AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE: WHAT DO WE NEED TO KNOW FOR COUNSELLING?

***Giorgina Barbara Piccoli,[1] Anna Pia,[2] Federica Neve Vigotti,[1] Gabriella Guzzo,[1] Roberta Clari,[1] Rossella Attini,[3] Agostino De Pascale,[4] Federica Solitro,[4] Vincenzo Arena,[5] Andrea Veltri[4]**

1. SS Nephrology, Department of Clinical and Biological Science, University of Turin, Turin, Italy
2. Division of Internal Medicine, University of Turin, Turin, Italy
3. Gynecology and Obstetrics, Department of Surgical Sciences, University of Turin, Turin, Italy
4. Department of Oncology, University of Turin, Turin, Italy
5. IRMET, Via Onorato Vigliani, Torino, Italy
**Correspondence to gbpiccoli@yahoo.it*

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ABSTRACT

In the new millennium, few kidney diseases changed their perspectives as much as autosomal dominant polycystic kidney disease (ADPKD). New diagnostic approaches, including the evaluation of renal or liver volume by computerised tomography (CT) scan, the detection of cyst infections by positron emission tomography (PET) scan, and new therapeutic approaches (including vaptans, mTOR inhibitors, and somatostatin analogues) pose new clinical and ethical dilemmas. Therefore, the analysis of the recent advances offers an occasion for reviewing our counselling policy. The aim of this narrative review is to discuss a few crucial points concerning counselling in ADPKD: should all ADPKD patients undergo genetic testing for characterisation of the involved gene? What is the role of prenatal counselling and preimplantation selection? Should all ADPKD patients be followed in a nephrology clinic? Which imaging to use in which patients? Whom should we treat, when, and by which drugs, and how to communicate the treatment options? The working conclusions highlight the trends towards earlier referral of ADPKD patients, the importance of offering the diet options, including low-salt, high-water intake, difficult to follow, but devoid of side-effects, and the expectancy for the new therapeutic options, alone or in combination, aimed at reduction of cyst volume and/or control of cyst growth.

Keywords: Polycystic kidney disease, genetic and prenatal diagnosis, complications, infection, dialysis, vaptans, mTOR inhibitors, liver cysts, somatostatin analogues, imaging.

INTRODUCTION

In the last few years the panorama faced by patients affected by autosomal dominant polycystic kidney disease (ADPKD), and by their treating physicians, has remarkably changed.[1,2] As usual, the progress brings more than new diagnostic techniques or therapeutic tools; it poses also new clinical and ethical problems and, in the era of patient empowerment, the analysis of the recent advances offers an occasion for reviewing our counselling policy.[3-5]

In this context, the present narrative, non-systematic review, has been focused on some 'hot' points in ADPKD, which the authors considered as fundamental for the clinicians. In keeping with the complexity of the disease, we have tried to highlight different opinions and uncertainties.[6]

Hence, we addressed our discussion at the following questions: should all ADPKD patients undergo genetic testing for characterisation of the involved gene? What is the role of prenatal counselling and preimplantation selection? Should all ADPKD patients be followed in a nephrology

clinic? Which imaging in which patients? Whom should we treat, when, and by which drugs, and how to communicate the treatment options?

SHOULD ALL ADPKD PATIENTS UNDERGO GENETIC TESTING?

ADPKD is the most common monogenic severe kidney disease, with an average incidence of 1 in 500-1,000 live births.[1,2,7,8] Mutations in the two major genes (polycystic kidney disease 1 [PKD1] on chromosome 16 and polycystic kidney disease 2 [PKD2] on chromosome 4) account for about 90% of cases, while, thus far, in the remaining approximately 10%, the genetic diagnosis is elusive and no mutation has been identified.[8-11]

While penetrance is complete, and virtually all patients with PKD1 or PKD2 mutations develop kidney cysts, the expressivity is highly variable, and the reasons for this wide variability are only partially understood.[12,13]

On average, PKD1 mutations correlate with a poorer renal prognosis and a younger age at start of renal replacement therapy (RRT); the peak of RRT start is presently in the late fifties in PKD1, and in the late seventies in PKD2 patients.[8-10] The difference is strong enough to suggest that the family history may predict the gene involved.[12] However, within-family variability is well documented, suggesting the presence of modifier effects of other genes, or from not yet defined environmental factors. In this regard, the clinical evolution of ADPKD may represent a challenging field for epigenetic analysis.[13]

