5]. This means that for an "innovation" – which by definition has not yet been officially recognised – to be able to move from the controlled research framework into the context of everyday medical practice, it must first meet strict technical and scientific validation criteria.

The Committee proposes substantiating its reply to this twofold problem (definition of the criteria on the one hand, and apprehension of the technical-cum-scientific problems on the other) on the basis of specific medical considerations pertaining to the treatment of the different types of alcoholic hepatitis and considerations of a legal nature relating to the patient's interest, the doctor's duties and the interest of society.

[4] Mathurin *et al, op. cit.,* 2011, p. 1799.
[5] Pelligrini C A, *Presidential Address at the American College of Surgeons - The surgeon of the future: Anchoring Innovation and Science with Moral Value. Bulletin of the American College of Surgeons*, December 2013: 9-14.

II. Medical and epidemiological aspects

2.1. Liver transplantation (LT): general points

Liver transplants have been carried out for some forty years worldwide and this surgical treatment is well organised and mastered in our country. A standardised medical operation chain comprising several medical teams runs from the organ donor to the transplant organ recipient, under the coordinating action of the organisation Eurotransplant[6], of which Belgium is a member.

Liver transplants are the most frequently performed organ transplants after kidney transplants, and currently constitute the only potentially curative treatment in the case of terminal liver failure. After all, the liver is a vital organ and its irreversible severe functional failure leads irremediably to the patient's death.

2.2. Liver transplantation (LT): basic medical data

The chances of survival after a liver transplant are 85% after one year and 75% after five years, with a good quality of life. Around 5,000 liver transplants are performed In Europe every year, 200 to 250 of which in Belgium. However, there is still a major disparity between the number of available organs and the demand for transplant organs. 20 to 30% of the patients on waiting lists in Belgium die because they are unable to receive a transplant organ in time (the average waiting time in Belgium being six months)[7].

What are the **main indications** for LT?

[6] The Eurotransplant foundation is an organisation providing services for transplantation centres, laboratories and hospitals performing transplants, and is based on cooperation between eight countries. Eurotransplant endeavours to ensure optimal use of the organs available by determining the best possible compatibility between organ and recipient. Allocation of organs is based on medical and ethical criteria. The organisation comprises an Assembly, a Board of Management, a Council and nine advisory committees. Doctors, scientists and decision-makers can thus contribute to the drafting of Eurotransplant's policy and the definition of its working method. Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia are members of Eurotransplant. Visit http://www.eurotransplant.org. The most recent report produced by the Eurotransplant International Foundation is available in the Annual Report 2012.

[7] Eurotransplant International Foundation, *Annual report* 2012 on organ removal and transplantation (http://www.eurotransplant.org/cms/mediaobject.php?file=AR2012.pdf). Belgian section of transplant coordinators: Statistics on removals and transplants, 2012, p. 11. See at: http://eodd2013.be/fr/contenu/statistiques. The transplanted organs come from either donors who have died or donors who are alive. As the Advisory Committee pointed out in its Opinion no. 50 of 9 May 2011 on certain ethical aspects of the amendments made by the law of 25 February 2007 to the law of 13 June 1986 on the removal and transplantation of organs, recourse to living donors is not without risk for the latter. In this situation and in the absence of corroborating and reliable scientific data on post-transplant monitoring, in respect of both the recipients and the donors, recourse to living donors could not be considered as a simple solution to the problem of shortage.

The main cause of severe liver failure[8] is **cirrhosis of the liver** further to damage to the liver cells (so-called "parenchymatous" cirrhosis) or to the liver's biliary ducts ("cholestatic" cirrhosis, which is rare in Belgium). Cirrhosis of the liver is a chronic disease that can lead to an alteration in the functioning of the liver to such an extent that the patient's life can be put at risk. When this stage is reached, consideration will be given to liver transplantation. The most frequent causes of the chronic disease that is cirrhosis of the liver are mainly *viral infections (hepatitis B and C)*[9] and chronic poisoning of the liver by alcohol. *Cirrhosis or chronic alcoholic hepatitis* (CAH) is the most frequent epidemiological indication for liver transplantation, ahead of indications for viral and cancerous causes. In some cases, a liver cancer may develop secondarily to the cirrhosis. If the tumour remains limited to the liver without any metastatic spread, its surgical removal and subsequent replacement by a transplanted liver may be recommended.

More rarely, *auto-immune disorders* (i.e. primitive biliary cirrhosis) may be involved, but there are also rare *genetic conditions* and so-called *accumulation diseases,* including haemochromatosis and Wilson's disease. However, these rare causes do not fall within the scope of this opinion paper.

Apart from chronic hepatitis, there are **acute** forms of **hepatitis**, which are appreciably less frequent but which represent a higher degree of emergency, implying a number of well-defined criteria having to be met. The most frequent causes of acute ("fulminant") hepatitis are *acute viral hepatitis, massive paracetamol poisoning* (further to a suicide attempt, for example) or *poisoning by other substances*[10]. This type of hepatitis is characterised by a very high mortality rate, which justifies the possibility of having recourse to a possible liver transplant in cases of extreme urgency.

The indication for liver transplantation will only be accepted **if the patient's condition is life threatening**. This is understood as being the patient's risk of dying if a transplant is not performed. It is therefore the degree of seriousness of the disease and the patient's chances of survival that serve as the main criteria[11]. This assessment is done by means of the MELD (Model of End-stage Liver Disease) score, which is internationally accepted as an evaluation criterion for a patient to be put on the waiting list for a transplant[12]. This classification

[8] "Liver failure is referred to as severe if the level of prothrombin (TP) is lower than 50%. Serious acute hepatitis is characterised by the coexistence of an ALF (Acute Liver Failure) and an encephalopathy, in which case we talk of fulminant hepatitis. It is estimated that only 10% of patients suffering acute hepatitis develop a severe form and less than 1% of them a serious form". Belafia F., Jung B., Jaber S., Paugam-Burtz C., Acute Liver Failure, 6th Congress of the French Society of Emergency Medicine, 2012.
[9] The agent of hepatitis D is a defective RNA virus, i.e. dependent on the B virus for its replication and expression. This new virus is endemic in certain populations, and in particular in the equatorial forests of Central Africa and Amazonia in Brazil where it is responsible for epidemics of fulminant hepatitis. It is also spread via drug addiction in Europe and Western countries.
[10] For example poisonous mushrooms such as death caps.
[11] For a summary of successive recommendations concerning the indications for LT, see: *Conférence de consensus. Indications de la transplantation hépatique*, Haute Autorité de Santé & ANAES, Lyon-Paris, 2005. http://www.has-sante.fr/portail/jcms/c_272409/fr/indications-de-la-transplantation-hepatique?xtmc=&xtcr=2
[12] "The MELD score is used to rate the severity of liver failure according to objective laboratory values: the level of creatinine (kidney function), the INR (coagulation measurement) and the level of bilirubin

therefore does not take account of the date of the request or the date of inclusion on the waiting list, but is done in function of the life prognosis. Some adjustments are possible in specific cases, such as liver cancers or some cases of acute hepatitis, which can then take on priority status. Aside from the medical criterion of severity of the condition (involving any associated or concomitant liver pathologies), a check is made of the presence of serious complaints other than liver ailments (e.g. heart/lungs), the use of other substances, psychiatric disorders, etc.[13].

