



Disponible en ligne sur

ScienceDirect
www.sciencedirect.com

Elsevier Masson France

EM|consulte
www.em-consulte.com

**Annales
d'Endocrinologie**
Annals of Endocrinology

Annales d'Endocrinologie xxx (2018) xxx–xxx

Consensus

Expert opinion on the metabolic complications of mTOR inhibitors

Avis d'experts sur les complications métaboliques des inhibiteurs de mTOR

Benjamin Bouillet^{a,b,*}, Perrine Buffier^a, Sarra Smati^c, Françoise Archambeaud^d, Bertrand Cariou^c,
Bruno Vergès^{a,b}

^a Service d'endocrinologie, diabétologie, maladies métaboliques, CHU de Dijon, 2, boulevard du Maréchal-de-Lattre, BP 77908, 21000 Dijon, France

^b Unité Inserm, LNC-UMR 1231, université de Bourgogne, Dijon, France

^c Clinique d'endocrinologie, Institut du Thorax, CHU de Nantes, Nantes, France

^d Service de médecine interne B, endocrinologie, 87042 Limoges cedex, France

Abstract

Using mTOR inhibitors (mTORi) as anticancer drugs led to hyperglycemia (12–50%) and hyperlipidemia (7–73%) in phase-III trials. These high rates require adapted treatment in cancer patients. Before initiating mTORi treatment, lipid profile screening should be systematic, with fasting glucose assay in non-diabetic patients and HbA_{1C} in diabetic patients. After initiation, lipid profile monitoring should be systematic, with fasting glucose assay in non-diabetic patients, every 2 weeks for the first month and then monthly. The HbA_{1C} target is $\leq 8\%$, before and after treatment initiation in known diabetic patients and in case of onset of diabetes under mTORi. LDL-cholesterol targets should be adapted to general health status and cardiovascular and oncologic prognosis. If treatment is indicated, pravastatin should be prescribed in first line; atorvastatin and simvastatin are contraindicated. Fenofibrate should be prescribed for hypertriglyceridemia > 5 g/l resisting dietary measures adapted to oncologic status. In non-controllable hypertriglyceridemia exceeding 10 g/l, mTORi treatment should be interrupted and specialist opinion should be sought. © 2018 Elsevier Masson SAS. All rights reserved.

Keywords: Diabetes; Dyslipidemia; mTOR inhibitors

Résumé

L'utilisation des inhibiteurs mTOR (mTORi) comme anticancéreux est responsable d'hyperglycémies (12–50 %) et d'hyperlipidémies (7–73 %) dans les études de phase III. Ces chiffres élevés justifient une prise en charge adaptée à la population oncologique. Avant l'instauration d'un traitement par mTORi, nous recommandons la réalisation d'une exploration d'une anomalie lipidique (EAL) chez tous les patients, d'une glycémie à jeun chez les patients non diabétiques et d'une HbA_{1C} chez les patients diabétiques. Après instauration du traitement, une surveillance de l'EAL (tous patients) et de la glycémie à jeun (patients non diabétique) est recommandée tous les 15 jours le premier mois puis mensuellement. Nous recommandons un objectif d'HbA_{1C} inférieur ou égal à 8 %, avant et après l'instauration du traitement chez les patients diabétiques connus et en cas d'apparition d'un diabète sous mTORi. Les objectifs de LDL-cholestérol devront être adaptés à l'état général et aux pronostics cardiovasculaire et oncologique du patient. En cas d'introduction d'un traitement, la pravastatine sera prescrite en première intention ; l'atorvastatine et la simvastatine sont contre-indiquées. Nous recommandons l'instauration de fénofibrate en cas d'hypertriglycéridémie > 5 g/L résistante aux mesures diététiques adaptées à l'état oncologique du patient. En cas d'hypertriglycéridémie non contrôlable > 10 g/L, nous suggérons la suspension temporaire de mTORi et la prise d'un avis spécialisé.

© 2018 Elsevier Masson SAS. Tous droits réservés.

Mots clés : Diabète ; Dyslipidémie ; Inhibiteurs mTOR

1. Recommendations: hyperglycemia and diabetes

R1. Diagnosis of diabetes under mTORi is based on 2 fasting glucose levels exceeding 126 mg/dl (7.0 mmol/l) or any glycemia > 200 mg/dl associated with signs of hyperglycemia.

* Corresponding author.

E-mail address: benjamin.bouillet@chu-dijon.fr (B. Bouillet).

R2. In case of diabetes under mTORi, metformin should be used in first line; the risk of malnutrition related to cancer requires dietary restrictions to be eased. Subsequent treatment follows classic guidelines for non-iatrogenic diabetes, adapted to the HbA_{1C} target.

R3. Diagnosis of diabetes under mTORi does not contraindicate continuation of mTORi treatment, except in case of threatening hyperglycemia despite optimal antidiabetic treatment, in which case mTORis should be interrupted until glycemia normalizes; resumption is to be discussed with the oncology team.

