# Defective Glycolysis and the Use of 2-Deoxy-D-Glucose in Polycystic Kidney Disease: from Animal Models to Humans

**Abstract**

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited renal disease characterized by bilateral renal cyst formation. ADPKD is one of the most common rare disorders, accounting for ~10% of all patients with end-stage renal disease (ESRD). ADPKD is a chronic disorder in which the gradual expansion of cysts that form in a minority of nephrons eventually causes loss of renal function due to the compression and degeneration of the surrounding normal parenchyma. Numerous deranged pathways were identified in the cyst-lining epithelia leading to the design of potential therapies. Several of these potential treatments proved effective in slowing down disease progression in pre-clinical animal studies, while only one has subsequently been proven to effectively slow down disease progression in patients and has recently been approved for therapy in Europe, Canada and Japan. Among the affected cellular function and pathways, recent investigations have described metabolic derangement in ADPKD as a major trait offering additional opportunities for targeted therapies. In particular, increased aerobic glycolysis (the Warburg effect) has been described as a prominent feature of ADPKD kidneys and its inhibition using the glucose analogue 2-deoxy-D-glucose (2DG) proved effective in slowing down disease progression in preclinical models of the disease. At the same time, previous clinical experiences were reported with 2DG showing that this compound is well tolerated in humans with minimal and reversible side effects. In this work we review the literature and discuss the possibility that 2DG would be a good candidate for a clinical trial in humans affected by ADPKD.

**Brief Overview of ADPKD**

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited renal disease that accounts for ~10% of all patients with end-stage renal disease (ESRD) in Europe [1]. Precise prevalence of this condition is unknown but according to the main epidemiological studies 3.29 to 3.96 :10.000 people is the most likely estimated prevalence in Europe [2]. ADPKD is characterised by the development of numerous fluid-filled renal cysts that originate in a small proportion (1−2%) of nephrons [3,4]. Although cysts develop starting early, due to compensatory hyperfiltration in non-cystic tubules, renal function decline does not usually become apparent until the fourth or fifth decade of life[4]. Progressive cyst formation leads to fibrotic degeneration of the surrounding parenchyma including the nephron units not directly affected by cyst formation. This process results in significant enlargement of the kidney and in additional symptoms such as pain, hypertension, haematuria, cyst and urinary tract infections and ultimately renal failure [4].

ADPKD is caused by mutations in the *PKD1* or *PKD2* genes, accounting for approximately 85% and 15% of cases, respectively [5]. Patients carrying *PKD1* mutations, particularly truncating mutations, show a faster progression towards loss of renal function as compared to those with inherited *PKD2* mutations. This is reflected in the median age at onset of ESRD being approximately 58 years and 79 years, respectively [6].

ADPKD has been for a long time a condition not susceptible of any specific treatment, but clinically manageable only through the control of its many complications. The paradigm has changed radically in recent years through the identification of several potential targets for therapy. These have been validated on cellular and animal models and in some cases had a translational outcome in small controlled pilot studies. Some of these studies have failed validation in medium or large randomized trials[7-9], while in at least one case, with the vasopressin antagonist tolvaptan, the process has come to the registration in Europe and other countries of the first drug active in ADPKD[10].

In this very focused review, we will highlight recent discoveries pointing to a central role of metabolic derangements in the pathogenesis of ADPKD. In particular, we will focus on the role of defective glycolysis (the Warburg effect) in ADPKD and in the possibility to target this deregulation by using a glucose analogue, 2-deoxy-D-glucose (2DG). We try to collect here all the evidence derived from animal studies and from humans that, taken together, define the possibility to use 2DG in clinical trials for ADPKD.