Hence, the question on the clinical relevance for genetic testing is not easily answered. Indeed, several authors hold that the genetic tests are of use only in selected situations, such as non-typical ADPKD, absence of family history, or in view of a living kidney donation.[14,15] Other authors, however, consider that the genetic analysis will influence, if not now then in the near future, the therapeutic choices.[16]

There are pragmatic limits to a universal extension of the genetic tests: the first one is obviously economical, the second one is linked to the tests used. While the new generation of genetic tests allow a specific definition of the involved mutation, the older tests, based upon a linkage analysis, are not able to provide such information and should probably be considered obsolete.[17]

The opinion of our group is that genetic analysis will be needed in all patients in the near future. As the genetic tests are undergoing profound changes, leading to simplification (and lower costs), our present attitude is to perform genetic testing in cases with treatment indications, severe disease, or unclear family history, and in patients who wish to have a child. We usually test one individual per family, being ready to extend genetic analysis as soon as the availability of the tests will increase and their cost will decrease.

WHAT IS THE ROLE FOR PRENATAL COUNSELLING AND PREIMPLANTATION SELECTION?

The prenatal counselling of ADPKD may be seen as very easy or exceedingly difficult. It is easy since ADPKD is an autosomal dominant disease with complete penetration.[1-3] It is difficult since ADPKD has different expressivity and the clinical manifestation may occur as late as the sixth-to-seventh decade of life.[7-11] If we consider that the history of RRT is only in its fifth decade of life, we appreciate that forecasting life with end-stage kidney disease in the next 50 years is almost impossible.[18-20]

Hence, in the face of the clinical uncertainty, several approaches are possible: a negative one underlines that 50% of the children inherit the gene, counselling the patients not to have children, also taking into account the possibility of pregnancy-related complications in the mother, or supporting pregnancy interruption in the presence of the affected gene in the foetus.[21-24]

Preimplantation selection is considered by some authors an alternative, because it avoids the physical and emotional trauma of a pregnancy termination in the case of an affected foetus.[25] The value of such a statement is different in the case of recessive polycystic disease, with its grim prognosis, and of ADPKD. Preimplantation diagnosis is synonymous with *in vitro* fertilisation; hence the clinical and ethical problems of *in vitro* fertilisation - including also a higher rate of malformation and prematurity - cannot be avoided, as well as the physical and emotional stress of the assisted fertilisation procedure.[26-31]

On the other hand, the continuous therapeutic advances may lead to a more optimistic view, underlying also that early (*in utero*) diagnosis may be of help in planning preventive interventions

(such as control of urinary tract infections [UTIs], dietary habits, and prompt treatment of hypertension) and is potentially effective in postponing overt kidney disease.[1-3]

In a setting where the uncertainties largely overcome the certitudes, the policy adopted in our outpatient clinic dedicated to pregnancy in chronic kidney disease (CKD), is to underline that we are not able to forecast the future of an affected baby. If a woman over 35 years and/or with impaired kidney function considers pregnancy termination in the case of an affected foetus, we remind that the chances of a further pregnancy are not 100% and that increasing maternal age is associated with a steep rise in chromosome derangements, leading to diseases whose severity is way above that of ADPKD.[32]

A detailed discussion on pregnancy in ADPKD is beyond the scope of this review; however, two open problems may be cited: the need for strict blood pressure (BP) control as, for unknown reasons, pre-eclampsia has been reported as more frequent in ADPKD, also with normal BP and kidney function at the start of pregnancy.[23,33,34] The second one is the risk of intracystic bleeding at delivery, linked to the increase in intra-abdominal pressure during parturition.[33-35] The old tenet that women with ADPKD should deliver with Caesarean section is no longer shared, as the risks of a surgical intervention and of catheter-associated UTI may exceed those of intracystic bleeding. However, the risk of intracystic bleeding has to be borne in mind and, at least in our centre, we suggest close ultrasound (US) monitoring of the largest cysts, also in non-symptomatic patients, at least in the proximity of delivery and immediately after.[36,37]

SHOULD ALL ADPKD PATIENTS BE FOLLOWED IN A NEPHROLOGY CLINIC?