R4. Fasting glucose should be assayed in non-diabetic patients ahead of initiation of mTORi therapy. In case of pre-existing diabetes, HbA_{1C} ≤ 8% should be achieved before initiation of mTORi therapy.

R5. HbA_{1C} target is ≤ 8% in mTORi-induced diabetes.

R6. In non-diabetic patients, fasting venous glucose should be assayed every 2 weeks for the first month, then monthly throughout mTORi treatment.

R7. During mTORi treatment, in patients with moderate fasting hyperglycemia or diabetes, glucose self-monitoring should be implemented at a rate adapted to the oncologic context. In case of good glucose control, self-monitoring may be spaced out. HbA_{1C} should be assayed every 3 months.

R8. At termination of mTORi treatment, when antidiabetic treatment has been introduced or increased, 4 weeks' glucose self-monitoring should be implemented to determine whether antidiabetic treatment should be stopped or reduced.

2. Recommendations: dyslipidemia

R1. LDL-cholesterol targets should be adapted to general health status and cardiovascular and oncologic prognosis. Current guidelines may be applied in patients with good oncologic prognosis; otherwise, less strict objectives are determined in case-by-case discussion between oncologist and endocrinologist, and regularly reassessed according to prognostic progression.

R2. Dietary restrictions are not to be enforced in patients who may be malnourished or at risk of malnutrition. Statins should be prescribed in first line in case of LDL-cholesterol elevation; pravastatin is recommended, with fluvastatin or rosuvastatin in second line. Simvastatin and atorvastatin are contraindicated, being enzymatic inducers of cytochrome P450 3A4 and thus interfering with the metabolism of everolimus and potentially reducing its action.

R3. Under mTORi, fenofibrate should be prescribed for hypertriglyceridemia > 5 g/l resisting adapted dietary measures. Omega-3 fatty acids (EPA-DHA 2 g/day) may be associated or used if fibrates are not tolerated or are contraindicated. In non-controllable hypertriglyceridemia exceeding 10 g/l, mTORi treatment should be interrupted and specialist opinion should be sought; resumption is to be discussed with the oncology team.

R4. Fasting Lipid profile should be screened before initiating mTORi treatment.

R5. During mTORi treatment, fasting lipid profile should be screened every 2 weeks during the first cycle then monthly at each new cycle.

R6. At termination of mTORi treatment, the lipid-lowering treatment should be stopped, with a check on fasting lipid profile at 2 months in previously untreated patients. Patients receiving lipid-lowering treatment prior to initiation of mTORi should resume the previous dose, with check on fasting lipid profile at 2 months.

3. mTOR-inhibitor-induced hyperglycemia and diabetes

3.1. Epidemiology

Use of mTORis as anticancer treatment is associated with disorders of glucose metabolism. Hyperglycemia was reported in 12–50% of patients in phase-III trials of everolimus [1–6] and temsirolimus [7–9], although severe hyperglycemia (G3–4, > 13.9 mmol/l) is less frequent (4–12%) (Table 1). No decompensation of ketosis or of ketoacidosis has been reported. In a meta-analysis of 24 clinical trials of everolimus and temsirolimus in various types of tumor in 4261 patients, the ratio of incidence of hyperglycemia under mTORi versus controls was 2.95, and 5.25 for severe hyperglycemia [10]. Rates of diabetes under mTORi are higher in advanced renal carcinoma [2,6–8], but mTORi-induced hyperglycemia was reported in all studies, regardless of type of cancer. It also cannot be ruled out that certain combined anticancer therapies including mTORis have greater diabetogenic potential. All of these data, however, give only a partial picture of the real impact of mTORis on glucose metabolism: the number of patients under antidiabetic treatment and any intensification of antidiabetic treatment under mTORi were not specified in the above studies, and poorly controlled diabetic patients were usually excluded.

A recent study reported a median time to maximal hyperglycemia of 58 days in 75 patients treated by everolimus or temsirolimus for renal carcinoma [11]. However, no studies have specifically assessed time to onset of hyperglycemia after initiation of mTORi.

Current data do not definitely demonstrate dose-dependency in mTORi-induction of hyperglycemia.

3.2. Pathophysiology

3.2.1. Impact of mTOR on glucose metabolism

mTOR effects on glucose balance are complex, with contrasting results according to the site of mTORC1 activity [12]. mTORC1 promotes insulin resistance in adipose tissue, by serine phosphorylation on IRS-1 (insulin receptor substrate-1), reducing PI3-kinase activation [13]. mTORC1 activity was elevated in adipose tissue, liver and muscle in animal models of insulin resistance, suggesting that mTORC1 impairs insulin sensitivity [13,14]. In the liver, IRS-1 phosphorylation by mTORC1 reduces PI3-kinase pathway activation, increasing gluconeogenesis.

