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Hepatitis C and dialysis. Are we doing what we should?

Hepatite C e diálise. Estamos a fazer o que devíamos?

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Patients with positive viral serology, mainly those infected with B, C or HI viruses are a matter of concern for nephrologists and other professionals in dialysis units. In this paper I will focus my attention more on hepatitis C patients, which are currently the most prevalent among all seropositive patients under dialysis treatment in Portugal.

Hepatitis C is an issue of great contemporaneity. It became matter of discussion and controversy with frequent news in the media. Some reasons are related to the great results that have been reported with the most recent therapies obtaining cure rates, in some patients, of more than 80%, but other reasons are not so centred on patients' interests and have hidden great economic concerns.

There have been huge advances in viral infection knowledge and that is why I ask if we are doing, at the present time, what is correct in terms of evaluation, monitoring and treatment of these patients. There are many unanswered questions concerning hepatitis C virus (HCV) positive patients: do dialysis patients receive adequate attention as to their clinical situation? That is, are there appropriate study and monitoring protocols for these patients? Do we know which patients we should treat or not? Are the best therapies defined? Are there studies on the use of various drugs in kidney failure? Does each transplantation centre have its own pre-transplantation protocols? Is what is being done what should actually be done?

Attempting to answer these questions, in June 2013, I organized a meeting entitled "Hepatitis C and Renal Failure" where I brought together renowned nephrologists, gastroenterologists and infectious diseases specialists to discuss those problems. Renal patients, since the early stages of the disease to the phases in which they receive dialysis, haemodialysis, peritoneal dialysis and, even, renal transplantation, pose several clinical problems. They are more susceptible to infection and there must be a definition of the best evaluation protocols or the best therapeutic approaches in the various stages of the disease.

The hepatitis C virus is known since the eighties of the 20th century. The older nephrologists still recall the time when there was no knowledge yet of this virus and hepatic cytolysis was called NANB (non-A, non-B) hepatitis[1] and, also, when that entity was the most frequent cause of liver enzymes elevation in haemodialysis patients[2]. The most sustained documentation came from studies relating to the post-transfusion hepatitis. The first publications that began to point to the viral aetiology are from 1989. This was the year when Michel Houghton and his collaborators, after several years of study, identified parts of the C virus[3] and, subsequently, developed a serological test capable of identifying the virus in infected individuals[4].

For some years the haemodialysis units in Portugal reported very high incidence and prevalence of this

entity. The registered prevalence nationwide grew till 1993, when 26.5% of dialyzed patients in this country were HCV positive and the highest incidence rate, 9.9%, recorded in 1991[5]. The evolution is summarized in Table I.

Table I

Incidence and prevalence of HCV+ patients in dialysis centers in Portugal

	Haemodialysis Patients (Total)	HCV+ patients on haemodialysis			
		Prevalent**		Incident**	
		n	%	n	%
1991	3390*	702	20.7	336	9.9
1993	4056*	1067	26.3	207	5.1
2000	6071	718	11.8	21	0.35
2013	10977	419	3.82	10***	0.09

* – Data from personal records. There were no records from de Portuguese Registry
** – The years 1991 and 1993 are the ones with greater incidence and prevalence, respectively, ever in Portugal
*** – There are no records of seroconversion in dialysis units in 2013

Observing these numbers we can easily say that the measures designed and implemented to address this big problem that invaded the haemodialysis centres had an almost complete success. Here it is worth noting that the daily work and persistence over time of the nursing staff, which was the guarantor of the implementation of those measures, and that those professionals have a great responsibility in these results. An excellent job was performed in terms of epidemiological control but, even so, we had under treatment in Portugal (haemodialysis and peritoneal dialysis), at the end of 2013, about 436 patients with hepatitis C. In fact, these constant control and surveillance measures continue to be of great usefulness and urgency in many countries in the world, mainly in the most populous or less developed[6].

On the other hand, at the meeting that I referred earlier, we could realize that the various institutions that have the responsibility of treating haemodialysis patients in Portugal do not have established strategies in terms of screening or treatment of these patients. For example, some perform virus RNA (ribonucleic acid) test in all positive patients but have laid down subsequent actions vis-à-vis the positivity of the exam. Some observed that these patients do not represent increase in expenses when they are compared to negative patients. This clearly suggests that these patients are monitored not differently from the others. We also could not identify co-morbidities, hospital admissions and mortality in this group of patients. The same can be said about the approach by the various renal transplant centres that have, each, their own protocols, and apply them to patients who, for the most part, are enrolled in more than one centre. Or, transplantation centres, simply, do not have protocols at all and depend on the opinions of infectious diseases specialists or gastroenterologists, most of whom have scant experience in the treatment of kidney patients and with whom it is not always easy to contact professionally for discussion of the problems that these patients present.

Why do HCV+ patients have a different approach of the other virus carriers in dialysis centres? Let us see:

The hepatitis B virus (HBV)+ patients receive haemodialysis treatment in separate rooms from the other patients. Their regular assessment, according to the Portuguese Good Practices Manual, does not include analysis for study of their infectivity, or viral replication, or for any consequences of long-term virus liver (chronic active hepatitis, cirrhosis, portal hypertension, HCC). If the patients are positive for the surface antigen they are evaluated for that analysis on an annual basis. Unprotected patients for HBV are subjected to vaccination programmes.

The human immunodeficiency virus (HIV)+ patients, who are already receiving haemodialysis treatment also in private clinics, are already under therapy for HIV and are more or less kept under control with hospital infectious diseases specialists, where the disease is monitored and the therapy provided free of charge.

