The management of chronic renal insufficiency in the conservative phase

Francesco Locatelli¹, Fernando Valderrábanò², Nicholas Hoenich³, Jürgen Bommer⁴, Karel Leunissen⁵ and Vincenzo Cambi⁶

¹Azienda Ospedale di Lecco, Lecco, Italy, ²University Hospital Gregorio Marañon, Madrid, Spain, ³Department of Nephrology, School of Clinical Medical Sciences, University of Newcastle, UK, ⁴University Hospital, Heidelberg, Germany, ⁵University Hospital, Maastricht, The Netherlands, and ⁶Department of Clinical Medicine, Nephrology and Preventive Medicine, University of Parma, Italy

Introduction

Locatelli: There has been a striking increase in the incidence of end-stage renal disease (ESRD) over the last 30 years world-wide [1]. The growing proportion of elderly patients mainly accounts for the number in the increase of these patients admitted to renal replacement therapy (RRT), with a dramatically high morbidity and mortality rate [1–3].

A number of physiological and metabolic changes may contribute not only towards progressive loss of renal function but also to increased mortality observed thereafter, during the dialytic phase. The detection and correction of these events may slow the progression of chronic renal insufficiency (CRI) and delay the need for dialysis. Thus the question of whether therapeutic interventions may retard the progression of CRI in man is extremely important not only clinically, but also in terms of patient suffering and the social and economic impact of regular RRT [4].

Pre-dialysis—overall objectives

Locatelli: I would like to start the discussion of the pre-dialysis phase by focusing on the overall objectives of treatment in this phase.

Leunissen: To maintain kidney function for as long as possible in the treatment of CRI and to prevent important co-morbidity (in particular cardiovascular morbidity) thus helping to improve the survival of the patient, both during dialysis treatment time and when a patient is transplanted. To treat CRI patients optimally, with regard not only to cardiovascular complications but also in relation to nutritional status (most patients are already malnourished when they start dialysis).

Valderrábano: I am co-ordinating a Spanish document on pre-dialysis treatment and, in my experience, the three important goals are to delay progression, to prevent co-morbidity (cardiovascular complications and anaemia) and to prepare patients for RRT.

Cambi: Our main goal is to keep the patient’s metabolic state as near to normal as possible. This means checking blood pressure, acid-base balance and nutrition, waiting until these are satisfactory; ensuring correct iron status and avoiding secondary hyperparathyroidism. Anaemia will come later and at that point it should be corrected. The majority of patients are old (the mean age of patients starting dialysis is 70 years) and most of them do not need immediate dialysis treatment if metabolic conditions are stable.

Hoenich: In the United Kingdom (UK) blood pressure control, nutrition and acid-base control provide the framework for pre-dialysis patient monitoring. Erythropoietin (EPO) treatment is not widely used in pre-dialysis patients due to its cost.

Bommer: Effective antihypertensive therapy, timely installation of vascular access, and appropriate start of dialysis are the targets in treating pre-ureaemic patients.

Protein and calorie intake

Locatelli: I suggest we add the level of protein intake in the pre-dialysis diet to the discussion. In my opinion a ‘controlled protein diet’ (that is a protein intake between 0.8 and 1 g/kg bw/day with a calorie intake no less than 30 Kcal/kg bw/day) should be used in ‘normal’ patients; in ‘selected’ patients you may try to reduce the protein intake according to the compliance of the patient. I wonder, however, if it is useful and safe to reduce the protein intake to less than 0.8 g/kg bw/day, considering the small advantage in slowing down the progression of the underlying disease towards ESRD and the need for dialysis, as well as the high risk of malnutrition [4–7].

I would like to stress the necessity of looking at urinary urea excretion as a good marker of protein
Acid-base balance

impossible and could also be dangerous to reduce later on during dialysis [13,14].

Locatelli: Patients with renal failure spontaneously eat very low protein diets and that may lead to malnutrition [10]. If you suggest a free diet, they eat very little protein; so the paradox is the highest amount compatible with 500–600 mg phosphate per day.

Locatelli: It seems to me there is a general consensus that one should not reduce protein intake too much, considering the problem of possible malnutrition of paramount importance [11,12]. It is well known that malnutrition is an important factor affecting survival later on during dialysis [13,14]. We have reached consensus that it would be quite impossible and could also be dangerous to reduce protein intake to less than 0.8 g/kg bw/day in the pre-dialysis phase. I wonder if there is a role for a vegetarian diet as a substitution for animal proteins [12,15].