Table 1
 Incidence of hyperglycemia in mTOR inhibitor phase III studies.

	Hyperglycemia (%)			
	Type of cancer	n	All grades (%) > 1.26 g/l	Grades 3–4 (%) > 2.51 g/l
<i>Everolimus</i>				
Everolimus vs Placebo [2]	Renal carcinoma	269	50	12
Everolimus Placebo [1]	Pancreatic neuroendocrine tumor	204	23	1
Everolimus + Octreotide Placebo + Octreotide [5]	Gastrointestinal neuroendocrine tumor	203	13	5
Everolimus Placebo [3]	Breast cancer	215	4	2
Everolimus + trastuzumab + paclitaxel Placebo + trastuzumab + paclitaxel [6]	Breast cancer Her2+	211	12	5
		238	2	0.5
		482	13	4
		238	2	<1
		472	13	6
		238	5	1
<i>Temsirolimus</i>				
Temsirolimus Interferon	Renal carcinoma	208	26	11
Temsirolimus + interferon [7]		200	11	2
Temsirolimus + letrozole Placebo + letrozole [9]	Breast cancer	208	17	6
Temsirolimus + bevacizumab Interferon + bevacizumab [8]	Metastatic renal carcinoma	550	13	4
		553	5	1
		400	22	6
		391	5	1

Grade 1: fasting glycemia 1.26–1.60 g/l; grade 2: fasting glycemia 1.61–2.50 g/l; grade 3: fasting glycemia 2.51–5 g/l; grade 4: fasting glycemia > 5 g/l.

Conversely, mTORC1 promotes oxidative metabolism in muscle. Mice with specific muscular mTORC1 knock-out showed reduced muscle mass and oxidation [15]. In liver, mTORC1 inhibits ketogenesis by reducing the activity of PPAR- α , the main transcriptional modulator of ketogenesis genes [16].

mTORC1 thus regulates islet of Langerhans β -cell mass and function. Constitutive activation of mTORC1 in β cells enhances insulin secretion by increasing the number and size of β cells [17]. Prolonged mTORC1 activation in β cells, however, exhausts their insulin-secreting capacity by increasing apoptosis [18]. Thus, under physiological conditions, fine regulation of mTOR activity seems to be a prerequisite of glucose balance control.

mTORC2 function is less well established. It exerts control over cell growth and metabolism via Akt and SGK1 (serum- and glucocorticoid-induced protein kinase-1) and regulates cytoskeletal organization by activating protein kinase C- α [19].

3.2.2. Impact of mTORi on glucose metabolism

The molecular mechanisms relating mTOR inhibition to onset of glucose metabolism disorder are complex and not fully known. There are unexplained divergences between preclinical *in vitro* and *in vivo* animal data and phase II and III studies in humans. As chronic mTORC1 activation induces insulin resistance, chronic inhibition of the mTOR pathway should improve glucose balance. And yet mTORis promote hyperglycemia. Laplante and Sabatini [12] suggested that mTORis exert a “Janus” effect on glucose metabolism, displaying a U-curve in which too weak or too strong activity has negative metabolic impact. In several rodent models rapamycin promoted

onset of diabetes, by impaired insulin secretion combined with severe insulin resistance [20,21].

3.2.2.1. mTORis and insulin resistance. In a diabetic mouse model, rapamycin reduced insulin sensitivity, with parallel decrease in Akt phosphorylation and increase in glycogen synthase kinase 3b (GSK3) activity, leading to a decrease in glycogen synthesis [20] and increase in Jun N-terminal kinase 2/3 (JNK2/3) and JNK1 phosphorylation [20]. Rapamycin was also shown to disturb the mTORC2 complex and abolish the inhibitory impact of PI3-kinase-Akt on liver gluconeogenesis [22].

Reduced glucose uptake secondary to impairment of the intracellular insulin signaling pathway was demonstrated in human adipocytes treated with rapamycin [23]. At organism level, replacing calcineurin inhibitors by sirolimus aggravated insulin resistance and impaired compensatory insulin secretion, thus promoting onset of diabetes [24].

3.2.2.2. mTORis and insulin secretion. mTORi-induced hyperglycemia is also related to reduced insulin secretion. Several studies showed that mTOR inhibition reduces β -cell insulin secretion [17]. mTOR inhibition by rapamycin leads to a 33% reduction in glucose-induced insulin secretion and a 50% reduction in β -cell mass by increased apoptosis [20]. A “beneficial” hyperglycemic effect of mTORis was shown in metastatic insulinoma patients with refractory hypoglycemia, with reduced intensity and frequency of hypoglycemia episodes [25].

3.3. Clinical and biologic diagnosis

The literature reports no symptomatic specificity for onset of hyperglycemia, and no clinical profile as being at particular risk. Biologic diagnosis is based on the usual criteria: 2 fasting glucose levels >126 mg/dl (7.0 mmol/l) or any glycemia >200 mg/dl associated with signs of hyperglycemia.

