Pulmonary toxicity of mTOR inhibitors. Comparisons of two populations: Solid organ recipients and cancer patients

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ABSTRACT

Introduction: Mammalian target of rapamycin (mTOR) inhibitors-associated pneumonitis (mTOR-IP) has long been described in solid organ recipients (T) patients but more recently in cancer (K) patients. Its overall characteristics have never been compared between these 2 populations. The aim of this study was to compare them in terms of presentation, severity and outcome in T and in K patients.

Material and Methods: We carried out a retrospective study in a single french tertiary center. Four databases were used to ensure the exhaustive collection of all mTOR-IP cases between 2001 and 2020. All clinical, biological, radiological, pathological and outcome data were reviewed.

Results: Thirty-nine patients with mTOR-IP were diagnosed during this period, 24 T and 15 K patients. The average dosage of everolimus and sirolimus was 2,65mg (± 1,78) and 2,75mg (± 0,96) in T patients, respectively, versus 8,75mg (± 2,26) for everolimus in K patients. The overall prevalence of mTOR-IP was 6.4% with a median time of occurrence of 7 months [IQR 3– 35 months]. mTOR-IP were significantly more frequent ($p < 0.001$) and occurred earlier ($p < 0.001$) in cancer patients. No clinical, functional, radiological, pathological nor outcome differences were otherwise observed between the 2 groups. Average everolimus blood levels at the time of mTOR-IP diagnosis were in the range of recommended therapeutic values.

Conclusion: Our study shows that mTOR-IP is comparable in terms of presentation in T and in K patients but that it occurs significantly earlier after drug introduction in the latter. This raises questions as to the potential role of the higher doses used in K patients as well as that of co-treatments in the pathogeny of the disease.

KEYWORDS : TOR Serine-Threonine Kinases; adverse drug reactions; interstitial lung disease; everolimus; sirolimus

Toxicité pulmonaire des inhibiteurs de mTOR. Comparaison de deux populations distinctes : les transplantés d'organe solide et les patients atteints de cancer

RESUME

Introduction : Les inhibiteurs de mTOR (mammalian target of rapamycin), initialement utilisés comme immunosuppresseurs en transplantation d'organe solide, ont vu leurs indications s'étendre au domaine de l'oncologie médicale en raison de leurs propriétés antitumorales. La toxicité pulmonaire des inhibiteurs de mTOR est rapportée dans les deux indications, mais peu d'études ont exploré les différences entre les pneumopathies aux inhibiteurs de mTOR (mTOR-PI) en transplantation (T) et en oncologie (K). L'objectif de notre étude est de comparer les mTOR-PI dans ces deux populations.

Méthodes : Notre étude rétrospective monocentrique a été réalisée dans un centre expert en pneumopathies interstitielles, en transplantation et en oncologie (Hôpital Européen Georges Pompidou). Quatre bases de données ont été utilisées afin d'assurer la collecte exhaustive de tous les cas de mTOR-PI entre 2001 et 2020. Toutes les données cliniques, biologiques, radiologiques et pathologiques ainsi que les résultats ont été collectés et analysés.

Résultats: Trente-neuf patients atteints de mTOR-PI ont été diagnostiqués pendant cette période, 24 en transplantation (T) et 15 en oncologie (K). La posologie moyenne de l'everolimus et du sirolimusétait respectivement de 2,65 mg (± 1,78) et 2,75mg (± 0,96) en T contre 8,75mg (± 2,26) pour l'everolimus en K. La prévalence globale de mTOR-PI était de 6,4 % avec un délai médian de survenue de 7 mois [IQR 3-35 mois]. Les mTOR-PI étaient significativement plus fréquentes ($p < 0,001$) et survenaient plus précocement ($p < 0,001$) chez les patients K. Aucune autre différence clinique, fonctionnelle, radiologique, pathologique ou de sévérité n'a été observée entre les deux groupes. Au moment du diagnostic de mTOR-PI, 14/18 (78%) des patients transplantés avaient un taux résiduel d'éverolimus dans les normes des valeurs thérapeutiques recommandées.

Conclusion: Les pneumopathies aux inhibiteurs de mTOR sont comparables en termes de présentation chez les patients T et K, mais elles surviennent significativement plus tôt après l'introduction du médicament chez ces derniers. Cela pourrait être en partie lié aux différences de posologie utilisées dans ces deux populations.

