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EDITORIAL (FOR SPECIAL ISSUES)

Clinical expectations for the new bioactive treatments: greater well-being or longer survival?

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During the symposium at the ESAO meeting in Warsaw – dedicated to innovative approaches in renal replacement therapies, and particularly to the introduction of bioactive membranes and renal replacement systems – we were asked to think about what the clinician takes away from these innovative approaches, and where clinicians expect innovation to be directed in the future in order to meet our needs.

In preparing this workshop, the original question – "Do we want better survival or better well being?" – was followed by many others. What do we expect from new technologies and where we would like to see the largest commitment to research directed? What lessons have we learned from knowing that some membranes remove potentially pathological proteins? Do we believe that the removal of uremic toxins is optimal? Could we improve it with some sort of special device or, rather, with better blood flow ensured by better vascular/pressure stability? Can purifying better (or selectively) an elderly patient who tends to malnutrition improve his or her clinical status? Should the best treatment prolong life (in theory, the removal or nonactivation of inflammatory molecules causes fewer cardiovascular complications) or should it improve the patient's feeling of wellness in the present time? Are we interested in extending the life of an 80-year-old patient or do we want him or her to live better? What technology do we ask for as nephrologists? Are the new devices useful or are they are merely a fascinating exercise?

We thought that the best way to answer these questions from the clinical point of view was to take 2 different cases illustrating the benefits and the limits of the renal replacement therapies that we offer patients. The clinical history and features of the first selected case are presented in Table I.

It can be seen that the patient was born when the World War I armistice was signed. He was admitted and treated with regular dialysis at the age of 92.5 years. He enjoyed himself and had good quality of life for 2 years. In addition to the medical parameters (controlled anemia, blood pressure within target, phosphate and calcium metabolism equilibrated, etc.), the patient was reading suspense novels during dialysis, playing cards 3 times a week with friends, and having daily walks with his younger, second wife, always well dressed. On May 8, 2013, his son died of carcinomatosis. He viewed this event as outside the normal order of life. After this happened, he hardly ate, became unreactive to external stimuli and decreased communication with nursing staff (depression features). His serum albumin went from 32.2 g/L to 24 g/L in 1 month, he had a pulmonary infection, became malnourished and palliative and supportive care was started. He died on July 17, 2013 (2 months after his son's death).

What does this case show us? It shows many things, but we will comment on 2 aspects: the first is acceptance of the treatment by the patient and, in this situation, the treatment was very well adapted and the patient had a happy, high quality life, appreciating all the good moments he shared with his wife, family and friends. It also shows us that a renal replacement treatment that was very well adapted to a given situation may no longer be so if the patient undergoes major changes. In this case, the patient did not accept the death of his son and decided that life was not worth pursuing. Regardless of the technical level of the treatment he was given, he died within 2 months' time. In a way, he restored the natural order of life by no longer surviving his dead son.

The second case is presented in Table II. This younger patient never accepted his renal disease. Dialysis was started because he had life-threatening pulmonary edema. His interdialysis body weight gain was well over 5% of his total body weight, sometimes over 10 kg in between 2 consecutive dialysis sessions. Standard dialysis schedules were not able to remove all the extracellular volume excess. High-dose furosemide was given to increase urinary output, facilitating extracellular volume excess removal by dialysis, restoring normal hydration and blood pressure control (illustrated in Fig. 1). Blisters in the fingers and toes appeared, probably associated with the high-dose furosemide treatment, which had to be stopped. Again the interdialysis body weight gain was well over the limits of the therapeutic possibilities of a standard dialysis schedule. He had to be treated with extra dialysis sessions very frequently and, even so, was admitted to intensive care on 2 more occasions with pulmonary edema. The patient was unhappy and behaved in a threatening manner toward the healthcare personnel.

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TABLE I - Case 1 illustrating the limit of aging on treatment in renal replacement therapy

Male
Birthday 25/11/1918
(2 weeks after the armistice of the 1st world war)
Medical records
Hypertension (followed up for many years)
Left ventricular hypertrophy
Atrial fibrillation in 2011 (beta-blockers and salicylic acid)
First nephrology referral for CKD in November 2010 (92 years old)
Others
Functional colon disease
Hernia of hiatus and gastro-oesophagus reflux
Zona virus infection in 2005
Bilateral phakectomy
Cardiac failure and Pulmonary oedema
First dialysis 25th of March 2011 (92.5 year-old)

TABLE II - Case 2 illustrating the limit of replacement therapy to a younger, noncompliant patient

Male
Birthday 15/07/1948
Medical records
Obesity (162 cm and 110 Kg)
Type II diabetes (treated from 2015 with oral anti-diabetic drugs)
Hypertension: known and treated since 2013
Acute renal disease needing RRT in 2013
Context of cardiac and respiratory failure
Recovering after one week
CKD progression during 2013 – 2015
1st regular dialysis on the 10th of August 2015 (67 years old)
Others
Cholecystectomy 17th of June 2016

From this case, we may take away at least 2 points concerning the needs for new, better-adapted treatments. One, in contrast to the first patient, this patient denied his disease and the disease-related treatments – he never accepted his kidney disease. The second feature is another limit of the renal replacement treatment: too big a fluid overload. It was well over the possibilities of removal provided by standard schedules, but also exceeded all the treatment schedules we could provide. Indeed, he had life-threatening complications following these excesses.