**Glucose metabolism and the Warburg Effect: Brief overview**

Glucose is the main source of energy for the cells. This simple sugar is metabolized through a process named glycolysis (Figure 1). Glucose is transported into the cell by facilitative transporters (GLUT1-4) and phosphorylated in position 6 by the enzyme hexokinase (Hexokinases 1 or 2, HKs) [11][12]. Eight additional enzymatic reactions take place in the cystosol leading to the generation of two pyruvate molecules per glucose molecule[11]. Of all these reactions, three are crucil because they are "unidirectional" (Figure 1). In the presence of oxygen, pyruvate is normally transported into mitochondria where it is converted into Acetyl-CoA that enters the tricarboxylic acid (TCA) to be fully oxydized and to generate approximately 16 molecules of ATP per molecule of pyruvate[11],[12] (Oxidative Phosphorylation or OXPHOS, Figure 1).

In the absence of oxygen, pyruvate is instead converted into lactate in the cytosol (Anaerobic glycolysis, Figure 1). In hyperproliferative conditions, such as in the case of cancer, cells tend to use this inefficient process, even when oxygen is available[12], for unclear reasons. This pathological condition is called "aerobic glycolysis" or the "Warburg effect" and it is one of the hallmarks of cancer[12]. Since generation of energy though aerobic glycolysis is much less efficient than oxydative phosphorylation (OXPHOS) in mitochondria, cells typically upregulate the entire process of glucose import and its cytosolic degradation[12]. The Warburg effect can be often observed also in response to defective mitochondrial activity and when other sources of energy fail to fuel mitochondria, such

as defective Fatty acids or aminoacids oxidation. Of interest, many different signaling pathwyas can drive upregulation of key glyoclyitic enzymes so that, in critical conditions such as Fatty Acids Oxidation defects, FAO), cells can upregulate the consumption of glucose and generate the minimal energy required for survival and/or proliferation.

**Defective Glucose metabolism in ADPKD: evidences from animal models**

Animal models of PKD have proven very helpful over the years in helping translational research to both understand the pathophysiology of the human disease and to identify potential new therapies. Animal models of PKD range from non-orthologous models (i.e. carrying mutations in genes other than the *Pkd1* or *Pkd2* genes) to the more faithful orthologous models (i.e. those carrying mutations in the same genes mutated in humans, *Pkd1* and *Pkd2*).

Using various models a number of recent studies have suggested that metabolic derangement appears to be a key feature of polycystic kidney disease, with some differences reported between orthologous and non-orthologous [13-18]. While the non-orthologous models of the disease are appropriate models for the ciliopathies in general and could be valuable confirmatory models for therapeutic approaches, the recent generation of mice carrying mutations in the *Pkd1* and *2* genes have become generally accepted as better models to mimick the human condition of ADPKD and further investigations should concentrate on these, at least to validate results obtained in non-orthologous models.

Previous studies have shown that defective glucose metabolism is a hallmark of ADPKD[14]. In particular, it was described that cells, murine PKD kidneys lacking the *Pkd1* gene and finally the epithelia lining the cysts derived from human specimens tend to rely heavily on glucose as an energy source and to convert it into lactate, indicating that they preferentially use anaerobic glycolysis even when oxygen is available to them [14]. Subsequent studies on *Pkd1* mutant cells have reported contradictory results with some studies confirming these original findings [16,19] and some others

failing to identify a prominent glycolytic response using cell lines [13,20]. While not all authors provided a possible explanation for the inconsistent results, one possibility is that different isolation, immortalization and/or culture conditions in cells might be responsible for strongly altering the baseline metabolic characteristic of cells, providing a possible explanation. To circumvent this possible limitation, Rowe et al. employed metabolic flux analysis *in vivo* using $^{13}$C-labelled glucose in orthologous PKD models with a variable degree of severity [14,18]. In all cases it was reported that cystic kidneys tend to uptake more glucose and to convert it into lactate [14,18]. Therefore, the use of metabolic flux analysis using $^{13}$C-labelled molecules could be used as a more accurate way for studying the phenomenon in animal models of the disease as widely accepted in other fields and possibly allowing to reconcile some of the inconsistencies [14,18].