The pattern of the ADPKD patients referred to outpatient nephrology units has been changing over time, with an overall earlier referral of the patients.[38] There are at least three reasons for this: the wider availability of US leading to preclinical diagnosis, the higher awareness, and the increasing therapeutic options.[1-3,7] Once more, the indications are not uniform and reflect both the sanitary system and the opinions of the physicians. As pointed out by a brilliant recent editorial in the *New England Journal of Medicine*, entitled: '*From sick care to health care — reengineering prevention into the U.S. system*',[39] disease prevention encompasses all efforts to anticipate the genesis of disease and forestall its progression to clinical manifestations. Hence, focus on prevention is not synonymous of elimination of the disease, but of 'morbidity compression,' extending the symptom-free lifespan.[39]

The chronic lack of resources of the healthcare systems often leads to a minimalist attitude, limiting the care to the patients with overt disease, with the idea that the present therapeutic tools contrast only the macro-effects of the disease, such as hypertension, and the metabolic cascade of maladaptive changes characteristic of advanced CKD.[40,41]

There is a wide agreement on the importance of timely treatment of the UTIs and on the full normalisation of hypertension, although opinions on the diet are mixed.[40-43] Some authors maintain that low protein diets are of minor efficacy in ADPKD patients, while on the contrary, animal studies suggest that an early start of moderate protein restriction may slow the progression of the disease.[44] Furthermore, the dietary approaches include also a very high water intake, and a drastic reduction of salt intake.[45-48] The potentials of this 'difficult' diet are underlined also by the promising and likewise 'difficult' results obtained with Tolvaptan, through the pharmacologic inhibition of the action of vasopressin on its receptors.[45,46] Promising results have occasionally been reported with the use of statins at the highest tolerated doses, and the recent studies on glucose metabolism may suggest an early approach to glycaemic intolerance.[49-52] Consequently, the start of follow-up is directly related to the therapeutic options (the more, the earlier) and to the indications for the new therapies.[53,54]

In our unit, ADPKD patients represent about 10% of cases who performed at least one nephrology consultation. In 2012, we started a baseline nuclear magnetic resonance assessment in all the patients with large kidney, symptomatic disease, or advanced CKD, leading to the selection for octreotide therapy, of a first group of cases with relevant symptoms and liver involvement. The availability of this option had a strong effect in recruiting more family members, often at earlier stages of the disease.

Our unit follows a policy of the wide use of low protein diets.[55,56] So far, ten ADPKD patients have been enrolled in a moderate protein restriction (0.6 g/kg/day) with a vegan schema, with the

addition of alpha keto-analogues.[55,56] Within the limitations of small numbers, and of the nonlinear glomerular filtration rate decrease, long-term stabilisation and prolongation of dialysis-free interval were attained at least in a few cases (Figure 1). The indications for a high-water, low-sodium diet are contextually given to all patients. We suggest following all ADPKD patents in pregnancy, considering them 'at risk pregnancies', paying particular attention to infectious complications and to the development of pregnancy-induced hypertension and pre-eclampsia.[36,37]

WHICH IMAGING IN WHICH PATIENTS?

Imaging is the basis not only of diagnosis, but also of the assessment of prognosis, since cyst growth correlates with the progression of renal function impairment.[57,58] However, the best way to assess progression is not yet established, and the same holds true for the detection of the complications. Each imaging method has advantages and drawbacks. US are the mainstay for family screening, and are the basis for diagnosis and follow-up in children and in pregnancy.[59] Their role is limited mainly by the operator dependence.[59]

Hence, CT and magnetic resonance imaging (MRI) scans, each with advantages and drawbacks, are now becoming the gold standard for the three-dimensional analysis of the involved kidneys or liver, allowing comparison over time.[59] Some problems remain open; for instance, it is not clear if the evolution of a few large cysts is superimposable to the effect of numerous small cysts (Figure 2).