R1. Diagnosis of diabetes under mTORi is based on 2 fasting glucose levels exceeding 126 mg/dl (7.0 mmol/l) or any glycemia >200 mg/dl associated with signs of hyperglycemia.

3.4. Treatment (according to 2 expert opinions [26,27])

Oncologic prognosis and malnutrition or risk of malnutrition require easing dietary restrictions. Physical activity has proven oncologic benefit, and should be adapted to individual possibilities. Pharmacologically, metformin is the first-line treatment, given mTORi pathophysiology, and should be initiated, when not contraindicated, as soon as diabetes is diagnosed. If glycemia is unsatisfactory under isolated metformin, drug strategy follows the recent position paper of the French Society of Diabetes, while adapted to the HbA_{1C} target (see below) [28].

R2. In case of diabetes under mTORi, metformin should be used in first line; the risk of malnutrition related to cancer requires dietary restrictions to be eased. Subsequent treatment follows classic guidelines for non-iatrogenic diabetes, adapted to the HbA_{1C} target.

In rare cases of persistent hyperglycemia exceeding 2.5 g/l (or HbA_{1C} >9%) despite optimal antidiabetic treatment, mTORis should be interrupted until glycemia stabilizes, then reintroduced at lower dose.

R3. Diagnosis of diabetes under mTORi does not contraindicate continuation of mTORi treatment, except in case of threatening hyperglycemia despite optimal antidiabetic treatment, in which case mTORis should be interrupted until glycemia normalizes; resumption is to be discussed with the oncology team.

3.5. Monitoring (according to 2 expert opinions [26,27])

3.5.1. Before mTORi treatment

In apparently non-diabetic patients, fasting glucose should be assayed to diagnose possible pre-existing abnormality in glucose metabolism, such as fasting hyperglycemia or diabetes. In known diabetic patients, HbA_{1C} should be assayed to assess glucose balance. An endocrinology consultation is strongly recommended [27]. Given the heightened risk of decompensation of hyperglycemia, adapted glucose balance is a prerequisite for initiation of mTORi.

According to current French guidelines, the HbA_{1C} target is ≤8% (proven severe comorbidity and/or limited life-expectancy) in pre-existing or mTORi-induced diabetes [28].

R4. Fasting glucose should be assayed in non-diabetic patients ahead of initiation of mTORi therapy. In case of pre-existing diabetes, HbA_{1C} ≤8% should be achieved before initiation of mTORi therapy.

R5. HbA_{1C} target is ≤8% in mTORi-induced diabetes.

3.5.2. During mTORi treatment

In normoglycemic patients, strict monitoring of fasting venous glycemia is recommended every two weeks for the first month of treatment, then monthly. In case of non-diabetic fasting hyperglycemia (1.10–1.26 g/l), glucose self-monitoring should be implemented; in known diabetes, glucose self-monitoring should be reinforced, with adaptation to the oncologic context. HbA_{1C} monitoring every 3 months should be systematic.

R6. In non-diabetic patients, fasting venous glucose should be assayed every 2 weeks for the first month, then monthly throughout mTORi treatment.

R7. During mTORi treatment, in patients with moderate fasting hyperglycemia or diabetes, glucose self-monitoring should be implemented at a rate adapted to the oncologic context. In case of good glucose control, self-monitoring may be spaced out. HbA_{1C} should be assayed every 3 months.

3.5.3. At end of mTORi treatment

Reinforced self-monitoring should be continued for 4 weeks when antidiabetic treatment has been introduced or intensified following initiation of mTORi, enabling antidiabetic treatment to be reduced or stopped as appropriate. HbA_{1C} should be assayed 3 months after termination of mTORi.

R8. At termination of mTORi treatment, when antidiabetic treatment has been introduced or increased, 4 weeks' glucose self-monitoring should be implemented to determine whether antidiabetic treatment should be stopped or reduced.

3.6. Predictive factors

No predictive factors for onset of hyperglycemia under mTORi have been identified.

4. mTOR-inhibitor-induced hyperlipidemia

4.1. Epidemiology

Use of mTORis as anticancer treatment is associated with disorders of lipid metabolism. Hypercholesterolemia (hyperChol) was reported in 12–88% of patients in phase-III trials of everolimus [2,3,29,30] and temsirolimus [7–9,31] (Table 2), with severe hyperChol (CT >4 g/l) in 1–8%. Hypertriglyceridemia (hyperTG) was reported in 7–73% of patients; severe hyperTG (TG >5 g/l) was rarer (1–6%). Low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) levels were not reported. LDL-C [32] and HDL-C elevation [32,33] was reported with everolimus in transplant patients, where doses are lower.

