Organ Transplantation From Nonstandard Risk Donors: Midway Between Rigid and Flexible Rules

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ABSTRACT

In order to bridge the gap between available organs and patients needing transplants, donor selection criteria for donors are increasingly being extended; the possibility of using organs from nonstandard risk donors has been introduced in many countries. This clearly poses considerable ethical issues that should be analyzed and taken into consideration by the competent bodies and institutions. In this article, we illustrate the Italian situation regarding the possibility of using organs from anti-hepatitis C virus (HCV) and HCV RNA-positive donors (anti-HCV+ve) in negative recipients (healthy subjects who have never come into contact with the hepatitis C virus) in light of the availability of new direct-acting antiviral drugs (DAAs) for hepatitis C treatment. We discuss the motivations behind the both favorable opinions of the Ethics Committee of the Italian National Institute of Health (Istituto Superiore di Sanità) and the Italian National Bioethics Committee (Comitato Nazionale per la Bioetica) discussing the main implications from an ethical point of view.

THE organ shortage and the consequent imbalance between available organs and candidates for transplantation have led many countries to expand donor selection criteria and accept, under specific conditions, organs from nonstandard risk donors [1,2].

According to current Italian provision, the category "standard risk donor" includes cases where the evaluation process did not detect a transmissible disease. Beyond this category, there is further situations in which the risk of disease transmission does not bar a priori using the donor organs of that donor (in whole or in part). Therefore, it is possible to extend the use of these nonstandard-risk organs in routine practice, through a series of restrictions or recommendations in the recipients, where indicated [3].

In the specific case of infectious diseases, according to the protocol adopted by the Italian National Transplant Center (Centro Nazionale Trapianti [CNT]) [3], a potential donor showing signs or symptoms of an infectious process can be considered suitable for donation with a "nonstandard," "negligible," or "acceptable" level of risk. Organs from anti-HCV+ve donors can be transplanted in all potential anti-HCV+ve recipients. These donors are considered to be at an "acceptable" level of risk.

Until 2017, a donor was considered to be positive for HCV in the presence of antibodies alone, regardless of evidence of viral replication. The organs were then transplanted with an acceptable risk in positive anti-HCV recipients. Following the therapeutic revolution brought along by the introduction of direct-acting antiviral drugs (DAAs) and the considerable increase in patients treated with a sustained virologic response, the most recent document adopted by the CNT (revised in 2017 and currently in force) distinguishes between anti-HCV+ve and anti-HCV positive with negative RNA (anti-HCV-ve) donors. Anti-HCV-ve donor organs can be transplanted in all recipients, upon gathering of specific informed consent,

Disclosure: C.P. is Chair of the Ethics Committee of the Italian National Institute of Health (Istituto Superiore di Sanità) and member of the Italian National Bioethics Committee (Comitato Nazionale per la Bioetica).

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.02.070

independently from the antibody status, with a negligible risk. The liver alone, representing the deposit of viral infection, continues to be transplanted in all the recipients but with an acceptable risk. Conversely, an anti-HCV+ve donor can only be used with an acceptable risk and only for life-saving conditions and organs. The transplantation of kidneys or lifesaving organs under elective conditions can only be performed in clinical trials. Today, following the success of DDA in HCV treatment, this is considered outdated. Unfortunately, important limitations of both ethical and clinical nature still exist and have yet to be resolved. In 2015, the Italian Medicine Agency (Agenzia Italiana del Farmaco [AIFA]) identified the categories of patients that could benefit of DAA therapy, with a refund by the National Health System. In these categories, the patients awaiting organ transplant (other than a liver) who showed a liver chronic infection with persistent hypertansaminase levels at least 6 months were included. As reported in literature, the infection transmission from a donor anti-HCV+ve to a recipient anti-HCV negative is about 40% to 50% [4–6]. This means that in 40% of cases, infection transmission to a previously healthy organ is possible, without any chance to be treated when early evidence of the viremia positivity comes up but only after 6 months of chronic hepatitis with persistent elevated transaminases. On the other hand, a clinical aspect should be taken into account since there is very poor scientific evidence based on the use of DAA drugs in anti-HCV-negative patients in currently available literature; a clinical study about the efficacy and safety of DAA in anti-HCV-negative recipients is needed. At the international level, at least 5 out of 10 studies involving the use of DAAs in negative anti-HCV recipients from anti-HCV positive donors are undergoing recruitment; these trials involve the transplant of kidney, heart, and thoracic organs [7–16]. One study, involving the kidney, is completed and published. This study shows that out of 10 noninfected kidney transplant recipients from an anti-HCV+ve donor, no treatment-related adverse events occurred, and HCV RNA was not detected in any recipient 12 weeks after treatment. All the recipients received DAAs before and after transplantation with a different therapeutic scheme based on their genotype [14].