MOTS CLES : sérine-thréonine kinases TOR ; effets secondaires indésirables des medicaments ; pneumopathies interstitielles ; everolimus ; sirolimus

ABBREVIATION LIST

Mammalian target of rapamycin	mTOR
Mtor-inhibitors-associated pneumonitis	mTOR-IP
Interquartile range	IQR
Interstitial lung disease	ILD
Fructokinase-binding protein	FKBP
Cluster differenciation	CD
Computerized tomography-scan	CT-scan
Mammalian target of rapamycin complex	mTORC
Phosphoinositide 3-kinase	PI3K
Protein kinase B	AKT
Transplant patients	T
Cancer patients	K
Comité d'évaluation des protocoles de recherche observationnels de la Société de Pneumologie de langue française	CEPRO
Programme de medicalisation des systèmes d'information	PMSI
High-resolution computed tomography	HRCT
Bronchoalveolar lavage	BAL
Pulmonary function test	PFT
Intensive care unit	ICU
Transplant population	TP
Polymorphonuclear	PNN
Reactive protein C	CRP
Forced vital capacity	FVC
Diffusing capacity for carbon monoxide	DLCO
Everolimus blood concentration	EBC

INTRODUCTION

Rapamycin (sirolimus) and the rapalogs (everolimus, temsirolimus) specifically inhibit the signalling complex mTORC 1 by binding to the intracellular protein FK506-binding protein (FKBP12) [1,2]. PI3K/AKT signalling pathway mediated by mTOR regulates cell division and blocks T lymphocytes proliferation and differentiation. The mTOR pathway also mediates angiogenesis-promoting signals, notably by increasing vascular endothelial growth factors [3,4]. mTORs inhibitors have therefore immunosuppressive and antineoangiogenesis properties, explaining their wide use in oncology therapeutic strategies. Sirolimus and analogs have first been approved for the prevention of solid organ transplant rejection [5–8]. Later on, temsirolimus (CCI-779, Wyeth) and everolimus (RAD-001, Novartis Pharma AG) have been developed and approved as anti-neoplastic agents [9–16]. Adverse drug reactions (ADR) to sirolimus and analogs have already been widely reported and their well-known main side effects are haematologic, metabolic, cutaneous, gastrointestinal, renal, thromboembolic and pulmonary [17–19].

mTOR inhibitors-associated pneumonitis (mTOR-IP) is a potentially severe ADR which may require dose reduction, suspension or even permanent discontinuation of the drug [20]. mTOR-IP has been first reported with sirolimus in renal transplant recipients [21–29]. Later on, it has also been reported with analogs in other allograft types [30–32] and in patients treated for malignancies [33–38]. Since the first description of mTOR-IP in graft recipients, transplant patient's management has largely evolved with new antirejection drugs or dosages, some of which having known potential interactions with mTOR inhibitors. In addition, mTOR-IP features have been less extensively reported in the context of malignancy. Finally mTOR-IP prevalence, reported to range between 3 and 54%, actually remains largely unknown and based on previous reports [2,35,39,40]. The aim of our study was to describe mTOR-IP features in terms of prevalence, clinical, imaging, functional and outcome

characteristics and to compare them in 2 distinct groups: transplant (TP) and cancer (K) patients.

MATERIALS AND METHODS

1. Population and databases

We carried out a retrospective study on mTOR-IP diagnosed in TP as well as in K patients in a single french university tertiary center (Centre de competence Maladies pulmonaires rares, Hôpital Européen Georges Pompidou, University of Paris). This study was approved by Institutional Review Board of the French Learned Society for Respiratory Medicine (reference: CEPRO 2020-046).

We analysed the medical files of all patients treated in our institution with an mTOR inhibitor between 2001 and 2020 and included all patients diagnosed with mTOR-IP. In order to exhaustively report all cases of mTOR-IP in our institution, we collected and crosschecked data from four databases: 1- the hospital-discharge summaries database system (PMSI) using the coding system '*drug-induced pneumonitis*, 2- Pharmacovigilance databases for all mTOR-IP cases reported in our facility to the Pharmacovigilance center, 3- Our local pharmacology unit where all mTOR inhibitors blood levels are monitored and 4- Databases from oncological clinical trials evaluating RAD-001 molecule (everolimus) in patients with kidney or breast cancer between 2007 and 2010. Altogether, this approach allowed us to collect the files of all patients treated with mTOR inhibitors during the target period in our hospital (n=608). All files were then reviewed by 3 of the authors (SG, JP and DIB), pulmonologists with an expertise in ILDs, and only patients diagnosed with a definite diagnosis of mTOR-IP were included after exclusion of all alternative diagnosis as detailed below.