Incidence of hyperChol and hyperTG was assessed in a meta-analysis [10] of 24 clinical trials comparing everolimus or temsirolimus versus control treatment in various solid tumors, in a total 4,261 patients. Rates of hyperTG and severe hyperTG (TG >5 g/l) were respectively 2.49- and 2.01-fold higher under mTORi, and hyperChol and severe hyperChol (CT >4 g/l) rates respectively 3.35- and 6.51-fold higher. This meta-analysis

Table 2
 Incidence of hypercholesterolemia and hypertriglyceridemia in mTOR inhibitor phase III studies.

	Type of cancer	n	Hypercholesterolemia				Hypertriglyceridemia				
			All grades (%)		Grades 3–4 (%)		All grades (%)		Grades 3–4 (%)		
<i>Everolimus</i>											
Everolimus vs Placebo [2]	Renal carcinoma	274137	77	35	4	0	73	34	1	0	
Everolimus Vs Placebo [29]	Breast cancer	18 21	88.9	76.2	0	0	72.2	38.1	0	0	
Everolimus +vinorelbine Vs Placebo + vinorelbine [30]	Breast cancer	280282	NC	NC	NC	NC	7.7	2	0.7	<1	
<i>Temsirolimus</i>											
Temsirolimus Vs Interferon Vs Temsirolimus + interferon [7]	Renal carcinoma	208200	24	4	26	1	0	2	NC	NC	NC
Temsirolimus Vs Sorafenib [31]	Renal carcinoma	249252	20	6	2	1	21	7	3	<1	
Temsirolimus + letrozole Vs Placebo + letrozole [9]	Breast cancer	550553	12	6	1	<0.5	NC	NC	NC	NC	
Temsirolimus + bevacizumab Vs Interferon + bevacizumab [8]	Metastatic renal carcinoma	393391	32	10	6	1	29	21	7	4	

Hypercholesterolemia: grade 1: <3 g/l; grade 2: 3–4 g/l; grade 3: 4–5 g/l; grade 4: >5 g/l. Hypertriglyceridemia: grade 1: 1–2 N; grade 2: 2.5–5 N; grade 3: 5–10 N; grade 4: >10 N.

included studies with mTORis in monotherapy and in association. A recent meta-analysis [34] included 15 phase II and III studies of mTORi monotherapy; mTORis were associated with 2.22-fold extra risk of hyperTG, 1.88-fold extra risk of severe hyperTG, 2.48-fold extra risk of hyperChol and 4.26-fold extra risk of severe hyperChol.

A retrospective study reported median times to maximal hyperChol and hyperTG of 28 and 56 days respectively, in 75 patients receiving everolimus or temsirolimus for renal carcinoma [11].

4.2. Pathophysiology

4.2.1. Impact of mTor on lipid metabolism

mTORC1 affects lipid metabolism at various levels.

- It increases the activity of transcription factor SREBP-1c, which stimulates expression of enzymes involved in lipogenesis. Impairment of mTORC1 activity by rapamycin was shown to block this SREBP-1c-induced expression [35].
- It increases expression of PPAR γ and promotes adipogenesis [36].
- It increases the activity of lipin-1, a phosphatidic acid phosphatase promoting triglyceride synthesis and PPAR γ activity [37], and leading to up-regulation of SREBP-1c expression.

The role of mTORC2 in lipid metabolism is much less clear: it may act on de-novo synthesis of sphingolipids by regulating ceramide synthase activity [38].

4.2.2. Impact of mTORis on lipid metabolism

The pathophysiology of mTORi-induced dyslipidemia has not been fully elucidated.

Concerning triglycerides, *in vitro*, rapamycin increases fatty-acid β -oxidation [39], and reduces fatty-acid flow toward storage pathways, thus reducing peripheral clearance rather than increasing liver synthesis. Rapamycin also reduces gene expression of lipogenesis enzymes such as acetyl-CoA carboxylase [39], fatty acid synthase [40] and stearyl-CoA desaturase [41]. It reduces VLDL catabolism, reducing lipoprotein lipase activity [42] by reducing the stimulatory effect of insulin on lipoprotein lipase [43], and reducing apolipoprotein C-III, a lipoprotein lipase inhibitor [44]. It increases adipose tissue fatty-acid release by increasing the action of hormone-sensitive lipase [44].

Concerning LDL-cholesterol, rapamycin reduces LDL-apoB100 catabolism [42]. *In vitro*, it reduces LDL-receptor (LDL-R) expression, thus reducing LDL uptake [45]. This is probably related to increased expression of PCSK9 (proprotein convertase subtilisin kexin type 9), an endogenous LDL-R inhibitor [46].

4.3. Clinical and biologic diagnosis

The present literature reports no specific symptomatology or clinical profile associated with mTORi-induced dyslipidemia. Lipid screening is therefore essential for diagnosis, with criteria defined in the recent French Health Authority guidelines [47].