Compared with kidney transplants, In the case of liver transplantation the problems to be solved are complex and the procedures to be followed, both for the patient and for the physicians, are very restrictive. After all, in the case of kidney failure there is an alternative to emergency transplantation, namely the use of artificial kidney technology, which makes it possible to treat a patient with kidney failure. For the liver, on the other hand, there is no external technological alternative capable of temporarily taking the place of the liver's function pending the moment of transplantation. Ultimately, and if no available transplant organ is forthcoming, the patient will die.

(metabolic function of the liver). This score, which can be graded on a scale from 0 to 50 points, indicates the risk of death without liver transplantation".
http://www.th-ulb.be/Generic/servlet/Main.html?p_modid=10784.
See also on this subject: Gex L., Bernard C., Spahr L., "*Scores in hepatology, Child-Pugh, MELD and Maddrey*", in*: Revue Médicale Suisse*, no. 264, Sept. 2010.
Consult: http://titan.medhyg.ch/mh/formation/article.php3?sid=35120.

[13] Van Vlieberghe H., MD. PhD. *Alcoholic hepatitis: a good indication for liver transplantation?* Interview session of the select committee on 10 December 2012.

2.3. **Chronic Alcoholic Hepatitis (CAH)** of the "terminal and irreversible cirrhosis of the liver" type

The first liver transplants were performed for indications other than those associated with chronic alcoholism, but over time the indication for CAH of the terminal and irreversible cirrhosis type has become predominant[14]. When this indication was included, a consensus emerged as to the importance of treating not only the diseased organ but also the addiction to alcohol, which constitutes both the cause of the chronic poisoning of the diseased organ and a future threat to the transplanted liver in the event of transplantation. It seemed rational and reasonable to demand that the potential recipient undertake beforehand to refrain from drinking alcohol.

The fruit of international consensus within the transplantation community, the specific, simple, measurable and strictly medical criterion for eligibility of CAH patients with a view to their inclusion on the waiting list is abstinence from any consumption of alcohol for a period of at least six consecutive months. It is widely applied by transplantation centres. Strictly speaking it is not a rule, and much less a legal rule, but a consensual criterion that by definition can be subject to review in function of medical data. It is not one of the criteria used by Eurotransplant. This condition of a period of abstinence imposed on potential transplant recipients also offers the not insignificant advantage that in some cases the liver function may improve, to the point of even rendering the transplantation option unnecessary.

The rule of six months' abstinence is observed by the Belgian teams. The aim they are pursuing is clear, namely the patient's survival and avoidance of his relapse into alcohol abuse after the transplantation. However, there remains the question of ascertaining the degree to which this six-month criterion is actually predictive of the success of the transplant. Research on this subject shows that in the long term approximately 25 to 35% of patients who have received a transplant relapse into their alcohol dependency[15].

[14] "Currently alcoholic cirrhosis is the primary indicator [sic] for liver transplants in France: slightly less than half of all liver transplants are performed on account of alcoholic cirrhosis, twice as many as for cirrhosis due to hepatitis C" (interview with Pr Henri Bismuth, founder of the hepatobiliary institute of the Paul-Brousse Hospital (Villejuif) and president of the National Academy of Surgery, published in *Le Figaro* on 17/02/2012). The scientific literature accepts that chronic liver diseases associated with alcohol consumption constitute the second most frequent indication for transplants (see: O'Shea R., Darasathy S. & Mc Cullough A.J., "*Alcoholic liver disease. AASLD Practice Guidelines*", in: Hepatology, Jan. 2010, p. 321; Ashwani K. Singal, Khusdeep S. Chaha, Khalid Rasheed, Bhupinderjit S. Anand, *"Liver transplantation in alcoholic liver disease: Current status and controversies*", in: World Journal of Gastroenterology, 2013 Sept. 28; 19 (36): 5954).

[15] Mathurin *et al*, *op. cit.,* 2011; 365; p. 1799. In a more recent article (2013), it is stated that in the context of the United States, relapse into alcohol consumption among patients who have received a transplant is estimated, depending on the studies, at between 10% and 60% of cases. This sizeable variation in prevalence in fact reveals a lack of consensus as to the definition of relapse. Those who define relapse as "harmful consumption", put at one or two glasses a day, note cases of relapse in approximately 15 to 20% of patients. See: Ashwani *et al, op. cit.* 2013 Sept. 28; 19 (36): 5956.

The fact that the abstinence rule used establishes a period of six months, and not three, nine or twelve, is not the result of irrefutable scientific studies, but is based on the fact that generally speaking the longer the period of abstinence, the better the prognosis of long-term remission will be. In this respect it has been demonstrated that 41% of patients who have received a transplant after a period of abstinence of less than six months relapse after the transplant, compared to only 12% of patients who have observed a period of abstinence of six months or more[16].

The clinical consensus secured for laying down the six-month period of abstinence as a criterion for admissibility of CAH patients to the LT programme is generally very well accepted by both physicians and patients. However, any rule of consensus in medicine is by definition provisional and may be modified further to the results of more precise research or new scientific advances. In the case at hand, current scientific data suggests that while the six-month rule constitutes a justified criterion of *inclusion* of patients on the waiting list for a possible transplant, it also represents a questionable criterion of *exclusion*. Indeed, if 41% of patients having received a transplant after a period of abstinence of less than six months relapse after the transplant, this also means that 59% do not relapse and should not be removed from the list on account of this potential risk of relapse. The major meta-analysis by Dom *et al*[17] concerning the risk for relapse of alcohol use after liver transplantation also highlights predictive factors other than the capacity for long-term abstinence, such as a low level of social support and a family history of alcohol abuse[18]. These authors conclude that future research is absolutely vital for improving prediction of the risk of relapse into alcohol use and promoting permanent abstinence after liver transplantation.

It will be recalled that the request for an opinion submitted to the Committee concerns non-observance of the rule of six months' abstinence prior to transplantation for acute alcoholic hepatitis (AAH), but does not concern CAH of the terminal and irreversible alcoholic cirrhosis variety.

[16] Foster P. F., Fabrega F., Karademir S., Sankary H. N., Mital, D. & Williams J. M. (1997), *Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation*. Hepatology, 25, 1469–1477.

[17] Dom *et al, Risk for relapse of alcohol use after liver transplantation for alcoholic liver disease: a review and proposal of a set of risk assessment criteria,* Acta Gastro-Enterologica Belgica, Vol. LXXIII, April-June 2010, p. 251.

[18] The article by Ashwani K. Singal & al, cited above, states that the main predictive factors for relapse are the lack of social and family support, but also include pre-existing psychiatric comorbidities, polyconsumption (other substances), failures in previous attempts to give up alcohol, the case of transplantation being performed at a young age, and alcoholism in the family (World Journal of Gastroenterology, 2013 Sept. 28; 19 (36): 5956).

2.4. Acute Alcoholic Hepatitis (AAH)

The advances made in diagnosis and prognosis tools (Child-Pugh, MELD score) have made it possible over time for the seriousness of liver complaints to be measured more accurately and for patients' survival prognosis to be established with greater precision, which is a decisive factor in their classification on the waiting list: patients granted priority are indeed those for whom the urgency is greatest. AAH represents an extremely serious form of explosive destruction of the liver as a result of massive alcohol consumption, be this staggered over time or in the form of occasional or repeated sessions of sudden, very heavy drinking ("binge drinking", for example)[19]. It is associated with a very high mortality rate in patients who do not respond to treatment with corticoids.

The article published in 2011 in the *New England Journal of Medicine* (NEJM) by a research team from Lille[20] (to which the transplantation team at the Erasmus Hospital in Brussels contributed) convincingly demonstrates the pertinence of liver transplantation in this indication, something that had already been tried for the first time in 1988[21]. This experimental study indeed showed, in a limited sample of patients, that immediate recourse to transplantation for some AAH patients not responding to traditional medical treatments (corticoids) could significantly improve their chances of survival and their health.