Cambi: I think that the issue is marginal. In my opinion it is a mistake to give a target to the name (vegetarian diet, hypoproteic diet) and not to target the consequences: acidosis, hyperkalaemia and hyperphosphataemia. A vegetarian diet lacks certain essential nutrients, so is not complete. Many patients with reduced appetite do not select proper food and become malnourished. If they are below the minimum level of protein, the type of protein that they could eat (soya, fish, egg) should be suggested.

Hoënich: I agree with the protein level of 0.8 g/kg bw/day (except possibly in very old patients when it may be too much) but a calorie intake of 35 Kcal/kg bw/day would be at the upper limit.

Locatelli: I agree that the protein intake of the elderly should be less than that of younger patients, particularly when they are in good health.

Leunissen: I agree with the importance of the relationship between calorie and protein intake. I think that we should not only define an upper limit of calorie intake of 35 Kcal/kg bw/day, but also a lower limit, because when patients get less energy, they will become catabolic and acidotic [16]. Poor dialysis will decrease the appetite and many patients on a prescribed protein intake of 0.8 g/kg bw/day cannot eat it because their appetite is not good enough.

Bonner: In the immediate pre-dialysis phase I suggest no protein or dietary restriction. Protein intake in the pre-dialytic period decreases with the progression of renal failure and in most patients a normal, free spontaneous protein intake is no more than 0.8 g/kg bw/day [10]. I am more concerned with malnutrition and feel that nutritional restriction could augment this [11]. In the rural population, more than in the urban population, patients generally do not eat what has been recommended: they tend to eat what they like to eat. Therefore, the food preferences of the individual patients should be respected in the dietary recommendations.

Locatelli: A free protein intake should not be recommended since patients reduce their protein intake spontaneously without any knowledge of the importance of the different nutrients in their diet. Therefore dietary recommendations should be given to the patients, enabling them to choose different nutrients to improve their general well-being, reduce acidosis and avoid malnutrition.

Leunissen: It is questionable whether one can overcome decreased protein synthesis by eating more protein as there is a balance between protein synthesis and protein degradation. When a patient is acidotic, there is a decrease in essential short chain amino acids intracellularly and it is impossible to increase this level by eating more protein.

Acid-base balance

Locatelli: What about the treatment of pre-dialysis acidosis? I am asking the panel to consider the level of bicarbonate needed in order to correct acidosis.

Valderrábano: Acidosis increases protein breakdown [17,18], decreases the content of some amino acids in muscle cells and promotes the liberation of calcium from bone. A patient with a creatinine clearance of 20–25 ml/min is generally symptomatic and has to be encouraged to increase protein intake because the majority of these patients consider proteins to be unhealthy.

Bonner: Giving a patient many tablets increases compliance problems. Phosphate binding and antihypertensive treatment are more important than the correction of acidosis.

Leunissen: In The Netherlands, most nephrology centres do not correct acidosis adequately in the pre-dialysis phase.

Locatelli: I would like to remind you that one of the advantages of low protein diets is the correction of acidosis. This was particularly important in earlier years (35 years ago) [19,20] when the 'low protein diet' was introduced at a time when dialysis facilities were not easily available and it was possible to recover patients from uraemic coma. This type of coma was more often related to metabolic acidosis than to the retention of nitrogen metabolites. Thus, my suggestion is to normalise plasma bicarbonate levels completely,
while also taking into account the increasingly recognised importance of acidosis in protein breakdown. **Cambi:** By using calcium carbonate, only small amounts of sodium bicarbonate are needed, thus maintaining acid-base balance and patient tolerance. **Valderrabano:** In Spain very few doctors give bicarbonate to pre-dialysis patients, mainly to those with pyelonephritis. **Bommer:** I suggest one should not raise plasma bicarbonate levels above 18–19 mEq/l. **Locatelli:** Thus, which seems strange to me, you don’t consider acidosis as an important clinical problem in pre-dialysis patients. Do you really consider that good correction of metabolic acidosis is obtained at plasma bicarbonate levels of 18–19 mEq/l? I suggest, in agreement with the other panelists, one should aim to reach a plasma bicarbonate level of not less than 22 mEq/l.