Based on these results preclinical studies were designed to test whether interfering with glycolysis could have a beneficial effect on disease progression at least in mice. Indeed, 2DG was able to revert the glycolytic response in PKD kidneys. Using, again, metabolic flux analysis *in vivo* by co-injecting in the mouse $^{13}$C-labelled glucose and 500mg/kg of 2DG [14], it was reported that 2DG was not able to counteract the increased uptake of glucose as expected [14,18], but was able to counteract its conversion into lactate. In addition, 2DG was able to retard disease progression in two distinct aggressive models of the disease [14], as well as in slowly progressive PKD model upon administration of low doses 2-DG for 2 and half months followed by *in vivo* analysis of kidney volumes [18]. Importantly, a subsequent very detailed study has addressed the role of glycolysis in a non-orthologous model of PKD, the Han:Sprd rat [16]. In this case, microarrays analysis of cystic versus non cystic kidneys shows a marked signature of increased glycolysis [16] although *in vivo* flux analysis using $^{13}$C-labelled glucose was not employed in this case to verify the biological role of this transcriptional de-regulation. However, the use of 2DG was proven to be effective in retarding disease progression in this study, including improving renal function [16]. Taken together these studies define metabolic regulation as a potential important factor in the pathogenesis and/or progression of

Polycystic Kidney Disease and as a potential target for therapy 1[14-16,18]. In particular, these studies show the efficacy of 2DG in retarding disease progression in preclinical models.

**Potential defects in Glucose Handling in ADPKD Patients**

Clinical abnormalities of glucose metabolism in terms of risk of diabetes and glucose intolerance have been described in a discrete number of published papers. Most of them have explored the risk of new onset diabetes in patients who have undergone kidney transplantation (NODAT): in fact the immunosuppressant regimen that transplant receiver is exposed to has an elevated diabetogenic potential. The evaluation of this population exposed to an increased diabetogenic state has the potential advantage of revealing a mild basal metabolic abnormality due to ADPKD itself. The identification of the same abnormality in the general ADPKD population would eventually require a much larger sample size to be revealed. The conclusions from the different authors are extremely heterogeneous, some of them reporting a positive association between transplantation and NODAT [21-29] while others not confirming the association [30-35].

Recently a metanalysis pooling together twelve of these studies tried to shed some light over the ambiguity of this conflicting topic [36]. Even considering the inherent limitations to this approach (and in particular the heterogeneity of the collected studies that differ in the definition of the outcome and in the ability to report confounders), still it is worth keeping it into account. In fact, the metaanalysis suggests a possible increased risk of diabetes in ADPKD; the pooled relative risk (RR) for NODAT in patients with ADPKD is statistically significant (RR = 1.92) as compared to those who received kidney transplants from other causes. A subanalysis for potential confounders for the risk of diabetes (risk adjusted for independent factors of diabetes) showed a significant risk associated to ADPKD (RR = 1.98). However, a further subanalysis comprising only studies that collected patients requiring insulin treatment could not confirm a significant positive association. In the attempt to justify this inconsistency, the authors suggest that the underlying mechanism of ADPKD-related NODAT could be insulin resistance, not reduction of insulin secretion. Notably the authors suggest

that all the studies had a short follow up and that the development of insulin treatment requirement could have needed a longer evaluation. Finally, the missing confirmation of the association because of reduction of statistical power (for this analysis 3 of 12 studies were selected) cannot be excluded.

There are other small-medium sized reports that analyzed insulin secretion [37] and insulin resistance [38,39] in nontransplant ADPKD patients with a variable rate of renal function. Data are conflicting for insulin resistance and overall insufficient for a conclusive statement for insulin secretion. Irrespective of the problem of the increasing risk of diabetes in ADPKD, a case control study evaluated the effect of diabetic condition in survival and other clinical characteristics of a cohort of ADPKD patients in a longitudinal follow up [40]. ADPKD patients affected by diabetes compared to patients without diabetes presented larger kidney and earlier hypertension onset; however renal survival was not significantly different between the two groups.