In the cases selected for this study, the survival rate at six months was 77% for patients who had received a transplant and 30% in the case of a comparable control group. This pilot study was approved by a scientific committee and conducted according to a rigorous scientific methodology. All the patients concerned gave their written consent for the transplantation in the framework of this study. The positive results of this pilot study have served to place the issue of acceptance of this new indication for liver transplantation in AAH by the medical world in particular and by society in general, well and truly on the agenda.

Two aspects of this study in particular deserve special attention.

a) The first concerns the accuracy of the biological criteria for selection of the patients.
   - The MELD, which rates the gravity of the case, also applies to AAH and on the basis of this score (which is always extremely high in this indication), these patients move to the top of the waiting list for a transplantation.

[19] "Excessive alcohol consumption… sometimes takes…the form of what is referred to in English by the term "binge drinking", i.e. the pursuit of the state of drunkenness in as short a period of time as possible". This is high-risk behaviour, which "may, in extreme cases, result in serious accidents, alcohol-induced comas, acts of violence or even deaths", Information Report no. 95 (2012-2013) by Mr André Reichardt and Ms Corinne Bouchoux, drafted on behalf of the information mission of the law commission, lodged with the Senate (Upper House of the French Parliament) on 31 October 2012.
[20] Mathurin et *al*, *op. cit*, see above, note 2.
[21] Starzl Th. E., Van Thiel D., Tzakis A. G., Iwatsuki S., Todo S., Marsh J. W., Koneru B., Staschak S., Stieber A. and Gordon R. D., *Orthotopic Liver Transplantation for Alcoholic Cirrhosis*, Journal of American Medical Association (JAMA) 1988; 260:2542-2544.

- A second rating, referred to as the "Lille" score, is used to identify those people who do not respond to corticoids from the seventh day of this treatment. A Lille score of ≥ 0.45 predicts nearly 80% of the deaths of patients with severe AAH. This enables an early and accurate identification of possible candidates for LT[22].

b) The second aspect concerns the very strict selection of potential candidates for transplantation. According to the article in the NEJM, the selection should be based not only on the aforementioned biological criteria, but also on the following criteria associated with the patient's family context and his environment understood in the broad sense of the word:
   - the AAH from which the patient is currently suffering is the first episode of liver decompensation (there is no medical history of previous liver complaints),
   - presence of close relatives supporting the patient,
   - absence of any major somatic or psychiatric co-morbidity,
   - the patient's agreement (with the support of members of his family) to accept total abstinence from alcohol for the rest of his life.

This rigorous selection process moreover demands that absolute consensus be reached in favour of transplantation, not only between the patient himself and his family, but also by the whole team: the nursing staff and the GP, a doctor trained in the treatment of addictions/alcoholism, an experienced hepatologist, the anaesthetist and the surgeon. There must be complete agreement of all the parties taking part for the patient to be accepted as a candidate for LT.

What is more, after the transplantation a follow-up programme to monitor abstinence from alcohol is implemented by means of regular contacts with the patients and their families. This aspect of subsequent follow-up and guidance and support to the patient is thus amply taken into account, and goes far beyond the purely technical aspect of the transplantation.

It is therefore understandable that in the selection criteria for AAH patients no reference is made to the six-month abstinence rule, as is the case for CAH. It is no longer relevant in this indication, inasmuch as after six months 70% of the patients will have died, meaning that any decision for a transplantation to be performed has to be taken at a much earlier stage.

We would point out that the authors of this pilot study very carefully mention the need for additional research to be conducted on several points, such as the rigorous evaluation of the long-term results of LT in both AAH and CAH, and the importance of demonstrating the reproducibility of their results by new studies of the criteria and procedures for selection of

[22] Mention can also be made of another score, namely the Maddrey score, which is used to determine the degree of severity of specifically alcoholic hepatitis. It is not a criterion used to determine the risk of death, which is precisely the function of the Lille score. See on this subject: Gex L., Bernard C., Spahr L., "*Scores and hepatology, Child-Pugh, MELD and Maddrey*", in*:* Revue Médicale Suisse, no. 264, Sept. 2010. Consult: http://titan.medhyg.ch/mh/formation/article.php3?sid=35120

AAH candidates for LT. These criteria and procedures aimed at ensuring the patient's abstinence in the postoperative period must be the subject of broader research with a view to confirming their relevance.

III. Legal aspects

There is no specific legal rule, either in Belgian law or in the international texts, stipulating that AAH patients are to be included in or excluded from the benefits of transplantation.

However, the medical and surgical practices referred to in this opinion paper are influenced by legal stipulations concerning the patient's interest, the doctor's duties and the interest of society.

3.1. The patient's interest

Article 23 of the Constitution declares that everyone has the right to lead a life in keeping with human dignity, and that to this end the law (or the decree) must guarantee economic, social and cultural rights, and determine the conditions under which these are exercised, *bearing in mind the corresponding obligations*. These rights include in particular "the right to social security, health protection and social, medical and legal assistance".

The Act of 22 August 2002 on patient's rights establishes the patient's right to receive from the professional practitioner **quality services that meet his needs**, in observance of his autonomy and without any distinction of any kind being made (Article 5).
Equal access to quality healthcare meeting the patient's needs is thus guaranteed, and there may be no question of this being subject to considerations of a moral nature depending on the patient's behaviour and lifestyle.

Having said that, the law on patient's rights also stipulates that "the patient must abide by the major duty incumbent upon him to **cooperate with the physician**; the latter is in fact only obliged to observe the law "*insofar as and to the extent that the patient cooperates to this end*" (Article 4). The preamble states in this respect that "whilst patients have duties vis-à-vis doctors and nurses, in particular in terms of providing them with all useful information and following their advice, it is not possible to force them to abide by these duties, under pain of infringing their individual freedoms". This being the case, in the way in which it is worded the law "aims to avoid a physician being criticised for disregard of his obligations towards a patient who, for example, had failed to give him all the information needed for a correct diagnosis to be made; nobody is obliged to do the impossible", something that "judiciously contributes to making the patient aware of his responsibilities". It was possible "therefore wholly to approve (…) the inclusion of this general reservation in the text, a proviso that serves as reassurance for the physician confronted with a negligent or heedless patient, and contains a host of perhaps still as yet largely unsuspected applications"[23].

Although it is not possible to *force the patient to follow the advice of the doctors and nurses*, this provision creates a degree of responsibility on the part of the patient.

In the case submitted to us, that of the AAH patient, in light of the urgency the only immediately useful "quality service" is liver transplantation. We would point out that the concept of "quality services" within the meaning of Article 5 of the law implies "effective, vigilant and qualitative healthcare in conformity with medical knowledge applicable at the time". This requirement is certainly not new, since under the terms of Article 34 of the medical code of professional ethics, the physician undertakes to give the patient attentive, conscientious care in conformity with medical knowledge applicable at the time, and these criteria are also used by jurisprudence to define the abstract boundaries of medical responsibility. But it now takes the form of a "genuine right that can be 'invoked' by the patient, along the lines of other hitherto jurisprudential rules"[24].