In this regard, more sophisticated approaches, aimed at assessing the fibrous kidney tissue, have been attempted.[60] The limits of this clever strategy, showing a strong correlation with renal functional impairment and the need for computerised tomography (CT) scan with contrast media, raise obvious issues of radioprotection and nephrotoxicity.[60]

Further problems arise in the presence of complications. CT scan is the gold standard for stone disease, of particular importance in these cases in which the altered kidney structure impairs the detection of stones.[61,62] CT angiography scan is the technique of choice for massive bleeding (Figure 3). The detection of infected cysts is more challenging because of the various, often non-specific, clinical manifestations ranging from mild abdominal discomfort to a severe life-threatening disease.[63-65] MRI and CT are both valuable in discriminating between non-complicated and complicated cysts, but are usually unable to discriminate between bleeding, infection, or neoplasia.[65,66] Furthermore, the presence of several 'complicated' cysts is common in severely enlarged liver or kidneys, further impairing the localisation of the infectious process.[63-66] Hence, scintigraphy with leukocytes labelled with indium or gallium was employed, with the limits being the lack of prompt availability, the high costs, and the relatively poor spatial discrimination.[67,68]

Consequently, fludeoxyglucose-PET (FDG-PET), able to identify metabolically active tissues, is becoming the gold diagnostic standard in this setting.[65,66,69] Among the advantages of this sophisticated technique is also that the tracer, a glucose analogue, is non-nephrotoxic also in advanced CKD stages (Figure 4).

WHOM SHOULD WE TREAT, WHEN, AND BY WHICH DRUGS, AND WHAT SHOULD WE ADVISE?

Finally, the great open question for the clinical nephrologist: is it already time for treating our patients with any, or a combination of new drugs? Indeed, in the new millennium, almost suddenly a rapidly growing number of drugs potentially slowing the progression of renal cysts has been tested in animals and in humans.[1-3,7,21,41-54] A detailed insight into the basic mechanisms and into the results is not in the scope of this clinical review. However, in a rapidly evolving world and in the presence of an increased involvement of the patients in their medical choices, often through long and perilous sailing on the vast seas of the Internet, every clinical nephrologist is increasingly questioned on the 'new therapies'. When we typed 'ADPKD therapy' into Google we found minimalist opinions such as: 'The only available treatment for kidney failure from ADPKD is dialysis. The only available cure is kidney transplantation.' Together with the crosslink to the paper: '*Therapy for polycystic kidney disease? It's water, stupid!*'[45] Wikipedia extensively cites Tolvaptan, the PKD foundation offers a detailed list of the on-going trials, while the PKD Charity UK dedicates a webpage to complementary therapies and includes data on diet, Tolvaptan, everolimus, somatostatin, and lanreotide. The latter represents the three major therapeutic approaches aimed at interfering at different levels with cyst formation and growth.