Considering all these heterogeneous data together a signal of an increased risk for diabetes in ADPKD can be suspected. This hypothesis is worth further evaluation in consideration of the potential of disclosing new unanticipated pathogenic pathways in this condition. Furthermore this risk is clinically relevant and could accordingly suggest modification in the patient management, for example in the choice of immunosuppressant regimen in transplant candidates.

**Mechanism of activity and safety profile of 2DG in animal models**

Glucose is the principal source of energy for the cell, which metabolizes it through a process named glycolysis. Glucose is transported into cells by facilitative transporters (GLUT1-4) and trapped when the enzyme hexokinase (or glucokinase in the liver) phosphorylates it in position 6 [41,11,12]. Eight additional enzymatic reactions occur in the cystoplasm leading to generation of two molecules of pyruvate [41,11,12] . In the presence of oxygen, the majority of pyruvate is imported into mitochondria where it is degraded through the tricarboxylic acid (TCA) to fuel the electron transport chain which eventually results in generation of approximately 15 molecules of ATP per molecule of pyruvate [41,11,12] .

In the absence of oxygen, pyruvate tends to be converted into lactate in the cytosol. In physiological conditions this process is called anaerobic glycolysis (also known as the Pasteur effect) and, although it is not as effective as the TCA cycle in generating ATP, it ensures cell survival in the absence of oxygen [41,11,12]. For reasons that are not fully understood, cancerous cells use this inefficient process, even in the presence of oxygen [12]. In this pathological condition the same process of pyruvate to lactate conversion is called aerobic glycolysis or the Warburg effect, considered a hallmarks of cancer [12]. Since generation of energy through aerobic glycolysis is much less efficient than energy production through oxidative phosphorylation in the mitochondria, cells relying on this process upregulate glucose import and its cytosolic degradation [12]. Many of the enzymes involved in glycolysis are targets of the hypoxia-inducible factor (HIF1$\alpha$), a transcription factor strongly upregulated in the absence of oxygen [42]. Reduction of oxygen is not the sole regulator of HIF1$\alpha$ levels, as the mTORC1 pathway is also able to regulate this molecule [41,42]. the discovery that the Warburg effect is observed in PKD opens interesting opportunities including the use of 2DG to slow down disease progression as indicated above. 2DG is uptaken by the cells, phosphorylated by hexokinase and trapped into the cell, but it cannot be further catabolized. Thus, this compound is in fact competing with glucose and preventing PKD mutant cells to use their favorite source of energy for proliferation and survival. The strategy had been extensively used in animal models of cancer prior to being tested in PKD [14,15,18].

The Warburg effect in PKD might also offer the opportunity to test additional compounds able to inhibit this process in different steps of the glycolytic cascade, a few of which are in phaseII/III clinical trials [11]. Thus, in principle, the defective glucose metabolism in PKD might offer additional opportunities for intervention besides 2DG, although this compound acts upstream in the very first step of the glycolytic cascade and might have several advantages over compounds able to act downstream [11]. Finally, it should be mentioned that a recent study has shown that food restriction has a great impact and retards the progression of PKD [20]. 2DG has also been considered in the past as a calorie restriction mimetic given its capability to reduce metabolic rates in cells, thus it is

reasonable to think that food restriction and 2DG likely act through similar mechanisms of action [14,20].

Several previous studies, including our performed in PKD models, have shown low doses of 2DG do not lead to toxicity effects even upon chronic administration [43,44]. It should be considered that a single study has shown that chronic prolonged ingestion of high doses of 2DG (250mg/kg/die) caused heart vacuolization in the rat [45]. Other studies have reported that chronic intraperitoneal injections of even higher doses (500 mg/kg/die) did not cause major toxicity in the rat [43]. Nevertheless the single study reporting toxicity has brought some degree of caution about the use of 2DG in humans. It should be considered however that subsequent studies in humans have shown that no serious side effects could be observed in response to 2DG administration (see below).