2. mTOR-IP diagnosis and data collection

Drug-induced pneumonitis diagnosis is based primarily on concordant timing of drug initiation, presence of condensations or infiltrates on chest high-resolution computed tomography (HRCT) and the absence of any alternative diagnosis [41]. In our study, mTOR-IP diagnosis was defined according to the following criteria 1- Exposure to mTOR inhibitor preceding the onset of pulmonary signs or symptoms; 2- Presence of HRCT abnormalities consistent with pulmonary ADR ; 3 - No documented pulmonary infection on respiratory samples including those obtained by endoscopic procedure; 4 - Exclusion of all other alternative pulmonary diseases including ADR due to other drugs. Medical records data were collected retrospectively including clinical, biological (including pharmacological dosages and BAL), functional (complete pulmonary function tests) and HRCT data at the time of diagnosis and at last follow-up. Pulmonary biopsies, when performed, obtained at the time of mTOR-IP diagnosis, were all reviewed by a pathologist (LG). Outcomes were evaluated through respiratory related hospitalization for mTOR-IP (whether or not in intensive care unit ICU), need for mTOR inhibitors discontinuation and/or need for steroid therapy, and mortality due to theADR. mTOR-IP time of diagnosis was defined by the date of first abnormal chest HRCT compatible with ADR.

3. Drug exposure

All patients included had at least one month of mTOR inhibitors treatment. The mTOR inhibitors blood concentrations were assessed by Liquid Chromatography coupled to tandem Mass Spectrometry (LC-MS/MS). Blood levels were compared between the period free of lung ADR and that of mTOR-IP diagnosis. We estimated the standard mean trough everolimus blood concentration in heart and lung TP without ADR to provide a standard therapeutic range. As the number of patients with mTOR inhibitor blood levels testing in the

K population was not sufficient, the therapeutic range of mTOR concentration in K patients was taken from the literature for comparison.

4. Statistical analysis

Given the small effect sizes, quantitative variables were compared between TP and K patients using Kruskal-Wallis Rank Sum t-test and categorical variables were compared using the exact Fisher test. We applied a non-parametric approach to estimate confident intervals. We compared mTOR-IP prevalence between the two groups of patients using a Chi-2 test. Student t-test was used to compare residual everolimus concentrations at the time of ILD to standard reference values. Given the non-random characteristics of the missing data, multiple imputation methods could not be applied to the analysis and the missing data were excluded from the statistical analysis. Statistical analysis was performed using R Studio software®.

RESULTS

After reconciliation of our databases, we found that 608 patients had been treated with mTOR inhibitors in our institution between January 2001 and September 2020. Among them, 44 patients had a suspicion of drug-induced pneumonitis with the referenced diagnosis of mTOR-IP in their medical records. After reviewing all medical records and CT-scans, 5 patients were excluded: 4 due to a concomitant respiratory infection and 1 due to missing data (no CT available). Finally, 39 patients with a definite mTOR-IP were included into the study [Figure 1], 24 were solid organ recipients and 15 had an active malignancy. Mean age was 58 ± 19 years and 17 (44%) were female. Their baseline clinical characteristics as well as the type and indications of molecules used are reported in Table 1. The mTOR-IP prevalence in all patients treated with mTOR inhibitors was 6.4% and was higher in K than in TP patients (11.9% vs 5.2%, respectively; $\chi_2 = 7.31$, $p < 0.01$). mTOR indications and –IP incidence

between 2001 and 2020 are reported in Supplementary Materials. The median time between mTOR inhibitor introduction and mTOR-IP diagnosis was 7 months [IQR 3 - 35] and it was significantly different between TP and K patients (12 months [IQR = 5 - 42] vs 3 months [IQR = 2 – 6.5], respectively, $p < 0.01$) (Table 2). In the TP group, immunosuppressive co-treatments were mycophenolate mofetil (55%), tacrolimus (40%), cyclosporine (14%) or azathioprin (9%). In addition, 65% of the transplant patients were treated with corticosteroids at an average daily dosage of 3.7 (± 2.5), 4.8 (± 6.0) and 6.0 (± 5.5) mg in heart, lung and kidney allograft recipients respectively. No K patient was receiving steroids nor any other immunosuppressant at the time of mTOR-IP diagnosis. In the K population, breast cancer was the first indication associated with mTOR-IP (33% of cases) (Table 3).