There remains the question of establishing whether one is allowed *to impose a treatment plan on the patient* (weaning of the patient off alcohol, support in the form of specialised assistance, etc.), with a view to fulfilling the objective to be attained, which is success of the liver transplant in the medium or long term. In theory the answer is no. According to the principle of self-determination and free disposal of one's body, the decision to follow the treatment, including the process of the patient being weaned off alcohol, must be taken *voluntarily* and any duress or obligation in this respect is inconceivable[25]. The patient's right to refuse the treatment proposed and the means with which it is applied, a corollary of the control over his body and his right to the respect of his physical integrity, is guaranteed by the law on patient's rights (Article 8, § 4) and the patient is not asked to give reasons.

[23] G. Genicot, *Droit médical et biomédical*, Larcier, 2010, pp. 116-117.
[24] G. Genicot, *op. cit.*, p. 117 and note 234.
[25] See in this respect, *mutatis mutandis*, the reflections contained in the Committee's Opinion no. 53 of 14 May 2012 on the refusal of medical care by a pregnant woman where this has consequences for the fetus.

Confronted with a refusal of this kind, the physician must be cautious and scrupulously inform the patient of the possible consequences of his decision (Article 8, § 2 of the same law). If need be, he should suggest alternative treatments, checking the proportionality between the risks they entail and their expected effectiveness. Once this has been done, if the patient continues to refuse *certain aspects of the proposed treatment*, the physician will be obliged to respect this decision but will be able to put an end to the care contract, whereupon in the event of any harm being occasioned pursuant to this refusal, the patient will only have himself to blame. This is the necessary consequence of his right to self-determination and free disposal of his body.

3.2. The physician's duties

The physician has **therapeutic freedom**, which means that he conscientiously assesses the care he needs to administer to the patient and has "the choice of the means to be used either for establishing the diagnosis or for setting up and carrying out the treatment, or for execution of the magistral preparations" (Article 11 of Royal Decree no. 78 of 10 November 1967 on the practising of the healthcare professions). Article 36 of the medical code of professional ethics also lays down the principle of the physician's diagnostic and therapeutic freedom, subject to certain conditions and restrictions, whilst Article 29 stipulates that he must "endeavour to inform his patient clearly of the reasons for any diagnostic or therapeutic measure proposed". "Irrespective of whether or not the physician has been freely chosen, the latter shall only take decisions dictated by his knowledge and his conscience" (Article 32). Generally, the physician must opt for the treatment that is *most effective* and *entails fewest risks* (proportionality criterion); his decision in this respect is not completely discretionary but is liable to be subject to *control*, in particular on the legal front, in terms of the error criterion, since the recognition of an error in the choice of treatment cannot be excluded[26].
On the other hand, the physician has the personal duty to **give help and assistance** to the patient, both from the legal point of view (failure to assist a person in peril, Article 422*a* of the Penal Code) and on the ethical front. This duty is liable to oblige him to perform an act indispensable for the patient's survival; a physician who gives emergency care to a patient whose life is in danger, to the detriment of other people who have been on the waiting list for some time but whose survival is not at danger to the same degree, may invoke the **state of necessity**. By saving the life of a person who was at risk of dying, even if his willingness to pull through is uncertain or perhaps questioned, he deems the saving of a life to be a higher value than the "merit" of another person in a less critical state of danger.

The physician must scrupulously **bring to the patient's attention** not only "all the information concerning him which he might need in order to understand his state of heath and probable evolution" (Article 7, §1 of the law on patient's rights), but also "the objective, nature, degree of urgency, duration, frequency, counter-indications, side effects and risks inherent in the intervention that are relevant for the patient, the after-care, possible alternatives and financial

[26] G. Genicot, *op. cit.*, pp. 380-382; see also on this point the Committee's Opinion No. 59 of 27 January 2014 on the ethical aspects of application of the euthanasia law of 28 May 2002.

repercussions", as well as "the possible consequences in the event of refusal or withdrawal of consent, and any other explanations deemed to be relevant by the patient or the professional practitioner" (Article 8, §2 of the law). He must thus inform the patient of the *possible consequences of his failure to follow the treatment* and the serious risks the patient may run if he fails to abide by the recommended treatment: a relapse into alcoholism creates a new risk of disease for the transplanted liver and thus leads to failure of the transplantation and a waste of the transplanted organ. If the physician is of the view that the patient's persistent behaviour is detrimental to his health, he must alert him to this and attempt to convince him. In the case of a CAH patient and any other patient, he must if necessary put forward the possible alternative treatments, subject to a check of the proportionality between the risks they entail and their expected effectiveness.

Various questions remain, for which the applicable legal framework does not provide clear-cut answers and which should therefore be assessed from an ethical standpoint.

Can the physician invoke a form of "**clause of conscience**" in this respect[27], if he is "ill at ease" dealing with a patient who repeatedly refuses to cooperate in the treatment of his disease (refusal to stop drinking or to receive specialised assistance)? Since the crux of the problem is the shortage of available organs, can the physician go as far as to terminate the care contract – whilst all the while making sure he does not abandon the patient to his fate when his life is in danger – if he is convinced, on the basis of corroborating information, that this patient will relapse into alcoholism after the transplantation, and a valuable organ (valuable on account of the scarcity of organs) will have been wasted when it could have saved another patient waiting for a transplant?

It is an established and accepted fact that the physician must guarantee his patients **continuity of care**. In addition to Article 5 of the Act of 22 August 2002 on patient's rights, which as we have seen requires that the patient must be able to receive "quality services that meet his needs", Article 8 §1 of Royal Decree No. 78 of 10 November 1967 on the practicing of the healthcare professions lays down that practitioners "may not knowingly and without legitimate reason attributable to them, discontinue a treatment under way without having first taken all steps designed to ensure that the care continues to be provided by another physician with the same legal qualification". Ensuring continuity of care is moreover an ethical duty (Article 113 of the Code of Ethics) and it is up to each physician to take the necessary measures, on a case-by-case basis, to guarantee that his patients continue to receive care (Article 114).

Could the combination of these rules imply that the physician has to leave selection of patients with priority status to the judgement of a fellow physician? Ought he to refer the matter to the hospital's ethics committee if the patient's state of health permits a period of reflection or

[27] Within the meaning of Article 9 of the European Convention on Human Rights, which guarantees the right to freedom of thought, conscience or religion, the grounds here not being of a religious nature but inspired by an acute sense of equity. On the clause of conscience in the (bio-)medical field, see, in detailed form, the Committee's aforementioned Opinion No. 59, in which this concept and its implications are explored in depth.

deliberation? Should the decision be collective? Should provision be made for formal and procedural conditions that the physician would have to observe if he wanted to make an objection on principle? It would most certainly be wise for his preferred choice to be *duly reasoned* in terms of the details of the case at hand and for it to be possible for this to be subjected to a *check* if necessary.

It is not certain that it would be expedient to allow a judge to assess *a posteriori* the fairness and relevance of the physicians' arbitration of the opposing interests in a specific case. Likewise, as regards the possible *civil liability* of a GP who supported his patient's transplantation request despite being aware of the latter's inveterate alcohol dependence, it is difficult to envisage him being reproached for having committed an *offence*, assuming he were able to justify and substantiate his decision in this particular case, whatever the inferred indirect harm resulting from "demotion" of the other patients on the waiting list, to the benefit of the AAH patient who has become a priority candidate for liver transplantation.

For the rest, in some respects there may be points of convergence between the physician's personal moral conscience and the interest of society commanding him to act "with due and proper diligence" in the allocation of rare organs, whereby judgement is based on an **ethical principle of equity and/or distributive fairness** as much as on **principles of effectiveness and efficiency**[28].