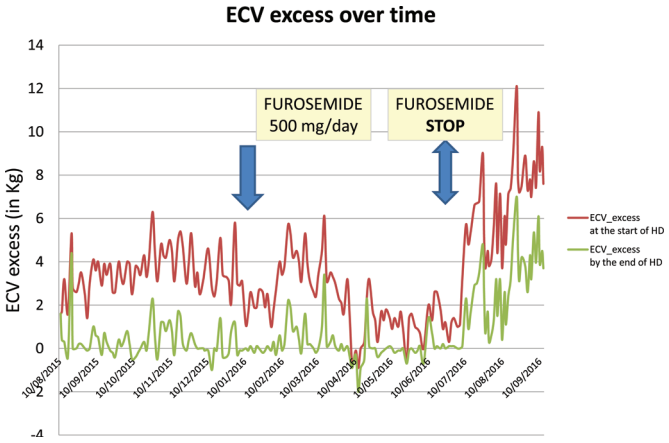

Fig. 1 - Body weight gain and dialysis treatment. Extracellular volume excess before and at the end of dialysis procedure is plotted. It may be noted that toward the end of the plotted period (corresponding to the withdrawal of diuretics) the prescribed body weight was rarely obtained by the end of the dialysis session (lower line at 0 value).

Therefore, the real question is how to go beyond the limits of present renal replacement therapy. First, we have to identify these limits. Then we should evaluate whether the present innovative treatment is likely to help in breaking through them, and what efforts should be made and explored by future research to efficiently improve the treatment. The limits discussed were treatment time, restoring metabolic functions of the kidneys and patient-linked individual factors.

Treatment time has been decreasing ever since dialysis therapy began. The first reported patient surviving end-stage chronic kidney disease (CKD) was uninterruptedly treated for 76 hours and had to be treated again after 3 days of treatment interruption, thus adding up to a schedule of around 100 hours treatment in a week's time. The most frequently used schedule at present is 4 hours, 3 times per week. This represents 12 hours out of a total of 168 hours in a 7-day period, which represents 7.14% of the time in treatment (1). Several schedules have been proposed as daily short sessions in dialysis centers (2) or night-long dialysis schedules (3). However, the initial high expectations have not been fully fulfilled by the reported studies (4). The approach of the wearable kidney thus seems very appropriate to overcome the barrier of time (5). Early reports with preliminary results are very encouraging (6).

The work of Rosalinde Masereeuw and Dimitrios Stomatialis shows the path to take regarding the second limit of restoring the metabolic functions of the kidney – by incorporating cells into membranes and dialysis systems (7). However, it is also of great importance to focus and promote all efforts toward prevention of CKD progression. In terms of impact on survival and well-being, every effort that manages to delay the moment the patient has to be taken into a renal replacement program is welcome. In this regard, new technology with the renal transfer of genetically engineered cells or injection of mesenchymal stem cells have shown some benefit in particular models of CKD (8, 9). Indeed, gene transfection with particu-

lar tools to preferentially target the kidney, such as ultrasound micro-bubble SMAD7 gene transfer in a rat model of diabetic nephropathy, has already proven its efficacy in preventing diabetic nephropathy and renal damage progression (10).

Finally, concerning the patient-linked, individual factors, there is no artificial system capable of solving them. The main, most profitable tool we have at our disposal is empathy. Personalized, empathetic medical support cannot be outdone by any other approach or technique. Empathetic medical practice has to be promoted among young doctors and is frequently forgotten in the medical curriculum. Increasing doctor-patient time, talking to patients and sharing their moments of worry and happiness, and preventing pain through adapted treatments are the major features of good quality treatment for chronic patients in dialysis. We rarely give enough consideration to this aspect.

In summary, to answer the various questions posed in our workshop, are we interested in **extending the life of an 80-year-old patient** or do we want **patients to live better**? The answer is incontestably both, extending life and improving its quality. As for the general considerations, what technology do we wish for as nephrologists? Every improvement in membrane technology is certainly welcome. Incorporating biology may break through one of the present limits of extracorporeal treatments: that of restoring the metabolic functions of the kidney. Our preference would lie in prevention: anything that can be done to delay or avoid CKD progression is worth developing and trying. Finally, do we find **technological developments to be useful** or are these new devices **only a fascinating exercise?**

The technical developments are certainly useful. They help to improve dialysis. With our accumulated experience we may state quite confidently that replacing acetate buffer by bicarbonate, substituting the first dialysis membranes with more biocompatible membranes, adding ultrafiltration controllers, improving the chemical and bacteriological quality of the dialysate, using high-convection systems, introducing control systems and quantifying dialysis has indeed resulted in better treatments, and many other technical improvements will hopefully contribute to better outcomes and survival. On the other hand, the paths taken by innovation should be chosen following in-depth thinking on the limits of the present treatments and the ways they may be surpassed.

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