As far as the respiratory condition is concerned, 80% of the patients were symptomatic at the time of diagnosis with dyspnoea (65%), cough (45%) and fever (42%) being the most frequent signs. Chest pain and expectoration were observed in less than 10% of cases. No haemoptysis was reported. No clinical difference according to mTOR inhibitor indication or co-treatment was observed [Supplementary materials].

Almost all patients had a fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) (n = 35/39, 90%). mTOR-IP was mainly associated with a lymphocytic alveolitis (26 ± 21% of total BAL cells with a median CD4/CD8 ratio of 3.2 [0.3-6.9], Table 4). A neutrophilic alveolitis (PMN > 20%) was observed in 8 cases with no bacterial documentation. Biological blood features included a moderate increase in CRP (mean = 61 ± 47 mg/L) [Supplementary materials]. The presence of CT abnormalities was one of the mTOR-IP diagnostic criteria. The main radiological abnormalities were ground glass opacities (92%), reticulations (77%), bronchiectasis (51%) and condensations (50%) (Table 4). HRCT lesions were always bilateral. Pulmonary function tests (PFT), available in 20 patients as a whole at diagnosis, are

shown in Table 4. PFT were abnormal in 15 patients (75%) with a decreased in forced vital capacity (FVC) in 9 and a decreased in the diffusing capacity for carbon monoxide (DLCO) in 13. Altogether, no differences were found in terms of biological, functional or radiological data between TP and K patients. Pulmonary biopsies were performed for diagnostic purposes in 7 patients (6 TP and 1 K patient). Their pathological features were comparable and characterized by interstitial and alveolar lymphocytic infiltration with rare and poorly formed granulomas in the interalveolar walls and some organization buds in the interstitial and alveolar areas [Figure 2].

As a whole, the clinical management of mTOR-IP patients (N = 39) was on an outpatient basis for 13 patients (33%), hospitalization in 20 (51%) and transfer to an intensive care unit in 6 (15%). No difference was found in terms of biological, HRCT or pathological data between outpatients and those requiring hospitalization. In contrast, an univariate analysis of risk factors in the ICU population showed that overweight and renal impairment were associated with development of severe mTOR-IP (Table 5, $p = 0.006$ and 0.007, respectively). The mTOR-inhibitor treatment was withdrawn in 32 patients (82%) and steroids were either largely increased (TP group) or introduced (K group) in 21 (54%) at an average dose of 0.5mg/kg for a median duration of 4.5 (± 3.7) months. Two patients died from mTOR-IP (1 K patient under sirolimus and 1 TP one under everolimus). No difference was found between TP and K patients in terms of management requirements (Table 6). After recovery from mTOR-IP, mTOR inhibitors were permanently withdrawn in 24 of 39 patients (62%). In some of the most severe patients the drug was not withdrawn but a dose reduction of 50% was operated while it remained unchanged in others. A switch from sirolimus to everolimus was performed in one case without any recurrence of the mTOR-IP thereafter. A late recurrence of mTOR-IP occurred in two patients treated with everolimus after 18 and 45 months, respectively.

Regarding pharmacological data, the everolimus trough levels (C0) at the period free from lung ADR was firstly calculated from dosages collected in all transplanted patients treated with mTOR inhibitors between 2001 and 2020 at our pharmacology centre. No statistically significant difference was found between this reference $C0_{ref}$, based on the data of our centre, and $C0_{mTOR\text{-}IP}$ found at the time of mTOR-IP diagnosis ($C0_{ref}$ = 6.9 +/- 2.7 ng/mL, $C0_{mTOR\text{-}IP}$ = 8.1 +/- 2.6 ng/mL, p = 0.10). As dosages are not routinely performed in oncology, the data are not reported. At the time of mTOR-IP diagnosis, one patient (17%) in the lung TP group and 3 (25%) in the heart TP group had an everolimus C0 above the therapeutic range [Figure 3]. Potential interactions with other immunosuppressive drugs were evaluated in transplant patients. In the TP group, 4 and 10 patients were treated with cyclosporine and tacrolimus, respectively. No cyclosporine or tacrolimus blood levels overdose was observed in any of them. No impact of any other antirejection co-treatments was found on mTOR inhibitor dosage. In the K group, mTOR inhibitors trough levels are usually not routinely monitored and the everolimus one was assessed in only one patient. His C0 was 21 ng/mL, largely above the theorical average C0 in patients with either renal (5.4 ng/mL) or breast carcinoma (13.2 ng/mL) [42].