3.3. The interest of society

It would seem that conciliation of private and collective interests should be analysed by the yardstick of the reference framework offered by the European Convention on Human Rights. This lays down (in Article 14) that enjoyment of the rights and freedoms set forth in the Convention "shall be secured without distinction on any ground such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth *or other status*". The Convention above all stipulates that there shall be no interference by a public authority with the exercise of the right to respect for private and family life (which is a vital factor in medical matters), "except such as is in accordance with the law and *is necessary* in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for *the protection of health or morals, or for the protection of the rights and freedoms of others* (Article 8, §2; italic highlighting added).
Therefore, from the point of view of fundamental rights, differences in the treatment accorded to different people are not by any means prohibited, but must, on pain of constituting cases of prohibited discrimination, be laid down by the law and *duly justified* by considerations aimed at the safeguarding of values or interests that are *at least equivalent, if not higher.* The

[28] The medical code of professional ethics stipulates incidentally, in Article 99 (The physician at the service of the community – The physician's social and economic responsibility), that "the physician must both respect the inalienable rights of the human being and *fulfil his duties towards the community*". On the distinction between effectiveness and efficiency, see below, part V: "Conclusions and recommendations".

measure taken must be strictly *necessary* for the preservation of these values or interests, which include, *inter alia*, *the protection of the rights and freedoms of others*.

As far as transplantation is concerned, and in a context of shortage of organs, the general rule of supply and demand prevailing in the commercial sector does not apply, given that the human body is protected by the *principle of non-proprietorship,* implying that it cannot have a market value[29].

From the criminal point of view, society cracks down on alcohol abuse by the person consuming it, but only to a certain degree (the suppression of public drunkenness and drink driving). For the rest, it is not the vocation of the law nor does the law have legitimacy to *interfere* – in an unjustified manner – *in each person's exercising of his individual freedom*, even if and when this takes the form of self-destructive behaviour. The question raised here consists in determining the position *medicine* should adopt vis-à-vis behaviour of this kind.

It is thus intrinsically perfectly admissible for society, through the agency of the law, to leave competence at national level for the setting of **criteria for the selection and allocation of scarce resources** to the medical profession or the transplantation centres, or even to an international organisation such as Eurotransplant. These criteria could if necessary constitute an obstacle for the selection of an AAH patient in function of the sole parameter of urgency and need.

It will then be up to the transplantation team to assess, under its responsibility, the application of these strict selection criteria on a case-by-case basis, in such a way as to limit the risk of arbitrariness. We come back to the therapeutic freedom of the physician, who acts "in the patient's interest (…) if need be carrying out multidisciplinary consultation" (Article 4 of the Act of 22 August 2002), and the legal and ethical requirement for there to be *justification of the decisions taken*, in the light of the societal options advanced at political level and, first and foremost, further in-depth scientific research on the subject.

III. Ethical reflections

4.1. Positioning of the problem

Chronic alcoholic hepatitis (CAH) was originally excluded from the list of indications for liver transplantation (LT), but has gradually been included in it, and over time has become one of the most frequent indications[30]. The inclusion of this form of hepatitis has been based on the use of well-defined criteria, one of which stipulating that candidate patients must abstain from all alcohol consumption for a period of six consecutive months.

[29] See on this point Committee Opinion no. 43 of 10 December 2007 on the problem of the commercialisation of human body parts.
[30] See *supra*, II, "Medical and epidemiological aspects", note 14.

Recent medical advances, both in terms of diagnosis and in the therapeutic field, have made it possible to target a new group of patients among those suffering alcoholic hepatitis: those in a situation of acute alcoholic hepatitis who have proved not to respond to traditional treatments and are thus exposed to a high risk of death in the very short term. A recent, much-commented scientific experiment conducted on a small group of patients showed that this type of patient could successfully benefit from liver transplantation. It thus suggests that from the medical viewpoint, recourse to this type of treatment could be justified among patients who by definition are unable to observe a period of abstinence from alcohol consumption of six consecutive months.

As stated above, the inclusion of AAH patients among potential LT beneficiaries is medically justified seeing as transplantation is liable to improve the survival rate of this specific population. This being the case, AAH should constitute a new indication for LT, and this group should be added to the waiting list of patients waiting for a transplant, and what's more in a priority position, in a situation characterised by a chronic scarcity of available organs[31]. This would thus have the effect of increasing mortality among patients on the waiting list.

The Committee feels that the matter thus revolves around the delicate issue of delimitation of the groups that are considered to be priority groups for access to this kind of treatment, and the question of the criteria adopted for putting this delimitation into practice. As regards principles, the Committee sees no justification in asserting the self-inflicted nature of the disease (which is present, for that matter, both in cases of CAH and AAH) with a view to depriving the patient of access to quality healthcare that meets his needs – a right he is legally and constitutionally guaranteed. Any patient must be able to have access to the best possible treatments liable to treat the condition he is suffering, provided their medical relevance has been validated by strict criteria.

The Committee is therefore unanimously of the opinion that AAH patients may not *in principle* be excluded from a possible transplantation. The ethical challenge involves identifying, parallel to the case of CAH patients, the conditions under the terms of which AAH patients

[31] See on this point the Committee's Opinion no. 50 of 9 May 2011 on certain ethical aspects of the amendments made by the law of 25 February 2007 to the law of 13 June 1986 concerning the removal and transplantation of organs. In relation to finite transplantation resources, it is worth mentioning a recent review article on fulminant liver decompensation brought about by causes other than alcoholism: Bernal W, Wendon J, *Acute Liver failure*. NEJM 2013; 369:2525-34.
"In the UK and the USA, non-alcoholic fulminant hepatitis is caused in more than50% of cases (UK 68%, USA 52%) by the ingestion of drugs, the most common of which being paracetamol (also called acetaminophen which is the active substance of numerous specialist drugs of the group of non-salicylic antipyretic analgesics). An acute liver decompensation may occur after a single massive ingestion. Malnourished and/or alcoholic patients are most at risk. Rare cases of idiosyncratic reaction (i.e. an individual's particular and unforeseeable predisposition to react to a drug) have also been reported. Whilst liver transplantation represents a therapeutic option for the most severe and most fulminant cases, it is only performed in 10% of cases". (from Simpson K J, Bates C M, Henderson N C *et al*, *The utilization of liver transplantation in the management of acute liver failure: comparison between acetaminophen and non-acetaminophen etiologies,* Liver Transpl. 2009;15:600-9.
Germani G., Theocharidou E., Adam R., *et al*, *Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database*, J Hepatol 2012; 57:288-96.

could be admitted for receipt of this treatment, bearing in mind the fact that it is impossible to impose upon them the consensual rule of six months' abstinence. It is therefore a question of drawing up *suitable, fair (equitable) and validated selection criteria* that can be used to identify from among these patients, those who present the lowest risks of relapse into alcoholism.

4.2. Anteriority and priority of medical and epidemiological data vis-à-vis ethical stances

According to the Committee, the response to the question as to whether it is expedient to include patients suffering from AAH should as far as possible be based on scientific considerations, chiefly the epidemiological and medical data. Whilst in the final analysis the adoption of an ethical stance is involved (i.e. implying to some degree *choices and values* that cannot be reduced to a mere logical deduction), this adoption of a position must be underpinned by an accurate knowledge of the situation brought about by the identification and therapeutic treatment of this specific condition (life expectancy, number of donors and applicants, profiles of the applicants, objective benefits of transplantation, etc.). This is especially necessary in the case of the pathologies involved here.