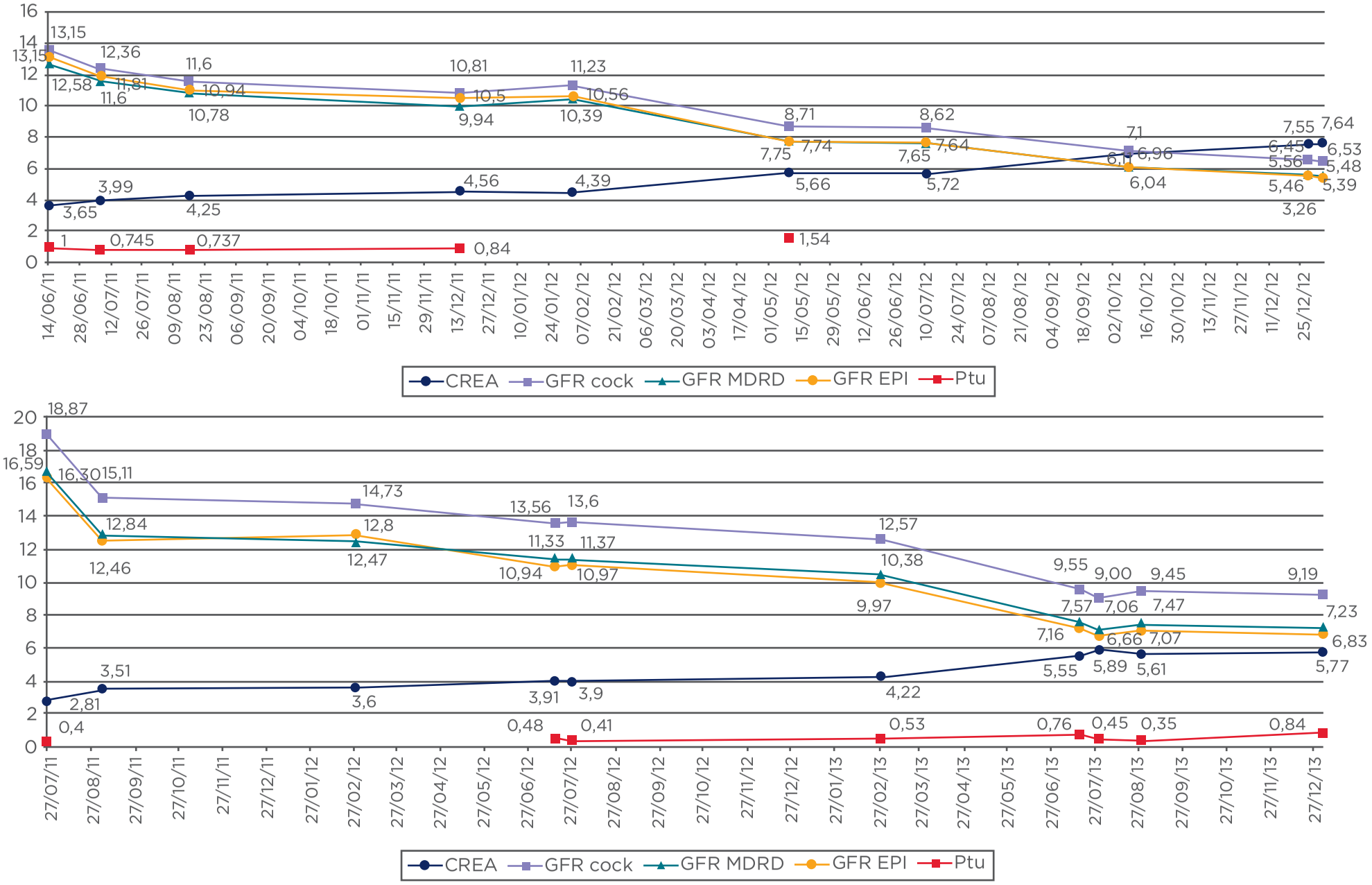

Figure 1: Long-term follow-up of ADPKD patients on a vegan supplemented (0.6 g/day) LPD.

ADPKD: autosomal dominant polycystic kidney disease; LPD: low protein diet; CREA: creatinine; GFR: glomerular filtration rate; cock: Cockcroft-Gault; MDRD: modification of diet in renal disease; EPI: epidemiology collaboration; Ptu: propylthiouracil.