**Blood pressure control**

**Locatelli:** The next topic is the most important one, namely that of pre-dialysis blood pressure control and preservation of renal function [6,21,22]. What is your personal opinion in this very hot field? I ask you to consider the following two aspects of the problem, namely the target blood pressure to be achieved, particularly in proteinuric patients, and which particular drugs (such as ACE inhibitors and angiotensin II receptor antagonists) should be used to further slow down CRI progression, possibly at lower levels of blood pressure (i.e. 120/80 mmHg) than that of the trials designed to date (140/90 mmHg). **Hoenich:** Control of blood pressure is, to date, the only intervention other than the treatment of primary disease that has been demonstrated in controlled trials to slow the progression of renal failure. ACE inhibitors have also been shown to have an effect, especially in diabetic patients [23]. **Valderrabano:** ACE inhibitors are useful in early phases of CRI where it is important to have strict control of blood pressure. **Cambi:** If the target is to correct blood pressure rather than to stabilize renal function, ACE inhibitors would achieve this, but nothing more. **Bommer:** ACE inhibitors are important in the treatment of patients with CRI, not only in the long-term preservation of kidney function but also in the prevention of vascular complications. Blood pressure reduction in borderline hypertensives with a decreased compliance of the major arteries (e.g. carotid, femoral and brachial) shows that during ACE inhibitor therapy the compliance may normalise, which is not the case with calcium antagonists. ACE inhibition has other beneficial effects on several complications in these patients [24–26]. However, in very old patients and diabetics with vascular lesions and a creatinine clearance of less than 35–35 ml/min one must be careful. **Locatelli:** I would like to clarify my previous statements. The control of blood pressure values at 120/80 mmHg is the first issue and it does not matter which kind of drugs are used [21]. The open question is if ACE inhibitors can slow down the progression of CRI better than other antihypertensive drugs while providing the same level of perfect blood pressure control (120/80 mmHg). There are no data available in the literature. Thus, prospective controlled randomized trials are needed to clarify this important aspect. However, I wonder if it is possible to reach the goal of blood pressure values of 120/80 mmHg in a control patient group which is not treated with ACE inhibitors or angiotensin II receptor antagonists, considering that in CRI patients one usually needs three or four drugs to normalise blood pressure values. Moreover, the importance of the level of proteinuria as a marker of CRI progression is increasingly recognized and, above all, the importance of reducing proteinuria as an important tool for slowing down CRI progression even in normotensive patients [4,27–29]. Thus, the goal is not only to look at blood pressure values but also at the levels of proteinuria. In this respect a treatment combining ACE inhibitors and angiotensin II receptor antagonists could be useful [26,30].

**Anaemia correction**

**Locatelli:** I suggest we discuss in more detail the topic of pre-dialysis anaemia: its definition, the target haematocrit (Hct) and the role of iron supplements (per os or i.v.) per se and in relation to the use of EPO. **Leunissen:** Because of reimbursement policies, EPO is only started after correcting iron status, although it could be started earlier. I would like to emphasize the importance of investigating further the long-term effect of a low Hct on left ventricular muscle mass. A study in the Netherlands is comparing this in three patient groups in whom the Hct is kept to 40–42%, to 36% or to 30% respectively. **Valderrabano:** In my opinion the management of anaemia is of primary importance. Iron (in some cases intravenous iron) is given before starting EPO which is used in all cases when the haemoglobin level is <11% (60% of cases). The response to EPO is very good, with 4000 to 6000 units per week, some patients will reach a Hct of 40% and there is no problem with hypertension in most instances. **Bommer:** I would like to stress that the age of the patient is very important. Whilst in older patients the situation is different, in those who are younger, EPO is not usually used during the pre-dialysis period because they can tolerate a low haemoglobin level (e.g. ~9 g/dl) and if they are treated with iron and are generally well nourished they do not experience dangerously low Hct levels. Furthermore, it is difficult to convince them to start dialysis at the optimal time if the anaemia has been corrected too early because they are feeling much better. Obviously anaemia should not be treated by EPO alone. **Hoenich:** The goals are to try to maintain haemoglobin and Hct at not less than 10 g/dl and 30% respectively for the majority of patients.
Locatelli: It seems clear to me that the importance of correcting anaemia in pre-dialysis patients is increasingly recognized, although there is a need for controlled and randomized trials aimed at evaluating the cost-benefit ratio of completely normalising Hct levels. In this respect the use of iron supplements is of paramount importance before and during the use of EPO, and also in patients not yet in dialysis [31,32].

Calcium—phosphorus metabolism

Locatelli: Let us change gear and discuss the use of vitamin D in patients still on conservative treatment, and ask how early during the course of CRI should one use vitamin D, particularly in relation to plasma calcium and parathyroid hormone levels.

Hoennich: There is no UK consensus about the management of renal bone disease in the pre-dialysis phase, with specialists disagreeing whether vitamin D and 1-alpha vitamin D should be started relatively early. Starting vitamin D, looking at serum PTH levels of patients and trying to maintain them at higher levels than in normal subjects is an option.