Social ideas and preconceptions regarding alcoholism

Like a good many other people who indulge in "risk behaviour", the patients in question, who are excessive consumers of alcohol, are often the subject of an *a priori* moral judgement that tends to consider alcohol addiction as the result of an originally voluntary and informed behaviour (drinkers are deemed to be aware of the risks they are running) and the pathologies (or damage) associated with them as being consequences falling under the patients' sole responsibility, and thus consequences they should assume *on their own*. The logical result of this kind of view is ultimately to base the distribution of care (and differences in treatment) on considerations of "merit" and "moral misconduct".

As highlighted by R. S. Brown[32], the matter of the treatment of alcoholic hepatitis has been the subject of controversy ever since liver transplantation has existed, on account of the ideas associated with alcoholism, which is often viewed as a self-inflicted disease, which would therefore imply the patient's individual responsibility (in the sense mentioned above), and due to the concerns as to how patients would behave after transplantation (risk of relapse and non-compliance with the requirements of the treatment). This explains why alcoholic patients were originally most often excluded from liver transplantations.

This view of alcoholism, which for that matter runs counter to the principles of equal access to healthcare and the principles of medical ethics espousing a concern to be useful to all patients, has undergone substantial changes in the medical sector today. Liver complaints

[32] Brown R S, *Transplantation for Alcoholic Hepatitis — Time to rethink the 6-Month 'Rule*', in New England Journal of Medicine, 365; 19, Nov. 10, 2011, p. 1836.

associated with alcohol consumption today constitute a major indication (the leading cause of LT in France in 2005, and the second in Europe and the United States in 2005[33]) and a consensus has come into being regarding the criteria to be adopted for inclusion of these patients in the list of LT recipients. In 2010 the AASLD (American Association for the Study of Liver Diseases) reported that liver diseases constituted the second most important indication for LT. In its recommendations, it stated that "appropriate patients with end-stage liver disease secondary to alcoholic cirrhosis should be considered for liver transplantation, just as other patients with decompensated liver disease, after careful evaluation of medical and psychosocial candidacy"[34].

This development is linked to that of psychiatric, psychological and - more widely - biomedical approaches[35] to addictions (or dependence behaviour), and in particular alcohol addiction. Recent approaches have helped alter the perception of alcoholic behaviour, which constitutes a specific category of behavioural disorders, as well as cognitive disorders[36]. Thus the medical dimension competes with the moral approach to the issue, albeit without negating it[37]. Whilst the moral connotation associated with the idea of a "self-inflicted" pathology does not belong here, this does not exclude the possibility or usefulness of an evaluation, *carried out by the patient himself*, of the moral issues that his alcoholic behaviour (towards himself and others) throws up. The medical approach may be seen as offering a series of tools designed to provide some effective "purchase" on a difficult situation, and liable to help the patient take control of his own life again[38].

The report of a consensus conference under the aegis of the Haute Autorité de Santé (HAS), published in 2005, indirectly attested to the change we have just highlighted: "Society and

[33] *Conférence de consensus. Indications de la transplantation hépatique*, Haute Autorité de Santé & ANAES, Lyon-Paris, 2005. http://www.has-sante.fr/portail/jcms/c_272409/fr/indications-de-la-transplantation-hepatique?xtmc=&xtcr=2

[34] O'Shea R., Darasathy S. & Mc Cullough A. J., *Alcoholic liver disease. AASLD Practice Guidelines*, *in* : *Hepatology*, Jan. 2010, p. 322

[35] A series of genetic markers may indeed be associated with the risk of alcohol dependence (and thus relapse into alcoholism). See in this respect: Gache P & Wenger O, « La transmission familiale de l'alcoolisme : mythe ou réalité ? », Hépato-Gastro. Volume 10, Numéro 5, 361-8, Septembre 2003, Mini revue1. We can highlight the conclusion: alcoholism is not passed on, but it is the predisposition to alcoholism that presents a polygenic transmission.

[36] For example, researchers recently revealed that "a cerebral atrophy played a role in the lack of motivation for giving up alcohol observed in some alcohol-dependents; this discovery bears witness to a cognitive disorder and not a simple refusal, modifying the way clinicians view these patients"; (report by Le Berre A.-P & *al*, *Readiness to change and brain damage in patients with chronic alcoholism*, Psychiatry Research : Neuroimaging 213 (2013), 202-209, in "La motivation au sevrage n'est pas qu'une question de volonté", Inserm actualités recherche, 30 August 2013 : http://www.inserm.fr/actualites/rubriques/actualites-recherche/la-motivation-au-sevrage-alcoolique-n-est-pas-qu-une-question-de-volonte

[37] See in particular Dargelos B., v°s Alcoolisme et Alcoolisme (Lutte contre l'), in *Dictionnaire de la pensée médicale*, Lecourt D. (dir.), P.U.F., Quadrige, 2004, pp. 17-24; Pommereau X., v° Addictions, in *Dictionnaire du corps*, Marzano M. (dir.), P.U.F., Quadrige, 2007, pp. 19-22. See also *L'Encyclopédie Médicale Larousse / Le Manuel Merck*, Larousse, 2007, pp. 649-652.

[38] During a conversation between F. Caeymaex and doctor C. Hanak (Psychiatry, alcohology, Brugmann), the latter stated that in any case, a moral or moralising approach towards a patient in a situation of physical and mental distress is counter-productive in a treatment perspective. Adopting a discourse of a moral nature with regard to alcoholic behaviour cannot in any case be the role of the doctor or nurse; it is the patient who, once he has overcome the distress or immediate medical emergency, can *then* possibly make moral evaluations regarding his own conduct and find support for this behaviour.

medical professionals have to change their view. The patient with alcoholic cirrhosis who is a candidate for LT should be considered as suffering from a double pathology, both alcohol-related and liver-related, and should therefore systematically receive a twofold specialised treatment"[39].

Function of the abstinence criterion in the case of chronic alcoholic hepatitis (CAH)

In this respect, it is necessary to recall the reasons underpinning use of the criterion of six consecutive months' abstinence by the transplantation teams. This condition for access to the treatment does not constitute a moral sanction of the alcoholic behaviour, but is based above all on medical reasons[40], and then on "socio-economic" reasons associated with the allocation of scarce resources:

- Observance of a six-month abstinence period may, in some cases (in particular in patients who have consumed alcohol recently[41]), improve the liver function to the point of rendering transplantation unnecessary;
- The patient's commitment to take part in a process aimed at helping him give up reduces the risks of a relapse into alcoholism, which would then once again compromise the patient's health (i.e. the health of his liver). The patient's compliance with the abstinence criterion is regarded as having a predictive value for post-transplant behaviour. For this reason it is thus asserted that it is not desirable for the transplanted organ to be exposed to a new chronic poisoning, since this could reduce the chances of the treatment's long-term success and therefore represent the misuse of scarce resources.

In other words, abstinence is required here as a behavioural factor decisively conditioning the success of the treatment of alcoholic hepatitis by transplantation in a long-term perspective. The objective pursued is therefore clear: to guarantee the best chances of the treatment succeeding and thereby to optimise use of the transplant organs available.

Whilst nobody doubts the need for the transplant recipient and his transplanted organ to avoid a relapse into massive alcohol consumption, some observations, backed up by the scientific literature, tend to show that, from a statistical point of view, observance of six months'

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[39] http://www.has-sante.fr/portail/upload/docs/application/pdf/Transplantation_hepatique_2005_court.pdf.
Idem supra : Conférence de consensus, Indications de la transplantation hépatique, texte des recommandations.