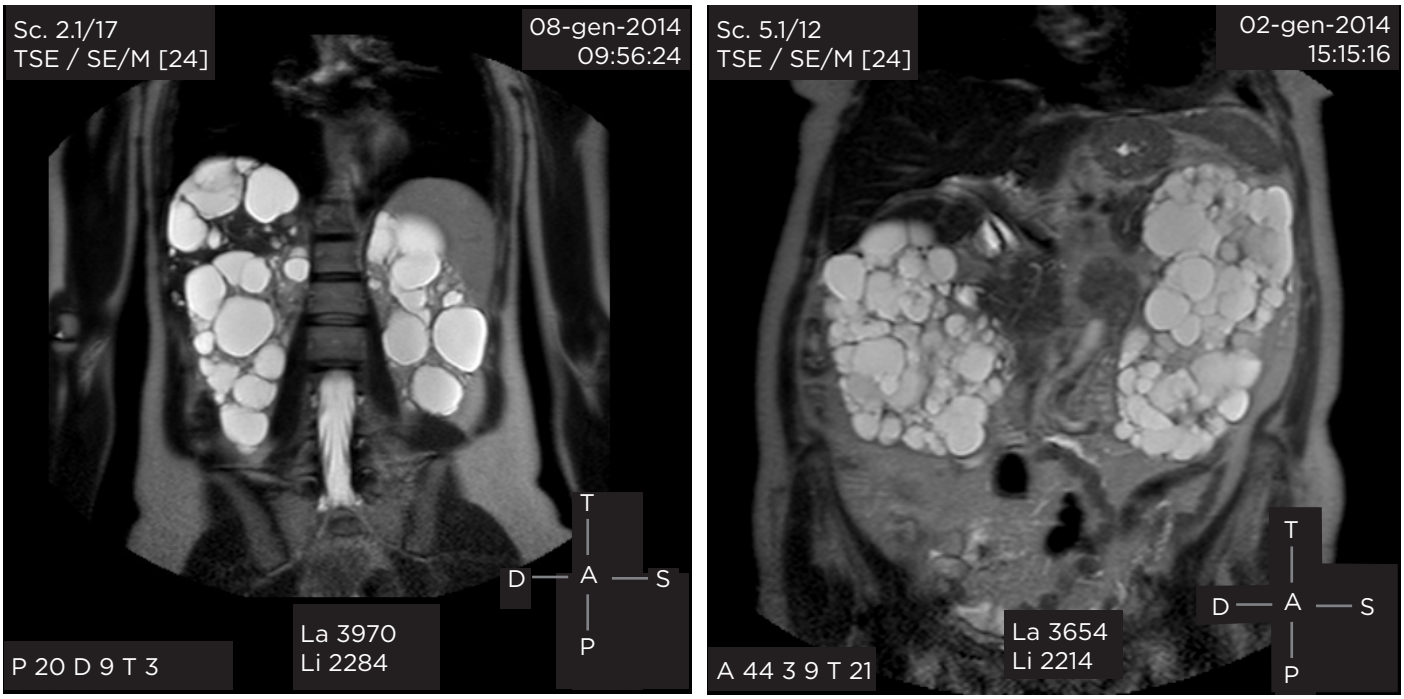

Figure 2: NMR in two cases, exemplificative of the spectrum of ADPKD: a few large renal cysts versus complete structural derangement, mainly linked to a myriad of small cysts.
NMR: nuclear magnetic resonance; ADPKD: autosomal dominant polycystic kidney disease.