4.4. Treatment (according to 2 expert opinions [26,27])

4.4.1. Hypercholesterolemia

Hypercholesterolemia is assessed on LDL-C levels, as only lowered LDL-C has been shown to reduce cardiovascular morbidity and mortality. Current guidelines for management of dyslipidemia [47] relate to the general population and cannot be transposed to the oncologic context.

LDL-C levels indicating lipid-lowering therapy (before or after initiation of mTORi) should be adapted to individual cardiovascular and oncologic prognosis. Despite a lack of evidence for this specific population, good oncologic prognosis allows current guidelines to be applied; otherwise, less strict objectives should be set on case-by-case discussion between oncologist and endocrinologist, and regularly reassessed according to prognostic progression.

Dietary restrictions on cholesterol and saturated fatty acids are not to be enforced in patients with or at risk of malnutrition. Physical activity should be adapted to the patient's possibilities and wishes.

For patients already under lipid-lowering therapy, targets are to be adapted to the individual clinical context [47,48]; lipid-lowering therapy may need to be adapted (see below) and dietary restrictions eased.

First-line treatment is by statins. Simvastatin and atorvastatin are contraindicated, as enzymatic induction of cytochrome P450 interferes with the metabolism and potentially reduces the activity of everolimus. Pravastatin is to be prescribed in first line; in case of poor tolerance, it may be replaced by fluvastatin; if efficacy is insufficient, these may be replaced by rosuvastatin 5–20 mg/day. Statin monitoring under mTORi is the same as in non-cancerous contexts. In case of statin intolerance, ezetimibe is implemented as monotherapy; it may also be associated to statins if they lack efficacy.

Efficacy is assessed on lipid profile after 2 months' treatment, repeated every 3 months until lipid targets are reached, and then twice yearly.

R1. LDL-cholesterol targets should be adapted to general health status and cardiovascular and oncologic prognosis. Current guidelines may be applied in patients with good oncologic prognosis; otherwise, less strict objectives are determined in case-by-case discussion between oncologist and endocrinologist, and regularly reassessed according to prognostic progression.

R2. Dietary restrictions are not to be enforced in patients who may be malnourished or at risk of malnutrition. Statins should be prescribed in first line in case of LDL-cholesterol elevation; pravastatin is recommended, with fluvastatin or rosuvastatin in second line. Simvastatin and atorvastatin are contraindicated, being enzymatic inducers of cytochrome P450 3AC and thus interfering with the metabolism of everolimus and potentially reducing its action.

4.4.2. Hypertriglyceridemia

In case of TG > 5 g/l, the patient should be reminded of the need to reduce consumption of sugars and to avoid alcohol, while keeping dietary restrictions flexible. Physical activity should be adapted to individual possibilities and wishes. Due to the risk of acute pancreatitis, first-line treatment is fenofibrate, if not contraindicated. Omega-3 fatty acids (EPA DHA 2 g/day) may be associated or used if fibrates are poorly tolerated or contraindicated [47]. Efficacy is assessed on lipid profile at 2 months. Gemfibrozil should be avoided, due to multiple drug interactions.

In uncontrollable hypertriglyceridemia exceeding 10 g/l, mTORi should be interrupted and specialist opinion sought; resumption is to be discussed with the oncology team.

Associating statins to fibrates requires specialist opinion.

R3. Under mTORi, fenofibrate should be prescribed for hypertriglyceridemia > 5 g/l resisting adapted dietary measures. Omega-3 fatty acids (EPA-DHA 2 g/day) may be associated or used if fibrates are not tolerated or are contraindicated. In non-controllable hypertriglyceridemia exceeding 10 g/l, mTORi treatment should be interrupted and specialist opinion should be sought; resumption is to be discussed with the oncology team.

4.5. Monitoring

4.5.1. Before mTORi treatment

Fasting lipid profile screening should be performed ahead of mTORi therapy.

R4. Fasting Lipid profile should be screened before initiating mTORi treatment.

4.5.2. During mTORi treatment

In case of normal lipid profile prior to mTORi treatment (with or without lipid-lowering), fasting lipid profile should be monitored every 2 weeks during the first mTORi cycle, then monthly at each new cycle.

R5. During mTORi treatment, fasting lipid profile should be screened every 2 weeks during the first cycle then monthly at each new cycle.

4.5.3. At end of mTORi treatment

If the mTORi disturbed lipid profile, requiring introduction or reinforcement of lipid-lowering therapy, the previous lipid-lowering dose should be resumed or lipid-lowering therapy introduced under mTORi should be stopped, with fasting lipid profile check 2 months after mTORi termination.

R6. At termination of mTORi treatment, the lipid-lowering treatment should be stopped, with a check on fasting lipid profile at 2 months in previously untreated patients. Patients receiving lipid-lowering treatment prior to initiation of mTORi should resume the previous dose, with check on lipid profile at 2 months.

4.6. Predictive factors

No predictive factors for onset of hyperlipidemia under mTORi have been identified.

Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–23.
- [2] Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a

- double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372: 449–56.
- [3] Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sasmund T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520–9.
- [4] Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet* 2013;381:125–32.
- [5] Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;378:2005–12.
- [6] Hurvitz SA, Andre F, Jiang Z, Shao Z, Mano MS, Neciosup SP, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial. *Lancet Oncol* 2015;16:816–29.
- [7] Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356:2271–81.
- [8] Rini BI, Bellmunt J, Clancy J, Wang K, Niethammer AG, Hariharan S, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. *J Clin Oncol* 2014;32:752–9.
- [9] Wolff AC, Lazar AA, Bondarenko I, Garin AM, Brincaat S, Chow L, et al. Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. *J Clin Oncol* 2013;31:195–202.
- [10] Sivendran S, Agarwal N, Gartrell B, Ying J, Boucher KM, Choueiri TK, et al. Metabolic complications with the use of mTOR inhibitors for cancer therapy. *Cancer Treat Rev* 2014;40:190–6.
- [11] Jebali M, Elaidi R, Brizard M, Fouque J, Takouchop C, Sabatier B, et al. Biological toxicities as surrogate markers of efficacy in patients treated with mTOR inhibitors for metastatic renal cell carcinoma. *BMC Cancer* 2017;17:27.
- [12] Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell* 2012;149:274–93.
- [13] Um SH, Frigerio F, Watanabe M, Picard F, Joaquin M, Sticker M, et al. Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity. *Nature* 2004;431:200–5.
- [14] Khamzina L, Veilleux A, Bergeron S, Marette A. Increased activation of the mammalian target of rapamycin pathway in liver and skeletal muscle of obese rats: possible involvement in obesity-linked insulin resistance. *Endocrinology* 2005;146:1473–81.
- [15] Bentzinger CF, Romanino K, Cloëtta D, Lin S, Mascarenhas JB, Oliveri F, et al. Skeletal muscle-specific ablation of raptor, but not of rictor, causes metabolic changes and results in muscle dystrophy. *Cell Metab* 2008;8:411–24.
- [16] Sengupta S, Peterson TR, Laplante M, Oh S, Sabatini DM. mTORC1 controls fasting-induced ketogenesis and its modulation by ageing. *Nature* 2010;468:1100–4.
- [17] Rachdi L, Balcazar N, Osorio-Duque F, Elghazi L, Weiss A, Gould A, et al. Disruption of Tsc2 in pancreatic beta cells induces beta cell mass expansion and improved glucose tolerance in a TORC1-dependent manner. *Proc Natl Acad Sci U S A* 2008;105:9250–5.
- [18] Shigeyama Y, Kobayashi T, Kido Y, Hashimoto N, Asahara S-I, Matsuda T, et al. Biphasic response of pancreatic beta-cell mass to ablation of tuberous sclerosis complex 2 in mice. *Mol Cell Biol* 2008;28:2971–9.
- [19] Jacinto E, Loewith R, Schmidt A, Lin S, Ruegg MA, Hall A, et al. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nat Cell Biol* 2004;6:1122–8.
- [20] Fraenkel M, Ketzinel-Gilad M, Ariav Y, Pappo O, Karaca M, Castel J, et al. mTOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. *Diabetes* 2008;57:945–57.
- [21] Houde VP, Brûlé S, Festuccia WT, Blanchard P-G, Bellmann K, Deshaies Y, et al. Chronic rapamycin treatment causes glucose intolerance and hyperlipidemia by upregulating hepatic gluconeogenesis and impairing lipid deposition in adipose tissue. *Diabetes* 2010;59:1338–48.
- [22] Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, et al. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science* 2012;335:1638–43.
- [23] Pereira MJ, Palming J, Rizell M, Aureliano M, Carvalho E, Svensson MK, et al. mTOR inhibition with rapamycin causes impaired insulin signalling and glucose uptake in human subcutaneous and omental adipocytes. *Mol Cell Endocrinol* 2012;355:96–105.
- [24] Teutonico A, Schena PF, Di Paolo S. Glucose metabolism in renal transplant recipients: effect of calcineurin inhibitor withdrawal and conversion to sirolimus. *J Am Soc Nephrol* 2005;16:3128–35.
- [25] Bernard V, Lombard-Bohas C, Taquet M-C, Caroli-Bosc F-X, Ruszniewski P, Niccoli P, et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. *Eur J Endocrinol* 2013;168: 665–74.
- [26] Busaidy NL, Farooki A, Dowlati A, Perentesis JP, Dancey JE, Doyle LA, et al. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. *J Clin Oncol* 2012;30:2919–28.
- [27] Lombard-Bohas C, Cariou B, Vergès B, Coriat R, N'guyen T, François E, et al. Management of metabolic disorders induced by everolimus in patients with differentiated neuroendocrine tumors: expert proposals. *Bull Cancer (Paris)* 2014;101:175–83.
- [28] Darmon P, Bauduceau B, Bordier L, Bringer J, Chabrier G, Charbonnel B, et al. Management of hyperglycemia in type 2 diabetes: Position Statement of the Francophone Diabetes Society. *Med Mal Metabol* 2017:11.
- [29] Maass N, Harbeck N, Mundhenke C, Lerchenmüller C, Barinoff J, Lück H-J, et al. Everolimus as treatment for breast cancer patients with bone metastases only: results of the phase II RADAR study. *J Cancer Res Clin Oncol* 2013;139:2047–56.
- [30] André F, O'Regan R, Ozguroglu M, Toi M, Xu B, Jerusalem G, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol* 2014;15:580–91.
- [31] Hutson TE, Escudier B, Esteban E, Bjarnason GA, Lim HY, Pittman KB, et al. Randomized phase III trial of temsirolimus versus sorafenib as second-line therapy after sunitinib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2014;32:760–7.
- [32] Spinelli GA, Felipe CR, Park SI, Mandia-Sampaio EL, Tedesco-Silva H, Medina-Pestana JO. Lipid profile changes during the first year after kidney transplantation: risk factors and influence of the immunosuppressive drug regimen. *Transplant Proc* 2011;43:3730–7.
- [33] Baur B, Oroszlan M, Hess O, Carrel T, Mohacs P. Efficacy and safety of sirolimus and everolimus in heart transplant patients: a retrospective analysis. *Transplant Proc* 2011;43:1853–61.
- [34] Lew S, Chamberlain RS. Risk of metabolic complications in patients with solid tumors treated with mTOR inhibitors: meta-analysis. *Anticancer Res* 2016;36:1711–8.
- [35] Porstmann T, Santos CR, Griffiths B, Cully M, Wu M, Leever S, et al. SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. *Cell Metab* 2008;8:224–36.
- [36] Zhang HH, Huang J, Düvel K, Boback B, Wu S, Squillace RM, et al. Insulin stimulates adipogenesis through the Akt-TSC2-mTORC1 pathway. *PLoS One* 2009;4:e6189.
- [37] Huffman TA, Mothe-Satney I, Lawrence JC. Insulin-stimulated phosphorylation of lipin mediated by the mammalian target of rapamycin. *Proc Natl Acad Sci U S A* 2002;99:1047–52.
- [38] Aronova S, Wedaman K, Aronov PA, Fontes K, Ramos K, Hammock BD, et al. Regulation of ceramide biosynthesis by TOR complex 2. *Cell Metab* 2008;7:148–58.
- [39] Brown NF, Stefanovic-Racic M, Sipula JJ, Perdomo G. The mammalian target of rapamycin regulates lipid metabolism in primary cultures of rat hepatocytes. *Metabolism* 2007;56:1500–7.