[40] "Continuing use of alcohol after the diagnosis of alcoholic liver cirrhosis correlates negatively with survival. In a recent study, Verril *et al* demonstrated that abstinence from alcohol at one month after the diagnosis of cirrhosis was the most important factor determining survival, with a 7-year survival of 72 % for the abstinent patients, versus 44 % for the patients continuing to drink". Dom & *al*, "Risk for relapse of alcohol use after liver transplantation for alcoholic liver disease: A review and proposal of a set of risk assessment criteria", in*: Acta Gastro-Enterologica Belgica,* Vol. LXXIII, April-June 2010, p. 247.

[41] O'Shea R, Darasathy S & Mc Cullough A.J, "*Alcoholic liver disease. AASLD Practice Guidelines"*, *in:* Hepatology, Jan. 2010, p. 321.

abstinence before liver transplantation does not constitute a wholly sound criterion for predicting non-relapse into alcohol consumption after the operation[42].

Furthermore, there is no precise definition of alcohol abuse, or even of what should be understood by "abstinence" or relapse. The very terms used in the "rule" applied are therefore subject to controversy. Lastly, when it comes to addictions it is obviously very difficult to predict the individual behaviour of different patients in the long term. Whilst the observance of a period of abstinence of six months or more probably constitutes a factor that helps prevent a subsequent relapse, what the encouraging results of the study conducted by the Lille CHR show on this particular point is that the fact of the patient not having been able to observe this abstinence period – since the transplantation had to be performed immediately – was not *necessarily* synonymous with relapse, provided this criterion was replaced by others.

4.3. Definition of medically well-founded inclusion and exclusion criteria for AAH

Contrary to any moralising position, the Committee feels that the question is not one of ascertaining which patients *deserve* to have access to transplantation, but rather one of establishing whether or not acute alcoholic hepatitis (in patients who do not respond to other treatments) should today be considered as a *new indication* for liver transplantation, given the situation of shortage of transplant organs. If not, for what reasons and on the basis of what criteria? If so, with what aim and under what conditions?

In other words, if it proves indispensable to treat different groups of candidate transplant patients differently, due to the organ shortage situation, it is absolutely vital for *objective selection criteria to be defined, which are determined by and made proportional to reasonable objectives in terms of usefulness for the patients and for the community. The patient's and the transplant organ's chances of survival are part of the criteria to be taken into account and help define "good use of the transplant organ*".

Consequently, in the presence of a new indication comprising a risk of failure, it is intrinsically legitimate for particularly strict criteria to be drawn up in order to justify, objectively and in a reasonably proportional manner, a differentiated access to care possibilities.

What is the patient's responsibility in this context?

The setting of eligibility criteria that are as objective as possible does not mean that the patient does not have any responsibility. Here, as in the case of many other complaints, this responsibility does not relate to behaviour and the taking of risks that occurred in the past,

[42] Beresford Th. P, Everson G.T, *Liver transplantation for Alcoholic Liver Disease: Bias, Beliefs, 6-Month Rule, and Relapse — But Where Are The Data? In: Liver Transplantation*, Vol. 6, No. 6 (November), 2000: p. 777-778.

but rather the patient's obligation and ability to cooperate with the care teams with a view to the treatment's success. This therefore concerns a proactive, but also a shared responsibility[43].

Moreover, it will be seen that the very strict eligibility criteria set by the medical experiments carried out at the CHR in Lille – aimed at ensuring the treatment had as great a chance as possible of succeeding – relate not only to the patient's physiological data, but also to relational factors pertaining to family members and/of friends, that are liable to reinforce the patient's *ability* to cooperate. Generally speaking, what has to be done is to secure and furnish the means enabling the patient to feel responsible for and committed to the success of the treatment.

Drafting specific consensual rules for AAH?

LT specialists feel that the inclusion of AAH in the indications for LT would put a question mark over one of the rules in force for the treatment of alcoholic hepatitis by means of transplantation. Patients with AAH (who do not respond to treatments with corticoids) cannot by definition be subjected to this imperative. Consequently, maintaining this rule for *all* alcohol-induced liver pathologies, which is the case at the moment, even though it is now possible to identify those patients with a very short life prognosis, clearly means that we are condemning a number of these patients. The objective consequence of the status quo is therefore that the number of patients on the waiting list does not increase, and above all that candidates who would have a priority position on it, are not included on it.

From an ethical standpoint, the problem would be posed as follows: isn't the uniform application of the rule of six consecutive months' abstinence to *all* patients with alcoholic hepatitis discriminatory[44]? Is it justifiable to impose one and the same access condition *indiscriminately* on those who can observe it and on those who cannot comply with it on account of their life expectancy? Does it not call into question the patients' right to quality services that meet their needs[45]?

It can be said that lengthy abstinence prior to transplantation is useful when this is possible — *according to some, it remains a good criterion for inclusion*[46] —, but it should not be adopted as a *criterion for exclusion* when patients are quite simply not in a position to observe it.

Consequently:

[43] See *supra*, "III. Legal aspects", especially 3.1. "The patient's interest".
[44] Same reflection in Weinrieb & *al* (2000), cited by Beresford Th. P & Everson G. T (art. cit., p. 777): "They express concern that the universal application of the 6-month rule to all patients with an alcoholic liver disease will be detrimental to those patients with severe pathologies who do not have the time actually to take part in a detoxification programme".
[45] See the legal framework above.
[46] Although definition of the length of pre-transplant abstinence as a predictive factor of post-transplant abstinence is open to discussion, and it is known that a whole host of factors, such as family case history and social support, play a vital role in the patient's ability to abstain from alcohol or to moderate his consumption.

— Considering that (1) the physicians' objective is to improve the life prognosis of patients with alcoholic hepatitis overall, thus including that of the sub-group today identified as those patients with AAH who do not respond to treatments;
— And considering that (2) the objective of society is to guarantee that everyone is afforded equal access to healthcare, whilst ensuring a reasoned allocation of scarce resources (a "good use" of transplant organs, i.e. protected in as great a measure as possible from the risk of relapse into alcoholism),

new consensual criteria specific to AAH need to be drawn up, so as to ensure insofar as is possible that the patient abstains from alcohol, or at the very least limits himself to a reasonable consumption from the point of view of health risks, after transplantation.

VI. Conclusions and recommendations

The Committee ranged itself unanimously behind the following conclusions

As far as principles are concerned, the Committee states that there is *no reason* either of a legal or ethical nature, for AAH patients not to be granted access to liver transplantation.

The general objective of liver transplantation must remain the improvement of the life prognosis of as many patients as possible, irrespective of the liver pathology they are suffering from. The objective also involves promoting "the patient's right to quality services" that meet his needs (Article 5 of the Act of 22 August 2002 on patient's rights), within the bounds of the physician's duties and freedoms[47].

However, in a context of a shortage of resources priority scales should continue to be established, on the basis of accurately defined and scientifically validated criteria, so as to enable a rational and reasonable allocation of the transplant organs available. The aim is to ensure a good use of the transplant organs: reserving them for those cases in which the chances of success of the treatment (i.e. successful transplant, the patient being restored to health and maintenance of the function of the transplanted liver in the long term) are highest.

For this same reason of scarcity of resources, it would also be desirable for the various transplantation centres to use *common criteria* in the allocation of transplant organs, since these are shared external resources. The continuous and collective evaluation of clinical results should also make it possible to adapt the relevance of these criteria in accordance with the evolution of knowledge.

In the case of alcoholic hepatitis, this means performing an eligibility examination on an individual basis, case by case, on the one hand establishing as accurate a diagnosis and survival prognosis as possible, and on the other hand evaluating the patient's capacity to avoid exposing the transplanted liver to a new overconsumption of alcohol, i.e. his capacity to

[47] Expounded *supra* in III. Legal Aspects.

overcome his dependence problem. Treatment of AAH patients should therefore be twofold, inasmuch as the liver pathology is associated with alcohol dependence.