One special consideration should be made with respect to the dosage of 2DG. In a first study high doses of 2DG were employed in the mouse (500mg/kg) for only two days and this resulted in a significant improvement in the size of the kidney[14]. For these studies, the animals were treated as pups at postnatal day 6 to 8. At this stage, animals tend to be very sensitive to any type of treatment and some degree of toxicity was observed, including mortality in a few pups both in the wild-type and in mutant mice (Chiaravalli, Rowe and Boletta, unpublished). It is hard to determine whether this toxicity is specifically due to the use of 2DG or rather due to the delicate nature of newborn animals, since treatment of mice at this age also resulted in some degree of mortality irrespectively of the molecule used, including metformin and tolvaptan (Chiaravalli, Rowe and Boletta, unpublished). In all cases, subsequent studies in the adult showed that animals treated with even very high doses of 2DG (500mg/kg) do not show any type of suffering [16,43]. Furthermore, when 2DG was used for 2.5 months in a slowly progressive model of PKD at a dosage of 100mg/kg/die for 5 days a week, no signs of toxicity were found [18]. A thorough histological and biochemical analysis of these animals revealed no signs of toxicity. Furthermore, behavioral studies further showed no evidence of toxicity of this compound. This is encouraging because based on the human equivalent dose [46] 100mg/kg

in the mouse correspond to approximately 8,1mg/kg in the human and this dose is several folds lower than the described tolerated dose of 63 mg/kg according to previous clinical trials (see below).

**Clinical studies safety profile of 2DG in humans**

A wide range of possible clinical indications has been proposed for 2DG. Among the most consistently reported in literature there are antiviral activity, caloric restriction activity and antineoplastic activity. Despite the increasing number of *in vitro* and preclinical reports for a wide group of indications, few human clinical trials have been published and these are exclusively related to the antineoplastic activity of 2DG [47-50].

The antiviral effect of 2-DG has been demonstrated *in vitro* against a variety of enveloped viruses [51-54]. Viruses dramatically modify cellular metabolism in the attempt to optimize their efficiency of replication. Virus-induced metabolism may provide increased pools of free nucleotides necessary for rapid viral genome replication as well as increased amino acid production for rapid virion assembly, lipid material may be needed to provide material for envelopment of the viral particles. Adjustments to metabolic pathways may be required to provide ATP in a rapid fashion for the high energy cost of replication. Despite of the interest in 2DG as antiviral agent and many publications of in vitro inhibition, clinical data regarding this strategy are not publicly available at this time [54,53,52].

2DG also has been proposed as a possible caloric restriction mimetic. Reduction in calorie intake produces a significant extension of both mean and maximal lifespan in laboratory rodents; this effect has been unambiguously reproduced in a number of different animal models and confirmed in nonhuman primates [55]. Because of this strong effect and high difficulty in adopting a stringent caloric regimen in the clinical setting, there is a significant interest in the pharmacological approach of caloric restriction mimetics and 2DG is a good candidate. Interestingly 2DG showed the ability to

extend lifespan in a nematode model [56], however rodents data are not conclusive yet [45,57,43,58,59] while human studies are not available.

The transition to aerobic glycolysis is advantageous to cancer cells because it confers to them a survival and proliferative advantage. While the general view is widely accepted by the scientific community, details and precise cellular mechanisms of aerobic glycolysis and its induction are elusive and still controversial [60-62,11]. Although aerobic glycolysis represents a replicative advantage, at the same time this could turn into weakness for neoplastic cells and indeed a therapeutic opportunity: in fact, at least some tumor types become almost completely dependent on the glycolytic pathway for their energetic need and inhibiting this process may obtain the death of the cancer cell itself. Although the Warburg effect is not completely applicable to all cancers, this phenomenon is a largely prevalent process between many neoplasms [60]. Accordingly the glucose analog 2-Deoxy-D-glucose (2DG) theoretically is a promising treatment for many cancers, either by itself, or in combination with radiotherapy or chemotherapy [63].