- [40] Peng T, Golub TR, Sabatini DM. The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. *Mol Cell Biol* 2002;22:5575–84.
- [41] Mauvoisin D, Rocque G, Arfa O, Radenne A, Boissier P, Mounier C. Role of the PI3-kinase/mTor pathway in the regulation of the stearoyl CoA desaturase (SCD1) gene expression by insulin in liver. *J Cell Commun Signal* 2007;1:113–25.
- [42] Hoogeveen RC, Ballantyne CM, Pownall HJ, Opekun AR, Hachey DL, Jaffe JS, et al. Effect of sirolimus on the metabolism of apoB100-containing lipoproteins in renal transplant patients. *Transplantation* 2001;72:1244–50.
- [43] Kraemer FB, Takeda D, Natu V, Sztalryd C. Insulin regulates lipoprotein lipase activity in rat adipose cells via wortmannin- and rapamycin-sensitive pathways. *Metabolism* 1998;47:555–9.
- [44] Morrisett JD, Abdel-Fattah G, Hoogeveen R, Mitchell E, Ballantyne CM, Pownall HJ, et al. Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients. *J Lipid Res* 2002;43:1170–80.
- [45] Ma KL, Ruan XZ, Powis SH, Chen Y, Moorhead JF, Varghese Z. Sirolimus modifies cholesterol homeostasis in hepatic cells: a potential molecular mechanism for sirolimus-associated dyslipidemia. *Transplantation* 2007;84:1029–36.
- [46] Ai D, Chen C, Han S, Ganda A, Murphy AJ, Haeusler R, et al. Regulation of hepatic LDL receptors by mTORC1 and PCSK9 in mice. *J Clin Invest* 2012;122:1262–70.
- [47] Haute Autorité de Santé- Recommandations: Principales dyslipidémies: stratégies de prise en charge.
- [48] French Society of Endocrinology (SFE), Francophone Society of Diabetes (SFD), New French Society of Atherosclerosis (NSFA), Béliard S, Bonnet F, Bouhanick B, et al. Consensus statement on the management of dyslipidaemias in adults. *Diabetes Metab* 2016;42:398–408.