Bommer: Nearly 50% of the German dialysis population has a 25OH vitamin D serum level below the normal range or close to the lower limit of normal and need supplementation. 5000–10,000 units of vitamin D3 once a week, given during dialysis, is an effective therapy. Compliance with vitamin D3 therapy can be checked by serum 25OH vitamin D measurements. Under such controlled vitamin D therapy a target iPTH level of about 200 pg/ml (three-fold upper limit of healthy controls) can be achieved in most of our HD patients. In contrast, the compliance was poor (about 10–20%) in our patients with daily calcitriol therapy.

Locatelli: Dr Bommer, you have discussed the use of vitamin D for the subsequent state, later on during dialysis, and I agree with your statements. In any case it is clear from your comments that most people agree to administer vitamin D supplementation in pre-dialysis patients, maintaining plasma PTH at levels higher than in the normal population, to prevent adynamic bone disease. Moreover, hypercalcaemia and hyperphosphataemia have been found to be associated with higher cardiac disease and death [33,34]. These considerations raise the question as to whether we should change our opinion on optimal plasma PTH, calcium and phosphate levels.

When to start dialysis

Locatelli: The last topic that I would like to discuss is very important indeed in pre-dialysis care: when to start dialysis [35]. This aspect has major personal implications for the patients but also relevant organizational and economic implications for society.

Cambi: There is a great difference between young and elderly patients. Amongst the latter, the problem is not so urgent because they comply more readily and can often be kept in a conservative phase much longer, provided that their hypertension is controlled.

Valderrábano: The Spanish situation is more or less the same. In fact in general, uraemic patients start dialysis when creatinine clearance is below 12 ml/min (in some cases below 15 ml/min) but always on a clinical basis. If the patient has anorexia, nausea, is markedly acidic or very hypertensive, conservative treatment should be arrested and dialysis should not be delayed. Previously, when we did not realise the importance of nutritional status, we started dialysis at a plasma creatinine of 7 mg%; 6 months later, plasma creatinine had risen to 14 mg% because muscle wasting had stopped and patients were in an anabolic state. If the patient is doing well, feels well, is not acidic and has well controlled blood pressure and anaemia correction, waiting is not a problem and dialysis may be delayed.

Hoennich: The decision would be based on the clinical well-being of the patient. The majority of patients at the commencement of dialysis would probably still have a residual renal function of between 12 and 15 ml/min, however the decision to start dialysis would not be governed by this alone.

Bommer: Even though a patient feels better (with EPO and a relatively high haemoglobin level), it is still important to start dialysis early enough and provide appropriate artificial kidney replacement of renal function. We usually start dialysis at a creatinine clearance of 12–15 ml/min and in diabetics even earlier because of more frequent fluid overload together with more severe cardiovascular problems and polyneuropathy.

Locatelli: It is very important to consider residual renal function, since its conservation may prevent a rapid increase of plasma β2-microglobulin, a well recognized, important factor of morbidity (and possibly mortality) in long-term haemodialysis patients [36,38]. Starting dialysis earlier means decreasing residual renal function more rapidly, except in CAPD.

Consensus on pre-dialysis treatments

Locatelli: To summarize the consensus with respect to the pre-dialysis phase, there was general or majority agreement on the following points.

Nutritional aspect: the diet should consist of a protein intake of 0.8 g/kg bw/day with an energy intake of no less than 30 and no more than 35 Kcal/kg bw/day.

Metabolic acidosis: plasma bicarbonate level should be at least 22 mEq/l, using a controlled protein diet, calcium carbonate and small doses of sodium bicarbonate.

Hypertension: target blood pressure should be 120/80 mmHg. ACE inhibitors and/or angiotensin II receptor antagonists may be necessary to reach this target and may be useful in slowing CRI progression and improving cardiac status. Controlled prospective randomised trials are needed in this field, with blood pressure values at the suggested levels of 120/80 mmHg.
and comparisons of ACE inhibitors (or angiotensin II receptor antagonists) with standard antihypertensive therapy. The goal of reducing proteinuria is of utmost importance and the association of ACE inhibitors and angiotensin II receptor antagonists could be an important tool, particularly in normotensive patients.

**Anaemia:** haemoglobin target should be 10–11 g/dL, starting with iron supplements before using EPO and continuously administering iron together with EPO therapy if necessary.

**Vitamin D:** should be used according to plasma PTH and calcium levels (PTH levels two to three times higher than the upper normal values in presence of normal plasma calcium values, to reduce the risk of adynamic bone disease).

**When to start dialysis:** the decision should be taken based on clinical status rather than on laboratory values only.

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