The first documentation of the use of 2DG in a human treatment was reported in 1958 in five patients affected by different type of malignancies (islet cell carcinoma, acute myeloid leukemia, chronic lymphocytic leukemia, acute lymphocytic leukemia, bronchogenic carcinoma)[50]. 2DG was administered intravenously and orally at dosage that ranged from 50 to 200 mg/kg. The authors described that the patients tolerated well the treatment with the exception of episodes of drowsiness, facial flush, diaphoresis, warmth that could be promptly reversed by glucose infusion. In one woman affected by acute myeloid leukemia tachycardia was recorded and the ECG showed premature ventricular beats that were not appreciated in a previous exam. In this study, all the patients developed hyperglycemia during infusion or oral administration of 2DG.

The first clinical experience of 2DG in a group of healthy subjects is reported in an American study in 1961. In this study 11 patients were tested to study the metabolic parameters related to plasma levels of free fatty acids, glucose and lactate [50].

Two studies in the 70s evaluated the 2DG as pharmacologic assessment of the procedure success in patients having undergone to surgical vagotomy [64,65]. The two studies report a case series of 85 patients of which 75 were investigated with continuous ECG (see below for further details). Subjects were administered a 60 mg / kg oral dose of 2DG, with the exception of two subjects that were treated by 50 mg/kg and 70 mg/kg respectively. The authors declared that in no case there were symptoms that advised discontinuation of the protocol. The reported symptoms were related to a hypoglycemic-like condition (drowsiness, hunger, sweating) and were rapidly reversible with the administration of glucose.

More recently another Clinical Trial about the use of 2DG was published in 2005 and evaluated the use of inhibition of glycolysis associated to radiotherapy in glioblastoma [49]. In this setting the driving idea is to enhance the efficacy of radiotherapy by selectively sensitizing cancer cells by 2DG. In this trial an escalating 2-DG dose during combined treatment (2-DG and radiotherapy) has been tested in untreated patients with histologically proven glioblastoma multiforme. Escalating 2-DG doses (200–250–300 mg/kg BW) were administered orally 30 min before irradiation after overnight fasting. The treatment was well tolerated at 2DG dosage up to 250 mg/kg. At the highest dosage (300 mg/k) two out of six patients experienced restlessness and could not complete the protocol. However even at the lower dosage (that was any way a relatively high dosage if compared to other neoplastic trials of 2DG) most of the patients referred symptoms resembling hypoglycemia. The discontinuous high dosage of 2DG used in this trial addresses the need of an acute treatment strategy for sensitization of cancer cells before radiotherapy: this therapeutic regimen has a different rationale compared to the aim of a continuous and chronic inhibition of cystogenesis that was adopted in preclinical experience of 2DG in the mouse ADPKD model [18,14].

A later study evaluated the use of 2DG in patients affected by prostatic cancer (9 patients) and other solid tumors (3 patients: nasopharynx, lung and cervix cancer). In this study an escalating approach has been adopted to evaluate the maximum tolerated dosage. This trial collected some interesting data about pharmacokinetics, FDG-PET imaging as a marker of drug uptake and p62 protein levels as

markers of autophagy. The starting dose for this study was 30mg/kg of 2DG administered orally on a daily schedule for 2 weeks (days 1–14) of a 3-week (21 days) cycle. During the study dose levels were increased from 30 to 45, and 60 mg/kg. The authors considered the dose of 45 mg/kg as the recommended dose for future phase II trials. The dose was chosen because of two patients that experienced a dose-limiting toxicity of grade 3 (asymptomatic QTc prolongation) at the dose of 60 mg/kg. The authors reported that none of the 5 patients treated at the dose of 45 mg/kg experienced any dose limiting toxicity or electrocardiac abnormality; fatigue and dizziness were the prevalent adverse events in these patients. The nature of the alteration of cardiac electrophysiology is not clear but could be related to myocardial toxicity. A toxicity of this nature has been reported in rats treated at high dose of 2DG [45], in humans two previous reports of prolonged QT interval were described in the already cited studies of 2DG stimulation of gastric acid production[64,65].