DISCUSSION

To the best of our knowledge, this study is the first one to report the prevalence and overall characteristics of mTOR-IP in both TP and K patients. We describe here in a large group (n=39) of patients with mTOR-IP (24 TP and 15 K) the clinical, functional, radiological, management and outcome characteristics of this rare but severe ADR.

Firstly, we found a prevalence of 6.4% of mTOR-IP among all patients treated with mTOR inhibitors in a single tertiary center between 2001 and 2020. We think that this is one of the main strengths of this study in that these data have been obtained by querying four

independent databases as described in the Materials and Methods section. We found a higher prevalence of mTOR-IP in K patients than in the TP ones (11.9% versus 5.2%, $p < 0.01$, respectively) whereas their clinical presentation, management and follow-up characteristics were quite comparable. This higher prevalence in the K group might have several explanations. Firstly, the chest CT-scan monitoring might be more systematic and frequent during cancer follow-up and this could could lead to a relative overdiagnosis in this population. Our study does not favor this hypothesis in that it did not show a higher prevalence of asymptomatic cases in the K group compared to the TP one. Secondly, a higher dosage of mTOR inhibitors as recommended in oncology might play a role in the development of symptomatic pulmonary ADR in this population. Thirdly, the fact that these patients do not routinely receive corticosteroids on a long term basis whether transplant recipients do might also underly part of the increased prevalence of the disease. Finally, a history of radiation therapy might also promote a pulmonary ADR particularly in patients with breast cancer.

We also show here that the main characteristics of mTOR-IP were quite comparable between the 2 groups. This might strongly argue for a common pathogeny, consistent with a pharmacological class effect, independent of the drug dosage, as developed in several studies [23]. However, a dose-dependent trigger could explain the earlier and more frequent occurrence of mTOR-IP in K patients. Indeed, different doses of active substances are now recommended or used in ongoing clinical trials for TP or K management : 0.5 – 2 mg and 5 – 10 mg, respectively [43–45] and some studies have reported a link between higher everolimus trough concentration and risk of ILD [32,46,47]. This dose-effect is also supported by clinical cases reporting mTOR-IP improvement after decreasing mTORi dosages [48]. Pharmacokinetic considerations, such as drug interactions, may also be involved in the pathogenesis of mTOR-IP. Interactions with immunosuppressive drugs used in

transplantation, in particular cyclosporine, which operates as an enzyme inhibitor and increases mTOR blood concentration, that may increase sirolimus concentration [49]. Drug interactions with azoles and long-term treatment with corticosteroids that respectively increase and decrease blood everolimus concentration, have also been reported and should be considered in transplant patients.

In our study, beside a significantly shorter delay of occurrence of mTOR-IP in the cancer population compared to the TP one, all their other characteristics were comparable and quite consistent with other drug-induced pneumonitis reported in the literature [50–52]. We noted indeed a rapidly evolving dyspnea (1 to 3 weeks), cough without expectoration and low grade fever in 50% of cases. The main biological finding was a moderate lymphocytic alveolitis exhibited by the bronchoalveolar lavage (BAL) with a predominance of CD4 cells; more rarely, a minor hypereosinophilia or a low grade alveolar haemorrhage was present in BAL, as it has been reported in the literature [26,27,53]. Although not specific for drug-induced pneumonitis, BAL is a crucial tool to rule out bacterial, viral or parasitic infection especially in immunocompromised patients [54] and should always be performed whenever possible. Chest CT-scan findings were mainly reticulations, ground glass opacities with a lower frequency of condensations or traction bronchiectasis. Honeycombing or fibrotic lesions were exceptional as well as pleural effusions and/or mediastinal lymphadenopathy which should always be investigated as an alternative diagnosis. In cases of doubtful diagnosis, transbronchial biopsies may be performed especially in lung transplant patients to rule out rejection. Histological analysis of our own samples showed inflammatory infiltrates with a predominance of lymphocytes both in the alveolar walls and the interstitial spaces, with sometimes the presence of poorly formed granulomas.