Patients with HCV+, mostly arriving at private haemodialysis clinics with the information of this positivity and receive dialysis treatment in a so-called "geographical isolation" within the centre, usually with dedicated dialysis monitor, and also in the vast majority of cases, do not receive any special attention to their clinical situation as compared to other patients. Therefore, the single focus of attention is addressed only to the control of disease transmission within the clinic, that is, the protection is directed to the remaining patients and professionals.

But this is not a Portuguese situation exclusively. An observational study published recently with Outcomes and Practice Patterns Study (DOPPS) data

relating to almost 50,000 patients under haemodialysis, in twelve countries during the period between 1996 and 2011, showing a prevalence of HCV + 9.5%, only 1% of patients with antiviral therapy prescription were receiving this medication. In addition, from the HCV+ patients wait-listed for renal transplantation, only 3.7% were receiving treatment[7].

Is this situation correct or should it be different? Should we monitor the disease and its complications in a more aggressive way? Should we treat, and who should we treat? I mention some arguments for and against the antiviral treatment in the population of patients with IRC.

For:

1. The HCV is associated with increased likelihood of chronic kidney disease (CKD) and the rate of progression to stage 5[8-10];
2. The HCV infection is a factor of increased global and cardiovascular mortality in HD patients[11-13];
3. Hepatitis C treatment can contribute to improve renal and cardiovascular outcomes in diabetics[14];
4. Eradication of infection in patients on haemodialysis is recommended[15];
5. Liver biopsy may reveal significant changes despite normal liver enzymology over time[16];
6. Big advances in therapies became available[17,18];
7. Some of the most recent medications have hepatic metabolism[19,20,21];
8. Some studies indicate good results, with high rates of sustained virological response (SVR), low rates of abandonment and accessory effects on haemodialysis patients[22,23,24];
9. Candidates for renal transplantation should receive treatment of hepatitis C. It should be said that, in spite of the risks, it is possible to treat patients with hepatitis C after renal transplantation without precipitating acute rejection[25];
10. Viral replication of HCV has affected renal graft survival in these patients[26];
11. However, there is evidence that renal patients with hepatitis C have a significantly worse prognosis of patient and graft in post-transplantation[27];
12. Patients who achieve SVR upon finishing this therapy prior to renal transplantation in general do not become positive after transplantation, even with intense immunosuppressive therapy[28];
13. It can be considered that treatment is prevention.

Against:

1. The experience with the new medications in renal failure is still very scarce. There are many references about the contraindication for the use in patients with creatinine clearance ‹ 30 ml/min[29,30];
2. Liver biopsy is considered necessary in some situations to start therapy and this procedure has increased risks in renal patients;
3. Renal patients, compared with those without kidney disease, have less necro-inflammation and liver fibrosis[31];
4. Old age and multiple co morbidities.

Therefore, if we want to change this perspective of not considering renal patients with hepatitis C as candidates for treatment (I shall not talk about transplant patients), my proposal would be to trigger the following procedures:

Facing the presence of a patient with HCV positivity, one should attempt to establish, firstly, if the kidney disease can be related, or attributable, to this virus. If so, and if there are no contraindications, therapy should be started[32,33].

If the renal disease cannot be related to HCV, then we should try to establish if we are in the presence of a chronic or acute infection:

1. If we are in the presence of an acute infection, there are no doubts about the indication for treatment if there are no contraindications;

2. In case of chronic infection established by the positivity of HCV in two determinations spaced 6 months apart, we should:

   a. Evaluate the presence of contraindications to therapy, in which situation the therapy should not be done. The main contraindications are:

      i. Old age. The majority of the studies excluded patients older than 60, although

some included patients up to 70 years old;

ii. Presence of serious co-morbidities. I believe that, here, we can define the term "serious" as the presence of morbid situations that shorten the patient's life expectancy;

b. Others, whose listing you may want to consider before taking any decision, but I may recall situations like uncontrolled anaemia, thrombocytopenia, depression or convulsive disease;
c. In the absence of contraindications, we should carry out the determination of RNA of HCV and determination of viral genotype;
d. If we have a positive result for HCV RNA we have the necessary condition to consider treatment;
e. Request the opinion of a specialist with experience in treating these patients, usually gastroenterology or infectious diseases specialist, with whom we should discuss the indications for treatment, the need to carry out liver biopsy (Fibroscan is a technique not yet validated for renal patients), the patient's opinion about the therapy and, eventually, the perspective of renal transplantation[34].

Before I finish, I would still like to draw attention to difficulties that the nephrologists in Portugal will find when they search evaluation and treatment of the disease caused by HCV for their chronic renal patients as a result of some constraints that the bundled payment system of dialysis treatment introduced. This payment scheme limited the scope of action for nephrologists with regard to the evaluation and treatment of co-morbidities of renal patients on dialysis in this country.

In terms of final reflection, I can say that my goal with this text, was to draw attention to the nephrologists who have HCV positive patients under their responsibility, and we all have them, that we should not be pleased with the good work that has been done over the years in terms of epidemiological control in haemodialysis clinics. Leaving these patients without treatment is a situation that will certainly be changed in the near future, considering the enormous developments related to the new medications that are giving us great expectations of cure. Unfortunately, renal patients, and especially those who are already on dialysis, have been out of the scope of the experience which has been accumulated with these new drugs.

This is certainly an area in which one can say that treatment is, or will be, prevention. So, answering the question posed in the title of this article, this is what I think we should do in the near future concerning HCV positive patients with renal failure.

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