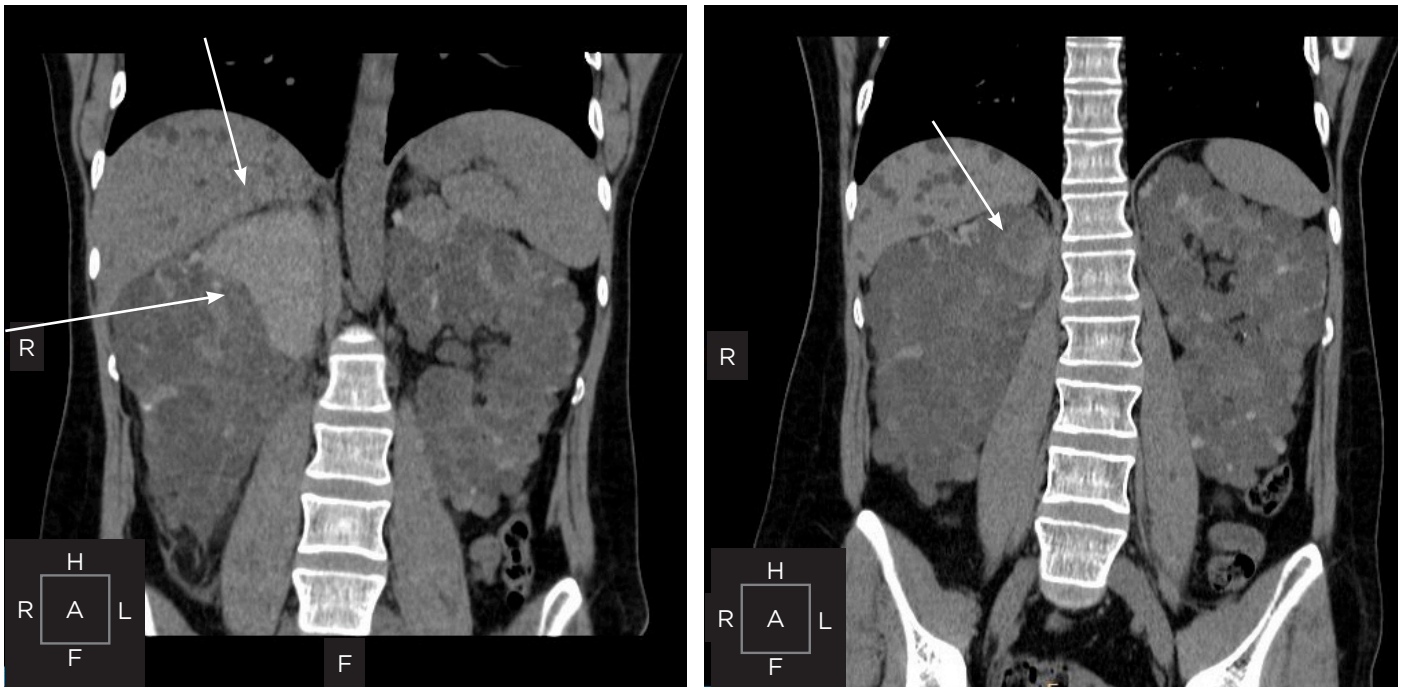

Figure 3: Massive intracystic bleeding, mimicking kidney rupture in the first computerised tomography scan, and evolution of the lesion over time. On the account of the residual chronic pain, and of the large polycystic kidneys and liver, the patient was started on once-monthly therapy with octreotide LAR.

All trials opened new questions and provoked further issues, such as the best compromise between toxicity, long-term risk and advantages - in particular in the case of rapamycin and the other mTOR inhibitors - and of the effect on quality of life in the case of Tolvaptan and other vaptans. The high costs of therapies, and of vaptans in particular, adds to the difficulty in widening the experience out of the research setting.[70-75]