About 30% of our patients could be managed on an outpatient basis and hospitalisation in an intensive care unit was required in less than 10% of cases. Treatment was based on

withdrawing the mTOR inhibitor (80% of cases) or reducing the dosage (20%). The drug could be reintroduced in 30% of cases; the recurrence rate was moderate, approximately around 5%. 18 on 21 patients (86%) who required steroids as part of the treatment of mTOR-IP had dyspnea or severe cough with oxygen requirement. Eight patients with chronic dyspnea (> 3 weeks) were not treated with corticosteroids and had a favourable outcome.

Overall, our clinical practice concerning these patients were quite in line with the guidelines for an optimal management of mTOR-IP in the breast cancer setting [55] recommending corticosteroids for a Grade 2b ADR and higher, defined by dyspnea or severe cough (48). mTOR inhibitors at a lower dose may be reintroduced if symptoms resolve to Grade 1, except for Grade 4 ILD. It should be underlined however that in the particular context of heart transplantation, the substantial risk reduction of graft loss when using everolimus [56,57] may prioritize this drug continuation along with steroids over its withdrawal if clinical symptoms are minor.

Our study also allowed us to define 2 significant risk factors for a severe outcome of ICU hospitalization, i.e. overweight and renal impairment. Indeed, our 6 cases requiring ICU were clinically characterised by a higher frequency of renal failure and/or overweight and biologically by a neutrophilic alveolitis in BAL. Renal impairment had been previously reported as a risk factor for the development mTOR-IP [58,59] and obesity is known to be associated with a poor prognosis in many situations of acute respiratory failure [60,61]. Neutrophilic alveolitis, independently of any infection documentation, might reflect a relative alveolar damage [62].

Our study has also some limitations. First of all, the diagnosis of mTOR-IP is a diagnosis of exclusion. However, diagnostic criteria used in our study are based on the princeps study by Morelon et al, used in a reference list of studies regarding mTOR-IP [2,21,40,63]. In addition,

all medical records, BAL and biopsies were reviewed by experts in interstitial diseases. We have excluded during this process all cases of concomitant infection for the sake of drug-induced pneumonitis diagnosis unicity. This might have led us to underdiagnose true cases of mTOR-IP as potential interactions with infections, especially Pneumocystis Jiroveci, have been mentioned [54,64,65]. The retrospective nature of our study is also a limitation because of missing data. The fact that we have not reviewed the chest CT- scans of the 608 patients under mTOR-I during the period considered (2001-2020) may have underestimated asymptomatic cases. This approach has been used in other studies, particularly in oncology, with a systematic reviewing of CT-scans performed as part of a therapeutic protocol. The prevalence of mTOR-IP was then higher, with 29% in the trials for temsirolimus and up to 54% of radiological abnormalities for everolimus in kidney cancer [2,12,35]. Again, this work had focused on patients with a clinical mTOR-IP diagnosis and not only radiological abnormalities which seemed to us far more relevant for clinicians dealing with such patients. Finally, the small size of our cohort, although larger than the majority of those in the literature, did not allow us to perform multivariate analyses, especially for severity risks factors. Despite of all of these limitations, we think that the approach we used in our retrospective study gave interesting data about presentation, prognosis, management and outcome of mTOR-IP in TP patients as well as in K ones.

CONCLUSION

Our study provides an updated overview of mTOR-IP characteristics and prevalence and points towards a common entity whatever the mTOR inhibitor indications and molecules. However, mTOR-IP occurs significantly earlier after drug introduction in K patients. This raises questions as to the potential role of the higher doses used in oncology as well as that of co-treatments in the pathogeny of the disease.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by Institutional Review Board of the French Learned Society for Respiratory Medicine (reference: CEPRO 2020-046).

INFORM CONSENT

Informed consent was obtained from all subjects included in the study, in accordance with current recommendations.

AVAILABILITY OF DATA AND MATERIAL

We inform the scientific community of the availability of the datasets used in this original article and their potential future uses.