Without casting doubt on the criterion currently adopted for the selection of patients with chronic alcoholic hepatitis (six consecutive months' abstinence), it is conceded that this has now become a questionable exclusion criteria if it is applied to all patients with alcoholic hepatitis. *In the light of new medical and scientific data that have been advanced, as well as in the perspective of respect for and effectiveness of patients' rights to quality healthcare and equal access to care,* ***there is no reason in principle for the new category represented by AAH patients to be excluded.***

However, the Committee expresses ***a reservation as to the immediate inclusion of these patients in everyday clinical practice.*** It stresses that going beyond a very controlled experimental framework is a process that requires great care. After all, the Committee notes that the current level of knowledge as regards AAH patients is still limited in three areas:

Firstly, the efficacy of the treatment, which has been demonstrated today by just one controlled study (albeit of a very high scientific quality), still has to be validated in the context of clinical practice and day-to-day reality. In other words, the study of LT results in a strictly controlled clinical research context must be continued, both in respect of strictly medical factors (success of the transplant) and in terms of the criteria used to identify those patients likely to overcome a dependence leading to massive alcohol consumption.

Secondly, the effectiveness of this treatment, i.e. its efficacy in a context of clinical practice, is also yet to be demonstrated. After all, the specialists stress that the strict conditions in which a clinical trial is conducted are not always guaranteed in the context of subsequent clinical practice. In the case at hand, the highly integrated character of the teams of professionals from different fields of specialisation (transplant surgeons, psychiatrists, psychologists and social workers) for the monitoring of the patients and the procedure defined for collective decision-making as to their eligibility are essential factors that have ensured the success of the controlled research. One is entitled to wonder whether these conditions can today be met in the context of everyday practice in Belgium's transplantation centres.

Thirdly, it must be noted that, in the absence of precise statistical data on the population of AAH patients potentially concerned, it is not possible to define an optimal resource allocation policy *in terms of figures,* or to determine its efficiency at this stage, or consequently to define the point of equilibrium between allocated resources (be it organs, technical devices or services) and the expected clinical results. Whatever the origin of liver pathologies requiring transplantation, we know that patients meeting all the selection criteria die if there is no organ available, mainly because of the increase in demand (brought about primarily by the advances made in screening or the increased prevalence of chronic viral or tumorous diseases).

Integrated multidisciplinary research (psychiatry, psychology, genetics, biomedical anthropology, etc.) on the numerous factors playing a role in relapse or non-relapse of transplant recipients should also be actively conducted in a field situation, taking into account the knowledge acquired in this respect. This research is an essential precondition for an informed debate on the possibility of AAH being included among the indications for LT for clinical practice. Parallel to this, the public should be clearly informed of **the risks of alcoholic hepatitis or cirrhosis**, by means of prevention campaigns directed chiefly at young people and focusing on increasingly frequent and alarming types of risk behaviour, such as "binge drinking" in particular.

The Committee unanimously makes the following recommendations:

1. ***The Committee is of the view that AAH should only be included among the indications for liver transplantation for everyday clinical practice if inclusion criteria such as to reasonably guarantee the long-term success of the treatment are precisely defined and scientifically validated***

For AAH patients we do not at the moment have any convincing selection criterion to replace the criterion of lengthy pre-transplantation abstinence applicable to CAH patients. There are no well-established consensual criteria likely to help determine which of the patients are best able to avoid exposing themselves to a relapse into alcoholism (the notion of relapse itself being the subject of debate), the absence of which is the condition for long-term success of the treatment. The matter of setting inclusion or exclusion criteria that are relevant, reliable and clear, both for the patients and for the physicians, is indispensable and imperative in a situation of scarcity of resources (organs).

Moreover there are at present hardly any systems designed to take charge of AAH patients by offering them treatment for alcoholism, since these patients most often arrive directly in the gastroenterology or transplantation wards. If we set the patient's undertaking to take part in a process aimed at helping him give up alcohol as a condition for access to a transplant treatment, he still has to be given the means to do this. That was the case in the controlled clinical trial that led to this request for an opinion, where there was a remarkable multidisciplinary and cross-disciplinary monitoring of alcoholic patients.

2. ***Therefore, these patients should be treated in the framework of specific research programmes, which are subject to the opinion of a medical ethics committee***

The aim of these programmes would be to test the pertinence of the selection criteria, targeting the personal and interpersonal resources the patient is likely to mobilise to give up his dependence on alcohol and thereby reduce his risk of relapse. This research falls primarily under the sphere of psychiatry, psychology and associated disciplines variously dealing with alcohol addiction and the ways of successfully treating it.

Apart from recourse to purely biological selection criteria relating to the severity of the complaint, the life prognosis and any somatic comorbidities, the Committee recommends, in light of the complexity of the factors determining alcoholic behaviour, that an analysis be made of the relevance of the selection criteria adopted in the controlled experiments carried out at the CHR in Lille, by means of the following questions in particular:

- To what extent are historical and psychological antecedents in terms of alcoholic behaviour determining factors for the future?
- Is psychiatric comorbidity necessarily an obstacle to the patient's undertaking to observe abstinence, and to the soundness and maintenance thereof?
- How can we identify and characterise a social environment (relational aspects and factors pertaining to the patient's family and professional life) that is conducive to achieving effective and lasting abstinence?

This research would also entail the devising and testing of *integrated care systems* that bring together psychiatric and mental health services, in a hospital context or on an outpatient basis, and the transplantation and gastroenterology care units likely to support patients expressing a wish to cooperate in the treatment in the long term, from the moment these patients start being attended to, in a perspective of shared responsibility between care personnel and patients.

The challenge consists in identifying inclusion or exclusion criteria that dovetail as effectively as possible with the objectives of long-term success of the treatment and maximisation of the life prognosis of all patients with liver pathologies, including pathologies associated with alcohol consumption. And secondly, integrated care systems that are as well adapted to these objectives as possible also need to be identified. In this twofold perspective, it is more than desirable for the results obtained from the controlled research conducted with AAH patients to serve as a source of improvement for CAH patients, in particular in terms of the supporting care provided to these patients.

The opinion was prepared in the select commission 2012/2, consisting of:

Joint chairmen	Joint reporters	Members	Member of the Bureau
F. Caeymaex	F. Caeymaex	S. De Bleeckere	M.-G. Pinsart
P. Cosyns	P. Cosyns	J. Messinne	
	G. Genicot	F. Mortier	
	L. Michel	R. Rubens	

Member of the secretariat
B. Orban

Experts interviewed

Prof. Vincent Donckier de Donceel, Senior Registrar Abdominal Transplantation, Chairman of the Transplantation Board, Erasmus Hospital, ULB.

Prof. Jan Lerut, Head of the Liver Transplantation and General Surgery Unit of the St Luc University Clinics.

Prof. Philippe Mathurin, M.D., Hepato-Gastroenterology services, Claude Huriez Hospital and CHU Lille.

Prof. Hans Van Vlierberghe, M.D. PhD, Senior Registrar, Gastroenterology Department, Ghent University Hospital.

Expert consulted
C. Hanak, Deputy Senior Registrar, Psychiatry and Medical Psychology Department, CHU Brugmann.

The working documents of the select commission - the question, personal contributions of the members, minutes of the meetings, documents consulted - are kept on file at the Committee's Documentation Centre where they are available to be consulted and copied.

This opinion is available to be consulted at **www.health.belgium.be/bioeth**

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