In these studies 75 patients (27 in the first report[65] and 48 in the second[64]) were recruited and exposed to 2DG. A group of these patients developed non-specific T wave flattening and QT prolongation, without any event of serious arrhythmias [64,65].

The late available study of 2DG in humans was published in 2013 and reports the result of an association regimen of 2DG and docetaxel, an anti-mitotic chemotherapy approved for treatment of locally advanced or metastatic breast cancer, head and neck cancer, gastric cancer, hormone-refractory prostate cancer and non small-cell lung cancer. In this study the authors applied a modified accelerated titration design to evaluate the maximum tolerated dosage (MTD) of 2DG. Notably the MTD was not formally defined in this study because patient did not experience any dose limiting toxicity specified by the protocol. Based on the overall tolerability of the treatment the authors suggested a 2DG dosage of 63 mg/kg in phase II trials. In fact starting from this dose and at the higher dose of 88 mg/kg patients presented plasma glucose levels above 300 mg/dL and symptoms of glucopenia (sweating, confusion, weakness and dizziness). Other significant adverse effects recorded during the trial at 63-88 mg/kg doses were gastrointestinal bleeding (6 %) and reversible grade 3 QTc prolongation (22 %). After the end of the study one patient died from a serious adverse event of

cardiac arrest 17 days after the last dose of 2DG. Final ECG done 10 days before death showed persistent T-wave inversion and no QTc prolongation. However, it should be noted that the eligibility criteria of patients in this study with advanced or metastatic solid tumors could have played a confounding role in relation to survival.

**Concluding remarks**

Unexpectedly metabolic deregulation has become an important key to understanding the pathophysiology of ADPKD. As previously reported, qualitatively suboptimal but converging data are available on a possible increased risk of insulin resistance in ADPKD patients. In parallel, widely replicated data in a large majority of independent research groups have recognized in animal models a profound metabolic derangement and in particular an increased glucose avidity by cystic cells (Warburg effect). Finally the metabolic interference by a known inhibitor of glycolysis, 2DG, has demonstrated in multiple animal models the ability of slowing the progression of cystic disease. All these elements suggest that this metabolic pathway may be a rational therapeutic target. The 2DG is a molecule for which a discrete previous clinical experience is provided. The demonstrated efficacy in murine models and apparent good tolerability profile in earlier clinical trials pose this molecule as the natural candidate in a pilot clinical trial. Nevertheless, other molecules that insist on the same metabolic pathway and in advanced stages of drug development are placed in a very interesting position in future therapeutic approach of ADPKD.

**Aknowledgements**

We are grateful to several colleagues and friends for helpful discussions, to Angela Pesenti Gritti for careful and essential collection of the literature and to Dr. S. Bramani for her generous and continuous support.

**Ethical Statement**

The authors declare that this review was written in compliance with the ethical requirements of Journal of Nephrology.

| | Singh D et al. 2005[49] | Stein M et al. 2010[48] | Raez LE et al 2013[47] |
|---|---|---|---|
| ***Phase*** | I | I | I |
| ***Disease*** | glioblastoma multiforme | Prostate Cancer or other solid tumor | Advanced Solid Tumor |
| ***Patients*** | 12 | 12 | 34 |
| ***Dose*** | 200–250–300 mg/kg | 30 – 45 – 60 mg/kg | Uptitration from 2 mg /kg to 88 mg /kg |
| ***Treatment Regimen and Duration*** | 7 administr. ; 1 per week | Daily admin. for 2 wks /on a 3 wks cycle; 6 weeks | 7 daily doses during weeks 1 and 3 of every 4-week cycle; (Docetaxel on day 1 of weeks 2, 3 and 4) ; duration 16 weeks |
| ***Toxicity*** | Excess sweating, transient disorientation, restlessness , vomit, headache | fatigue, QTc prolongation | hyperglicemia, excess sweating, disorientation, fatigue, gastric bleeding, QTc prolongation, 1 death |

*Table 1: main charecteristics and data of published clinical trial of 2DG*

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