COMPETING INTERESTS

The authors declare that they have no competing interests

FUNDING SOURCE

No funding

AUTHORS CONTRIBUTION

SG, JP and DIB analysed and interpreted the patient clinical, radiological and outcome data regarding mTOR-IP disease. LG performed the histological examination and was a major contributor in writing the manuscript. EB analysed the pharmacological and was a major contributor in writing the manuscript. ALL analysed epidemiological data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Table 1 – Patients demographic and clinical characteristics at baseline

CHARACTERISTICS	***Overall population (OP) N = 39***	***Cancer population (K) N = 15***	***Transplantation population (TP) N = 24***	*p-value*
Female sex - N (%)	17 (44%)	7 (47%)	10 (42%)	1.000
Age - Yr (± sd)	58 (± 19)	69 (± 9)	51 (± 20)	0.002
Smoker - N (%)	14 (36%)	4 (27%)	10 (42%)	0.544
Comorbidities - N (%)				
Arterial Hypertension	22 (56%)	7 (47%)	15 (63%)	0.523
Diabetes	7 (18%)	1 (7%)	6 (25%)	0.306
Dyslipidemia	14 (36%)	5 (33%)	9 (38%)	1.000
Stroke	2 (5%)	1 (7%)	1 (4%)	1.000
Heart attack	5 (13%)	2(13%)	3 (13%)	1.000
Renal Failure	11 (29%)	3 (21%)	8 (33%)	0.682
mTORi indication - N (%)				
Heart allograft rejection	-	-	13 (54%)	-
Lung allograft rejection	-	-	6 (25%)	-
Renal allograft rejection	-	-	5 (21%)	-
Renal cancer	-	8 (53%)	-	-
Breast cancer		5 (33%)		
Neuroendocrine cancer	-	2 (13%)	-	-
mTORi molecule - N (%)				0.057
Everolimus	33 (85%)	13 (87%)	20 (83%)	
Sirolimus	4 (10%)	0 (0)	4 (17%)	
Temsirolimus	2 (5%)	2 (13%)	0 (0)	
mTOR inhibitor dose - mean (± sd) (mg)				
Everolimus		8.75 (± 2.26)	2.65 (± 1.78)	< 0.001
Sirolimus		-	2.75 (± 0.96)	
Temsirolimus		NA	-	

Abbreviations: OP (Overall population) ; K (Cancer population) ; TP (Transplantation population) ; N (number) ; Yr (Year) ; sd (standard deviation) ; mTORi (mammalian target of rapamycin inhibitor) ; mg (milligrams).

Table 2 - Time between mTOR inhibitors introduction and mTOR-IP development according to type of molecule and indication (months)

POPULATION	*Time between mTOR introduction and mTOR-IP Median [IQR]*	*p-value*
Overall population	7 [3 – 35]	
By indication		< 0.001
Transplantation population	12 [5 – 42]	
Cancer population	3 [2 – 6.5]	
By treatment		< 0.47
Everolimus	8 [4 – 37]	
Sirolimus/Temsirolimus	4 [2 – 10]	

Abbreviations: mTOR-IP (mTOR-inhibitors-associated pneumonitis) ; IQR (Interquartil Range)

Table 3 – Prevalence of mTOR-induced IP according to indications and type of molecules

	Overall population N	***mTOR-IP N***	***Prevalence - %***
ALL PATIENTS	608	39	6.4%
BY INDICATION			
TRANSPLANTATION	465	24	5.2%
Heart transplantation	238	13	5.5%
Kidney transplantation	91	5	5.5%
Lung transplantation	132	6	4.5%
Other transplantation	4	0	-
CANCER	119	15	12.6%
Renal cancer	99	8	8.1%
Breast cancer	15	5	33.3%
Other cancer	5	2	-
OTHER INDICATIONS	24	0	
BY TREATMENT			
EVEROLIMUS	515	33	6.4%
SIROLIMUS	64	4	6.3%
TEMSIROLIMUS	29	2	6.9%

Abbreviations: mTOR-IP (mTOR-inhibitors-associated pneumonitis) ; sd (standard deviation)

Table 4 – Biological, radiological and functional characteristics of patients with mTOR-IP