METHODS AND MATERIALS

In 2017, the Italian National Transplant Center (CNT) asked the Ethics Committee of the Italian National Institute of Health (ISS EC) to express an opinion on the possibility to transplant solid organs (except for liver) from anti-HCV+ve donors in anti-HCV-negative patients. The opinion was required following the request to the Agency to modify eligibility criteria for the treatment of chronic hepatitis C. In fact, according to the Agency's last provisions dated March 24, 2017 (n. 500, art. 1, criterion 6) [17], transplanted patients of solid organs (nonliver) may obtain a reimbursement for DAAs only in case of "chronic hepatitis," that is, 6 months after infection onset and alteration of liver enzymes.

The ISS EC expressed a favorable opinion; at the beginning of 2018, the Agency pledged to redefine criteria for the reimbursement of DAAs in order to meet the needs of patients waiting for solid organ transplants. However, the Agency made the decision conditional on the obtainment of a favorable ethical opinion from the Italian Committee of Bioethics (Comitato Nazionale per la Bioetica [ICB]), too. The CNT thus consulted the ICB, which published a document on July 12, 2018.

RESULTS

The ISS EC expressed a favorable opinion about the possibility of using organs from anti-HCV-positive and HCV-RNA-positive donors in anti-HCV-negative patients, but it also stressed the importance of the informed consent in this particular situation. For the transplantation of nonstandard risk organs, a double consent mechanism was recommended. At the time of enrollment on the waiting list, the patient should declare his/her availability (or unavailability) to receive a nonstandard risk organ. When the organ is available, he/she should be asked to express a second consent or dissent. The ISS EC also suggested considering a set of recommendations on this topic (The Varese Charter, unpublished data, 2018). Finally, the ISS EC recommended performing appropriate clinical studies, even monitoring the drug administration during the post-transplant phase.

Taking into consideration the opinion already expressed by the ISS EC, the ICB also issued a positive opinion on the question [18].

On the basis of the current trend in international transplantation that is more favorable to the treatment of the person who received the organ rather than the selection of donors, ICB focused on the following arguments:

1. Elective ethical principles are the respect for the recipient's autonomy and the right to the enjoyment of the highest attainable standard of health. In fact, there are not sufficient reasons to preclude patients from an option that guarantees their primary interest, such as the improvement of their state of health in less time.

2. Regarding the ethical nature of the practice, it is crucial to acquire a free, preventive, fully informed, and verified consent, deriving from a deliberative process that evolves from the patient-doctor relationship. In the case at hand, it is emphasized that the use of organs needs a double consent procedure to ensure a maximum pondered decision.

3. In addition to offering benefits, in terms of waiting times for individuals who want to join the organ allocation program from nonstandard risk donors, the use of these organs could result in increasing the chances of health and survival for all.

Both positions assume the possibility of modifying the AIFA criterion so that the DAAs can be prescribed immediately after the transplant or at the first evidence of positive viremia.

Table 1. HCV Positive Donors vs HCV Negative Donors in Italy

Year		Total Donors			Used Donors			Ratio Between Total Donors and Used Donors	
		HCV+	HCV-	Total	HCV+	HCV-	Total	HCV+	HCV-
2015	N	62	1307	1369	29	1136	1165	47%	87%
	%	4.5%	95.5%	100%	2.5%	97.5%	100%	95% CI: 34%-59%	95% CI: 85%-89%
2016	N	59	1419	1478	26	1272	1298	44%	90%
	%	4.0%	96.0%	100%	2.0%	98.00%	100%	95% CI: 31%-57%	95% CI: 88%-91%
2017	N	77	1641	1718	31	1406	1437	40%	86%
	%	4.5%	95.5%	100%	2.1%	97.9%	100%	95% CI: 29%-51%	95% CI: 84%-87%
2018*	N	47	1191	1238	18	999	1017	38%	84%
	%	3.8%	96.2%	100%	1.8%	98.2%	100%	95% CI: 24%-52%	95% CI: 82%-86%
TOTAL	N	245	5558	5803	104	4813	4917	42%	87%
	%	4.2%	95.8%	100%	2.1%	97.9%	100%	95% CI: 36%-49%	95% CI: 86%-87%

Abbreviations: CI, confidence interval; HCV, hepatitis C virus.
*Data updated as of 30 September 2018.