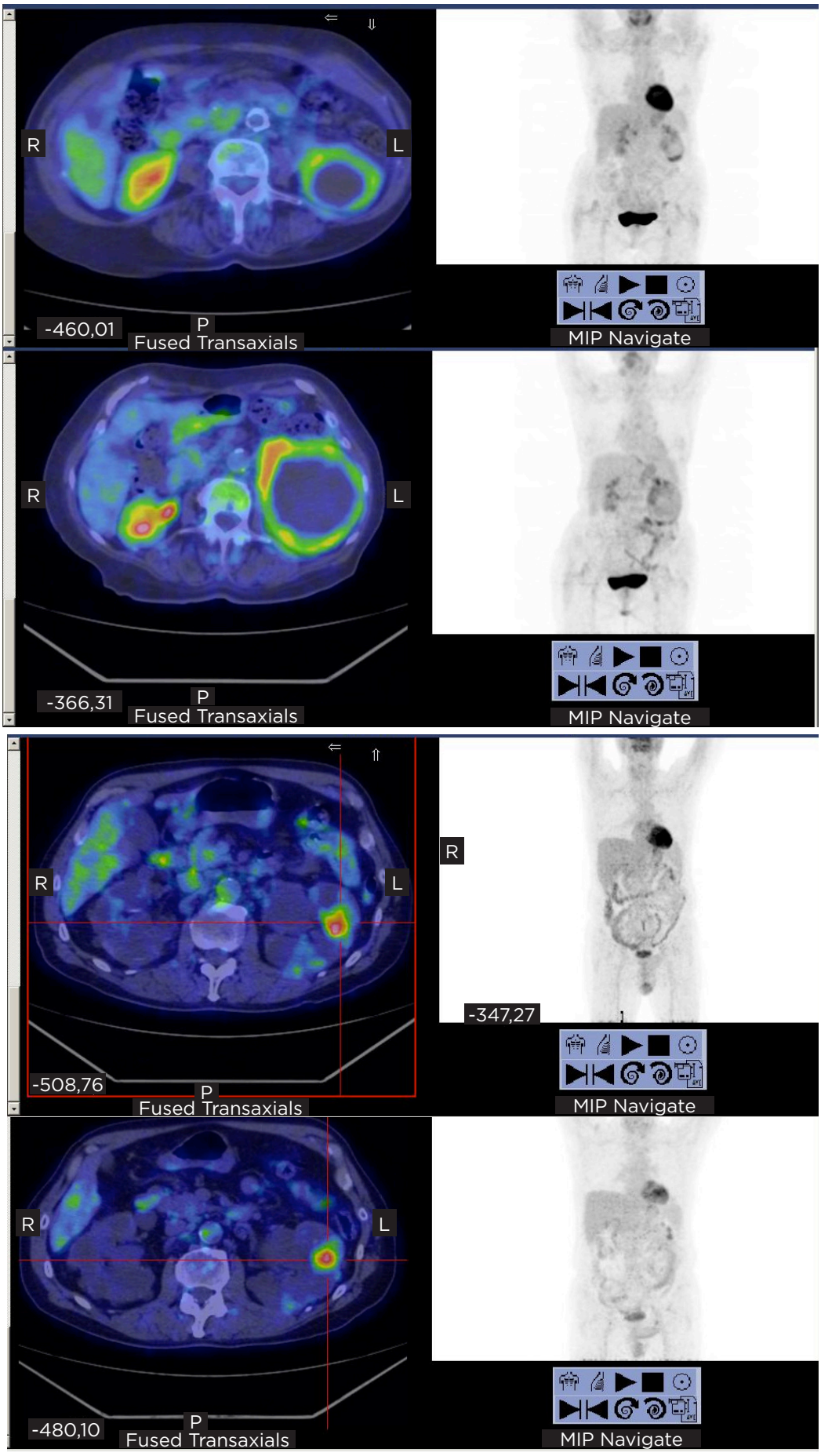

Figure 4: Fludeoxyglucose-positron emission tomography scan of infected liver and kidney cysts, and evolution after long-term antibiotic therapy.

A partial exception to the inconsistency of the trial results regards somatostatin, or its analogues in the hepatorenal variant of ADPKD, as well as in the isolated polycystic liver, genetically different but phenotypically similar. The reduction of the cysts, overall significant in the large polycystic livers, is also recorded in the kidneys, albeit at a lower degree. However, as highlighted by the ALADIN study, the lack of significant side-effects and the absence of a 'rebound effect' after discontinuation may alter the cost-benefit balance in favour of therapy, whose effects appear to be more consistent in women of childbearing age.[74-76]

Hence, the discussion on the indications is ongoing, at least in the countries where ADPKD with liver involvement is considered as a rare disease, easing the prescription process. Consequently, octreotide and analogues are slowly entering into clinical practice, while the other options are still limited to the research setting. Regarding patients with isolated kidney involvement, mainly because of prescription constraints, the 'new' therapeutic options are presently limited to the research setting.

Three main indications are presently followed for octeotide therapy: the presence of large and rapidly growing cysts, chronic pain, and abdominal distension.[54] However, the suggestion that the best results are recorded in relatively young patients, and the focus shift from reduction of the volume to stabilisation of the lesions, may lead to an anticipation of this therapy whose costs are, however, a relevant drawback in this era of healthcare cost constraints.[76]

In this interlocutory phase, our choice has been to start treatment for ADPKD patients with liver involvement and symptomatic disease. The discussion on the rapid progress of knowledge should, in our opinion, be a part of the counselling to patients and should be the basis for planning a regular follow-up also in presymptomatic cases.

CONCLUSIONS

The working conclusions of this clinical non-systematic review may be summarised in four major points. The first is the increasing knowledge in the face of therapeutic uncertainties. The balance between rapidly growing knowledge and a long list of unanswered questions poses a challenge for counselling, but may also set the basis for a constructive patient-physician relationship. The second is the suggestion to start follow-up early and to characterise the preclinical cases since the indications to 'new' treatments are changing and the timing for intervention is switching to earlier phases. Furthermore, an earlier follow-up may allow easier timely interventions on BP and on UTIs. The third is to consider that dietary interventions are not expensive and may be effective. Following a diet may be difficult and is probably not 'fitting' for all patients but, considering the high costs and the low availability of other 'specific' treatments, a diet trial may be worth offering to all cases, at least for selecting those in which a better balance compliance-diet may be attained. Lastly, we would like to call for attention on some specific situations: pregnancy that should be followed as a high-risk condition, also in the presence of normal renal function and BP; intracystic infections, whose diagnostic gold standard is the PET scan; the association with polycystic liver; and the presently better defined 'niche' for 'new' treatments. All of these are but working conclusions and the authors are aware that all of them may be shortly out-dated by the rapid improvement in diagnosis and therapy that render this disease a fascinating field not only for the researcher, but also for the clinical nephrologist.

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