	Overall population (OP)	***Cancer population (K)***	***Transplantation population (TP)***	***p-value***
BRONCHOALVEOLAR CHARACTERISTICS	N = 29	N = 11	N = 18	
Cellularity (.10^3 cells/ml) – mean (± sd)	380 (± 271)	378 (± 285)	381 (± 271)	0.848
Lymphocytes – mean (± sd)	26 (± 21)	33 (± 24)	22 (± 19)	0.271
CD4/CD8 report- mean (± sd)	3 (± 2)	4 (± 2)	2 (± 2)	0.234
RADIOLOGICAL FUNDINGS	N = 39	N = 15	N = 24	
Ground glass opacities – N (%)	36 (92%)	15 (100%)	21 (88%)	0.271
Reticulations – N (%)	30 (77%)	14 (93%)	16 (67%)	0.115
Condensations – N (%)	19 (50%)	9 (64%)	10 (42%)	0.313
Bronchiectasis – N (%)	20 (51%)	11 (73%)	9 (38%)	0.048
RESPIRATORY FUNCTIONS TESTS	N = 20	N = 8	N = 12	
FVC (%) – median [IQR]	80 [69 – 91]	96 [81 – 111]	78 [60 – 80]	0.011
DLCO (%) – median [IQR]	52 [41 – 60]	63 [41 – 75]	52 [39 – 52]	0.155
KCO (%) – median [IQR]	66 [57 – 80]	68 [64 – 89]	58 [54 – 74]	0.203

Abbreviations: mTOR-IP (mTOR-inhibitors-associated pneumonitis) ; OP (Overall population) ; K (Cancer population) ; TP (Transplantation population) ; N (number) ; ml (millilitres) ; sd (standard deviation) ; CD (cluster of differentiation) ; FCV (Forced Vital Capacity, % predicted) ; DLCO (diffusing capacity for carbon monoxide, % predicted) ; KCO (volume standardized measure of DLCO, predicted).

Table 5 - Risk factors for severe mTOR-IP (univariate analysis)

INTENSIVE CARE UNIT HOSPITALISATION	**YES (N = 6) N (%)**	**NO (N = 33) N (%)**	**P-VALUE (UNIVARIATE ANALYSIS)**
BMI > 30 KG/M² - N (%)	3 (50%)	1 (3%)	0.006
BAL PNN > 30% - N (%)	3 (50%)	2 (7%)	0.007
GLOBULAR FILTRATION RATE < 30 ML/MIN/1.73M² - N (%)	5 (83%)	6 (19%)	0.007

Abbreviations: mTOR-IP (mTOR-inhibitors-associated pneumonitis) ; BMI (Body Mass Index) ; BAL (bronchoalveolar lavage) ; PNN (polymorphonuclear) ; kg (kilograms) ; m (meters) ; N (number) ; ml (millilitres).

Table 6 - Management of mTOR-IP

	Overall population (OP) (N = 39)	***Cancer population (K) (N = 15)***	***Transplantation population (TP) (N = 24)***	***p-value***
Place of care - N (%)				0.745
Outpatient	13 (33%)	4 (27%)	9 (38%)	
Conventionnal hospitalisation	20 (51%)	9 (60%)	11 (46%)	
Intensive care unit	6 (15%)	2 (13%)	4 (17%)	
Treatment - N (%)				
Oxygen	12 (31%)	6 (40%)	6 (25%)	0.478
Non-invasive ventilation	4 (10%)	2 (13%)	2 (8%)	0.631
Invasive ventilation	3 (8%)	1 (7%)	2 (8%)	1.000
Corticosteroids	21 (54%)	6 (40%)	15 (63%)	0.203
Dose (mg/kg) -mean (± sd)	0.5 (± 0.5)	0.4 (± 0.6)	0.5 (± 0.5)	0.454
mTORi management - N (%)				0.818
Stop	32 (82%)	13 (86%)	19 (79%)	
Continued	7 (18%)	2 (14%)	5 (21%)	
Intra-hospital mortality - N (%)	2 (5%)	1 (6%)	1 (4%)	1.000

Abbreviations: mTOR-IP (mTOR-inhibitors-associated pneumonitis) ; OP (Overall population) ; K (Cancer population) ; TP (Transplantation population) ; N (number) ; mg (milligrams) ; kg (kilograms) ; mTORi (mammalian target of rapamycin inhibitor).

Figure 1 – Flow-Chart: selection of the target, eligible and study population

Figure 2 – Pathological characteristics of mTOR-IP: transbronchial biopsy

Figure 3 - Evolution of everolimus C0 blood levels at the time of mTOR-IP diagnosis and during the two previous everolimus blood levels assessment (D-1 and D-2) in the lung (N= 6) and heart (N = 12) transplantation population (TP)