DISCUSSION AND CONCLUSIONS

In the era of DAAs, it has become legitimate to consider the possibility of using anti-HCV-positive donors even in anti-HCV-negative recipients and not only in conditions of clinical urgency. In 2017, the ratio between the number of patients who went off the list because of transplant and the total number of patients who went through the list during the year (intention to treat) amounted to 53.3%, with an average waiting time of 1.6 years and a mortality rate of 3.7%. This means that only about 50% of the recipients admitted to the list underwent transplant during their first year on the list [2]. Hence, there is a dire need to implement strategies to expand the pool of available donors. Between 2015 and September 30, 2018, 245 anti-HCV-positive donors were reported in Italy, 4.2% of total donors. Out of these, a mere 104 have been used, that is, less than 50%. The comparison between this particular population and that of negative HCV donors shows that if we could use the anti-HCV-positive donors as the negative ones, we could hypothesize an increase in their use of about 40%, resulting in an expansion of the total donor pool of about 2% (Table 1). Furthermore, it should be noted that viral replication activity was hardly evaluated before 2017; the analysis has been possible in about 70% of cases, and the viremia turned out to be negative in 47% of cases (Table 2). Additionally, the proportion of utilized organs is lower, especially of kidneys, since heart and lung suitability can be influenced by age and the liver by the disease caused by the virus. In light of this, it would be interesting to assess the causes of the refusal of unused organs and the viral replication activity of refused donors from the very beginning. This could probably lead researchers to realize that many other donors and organs could be used and the donor pool expanded further. Clinical studies are clearly needed to deepen the matter. If the use of organs from marginal and nonstandard risk donors is primarily a clinical issue [1], this does not exempt anyone from implicit ethical considerations. Each of the so-called principles of bioethics is indeed involved in the decision to allow organ transplantation from nonstandard risk donors: benefit-risk ratio; autonomy versus consent of recipients; justice versus allocation, management of waiting lists, follow-up, and recipients' health care. As far as the possibility to use organs from anti-HCV-positive and HCV-RNA-positive donors for transplantation in anti-HCV-negative patients is concerned, both the ISS EC and the ICB identified recipients' autonomy as the elective ethical principle, thus focusing on the need to acquire a free, preventive, fully informed, and verified consent. The principles of beneficence and nonmaleficence are also crucial.

A case-by-case assessment is essential; a clinician has not only the duty to provide the patient with all the information necessary for a free and informed consent but also the responsibility to assess the risk between staying on the list and receiving an organ that could transmit a pathology. In principle, however, as underlined by the ICB, there is no sufficient reason to exclude patients from an option that can ensure an improvement in their health in a shorter time, which would offset the residual risk associated with transplantation of an organ from a nonstandard risk donor.

The complexity of communication in the specific case calls necessarily for stronger relations between physicians and patients [19] because, once the scientific requirements are met, the decision becomes personal and specific to each individual case. A dual consent procedure is the proper mechanism since

Table 2. HCV Positive Donors: Grafts Transplanted (2015-2017)

Year	Used HCV + donors	HCV RNA evaluated	HCV RNA negative	% HCV RNA negative (on evaluated)	Grafts transplanted
2015	29	22	8	36%	2 hearts; 19 livers; 20 kidneys
2016	26	23	8	35%	1 heart; 17 livers; 20 kidneys
2017	31	18	11	61%	4 hearts; 23 livers; 22 kidneys

Abbreviation: HCV, hepatitis C virus.

it gives the best guarantees of effective awareness and freedom of choice on the part of the person giving consent.

Finally, there is a need for more clinical studies; since DAAs have just recently been introduced in the market, possible long-term effects still need to be analyzed. This aspect should be clearly communicated to the patient and included in a general approach to the definition of the problem.

The CNT and the ISS are still working to define the next steps for a proper framing of the problem.

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