Pulmonary toxicity of mTOR inhibitors in kidney transplantation: A single-center experience

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Abstract

Objective: The purpose of this report was to describe the clinical features of mammalian target of rapamycin inhibitors (mTORi) pulmonary toxicity in kidney recipients. **Material and methods:** We analyzed clinical, analytical, and image data of all kidney recipients who were immunosuppressed with everolimus or sirolimus, between 2013 and 2018. **Results:** From a pool of 379 recipients, 12 presented evidence of mTORi-induced hypersensitivity pneumonitis. The median age at onset of pneumonitis was 62.8 years. The majority had chronic graft dysfunction, with a median serum creatinine of 1.9 mg/dL. All patients were under mTORi for at least 2 years. The most common symptoms were cough and fever. Chest computerized tomography documented ground-glass opacities and lower lobe involvement in all patients. Two required mechanical ventilation, one of which died (the only dead in this series). **Conclusions:** The size of this sample does not allow inferring about risk factors or prognosis predictors. However, most patients were male, with chronic graft dysfunction and exposure to mTORi for at least 2 years. mTORi-induced pneumonitis is rare but potentially fatal. It should be included in the differential diagnosis of pulmonary conditions in these patients.

Key words: Hypersensitivity pneumonitis. Mammalian target of rapamycin inhibitors. Kidney transplantation. Pulmonary toxicity.

Toxicidad pulmonar de los inhibidores de mTOR en pacientes con trasplante de riñón: experiencia de un centro

Resumen

Objetivo: El propósito de este trabajo fue describir las características clínicas de la toxicidad pulmonar de mTORi en receptores renales. **Materiales y métodos:** Analizamos datos clínicos, analíticos e de imagen de los pacientes con trasplante de riñón inmunosuprimidos con everolimus (EVR) o sirolimus (SRL), entre 2013 y 2018. **Resultados:** De un grupo de 379 receptores, 12 presentaron evidencia de HP inducida por mTORi. La mediana de edad al inicio de la neumonitis fue 62,8 años. La mayoría presentaba disfunción crónica del injerto (creatinina mediana de 1,9 mg/dL). En el diagnóstico, todos los pacientes estaban inmunosuprimidos con mTORi durante al menos 2 años. Los síntomas más comunes fueron

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tos y fiebre. La tomografía computarizada de tórax documentó opacidades en vidrio deslustrado y afectación del lóbulo inferior en todos los pacientes. Dos requirieron ventilación mecánica, uno de los cuales falleció. **Conclusiones:** El tamaño de esta muestra no permite inferir sobre factores de riesgo o de pronóstico. La mayoría de los pacientes eran hombres, con disfunción crónica del injerto y exposición a mTORi durante al menos 2 años. La neumonitis inducida por mTORi es rara pero potencialmente mortal. Debe incluirse en el diagnóstico diferencial de afecciones pulmonares en estos pacientes.

Palabras clave: Inhibidores de mTOR. Neumonitis por hipersensibilidad. Trasplante de riñón. Toxicidad pulmonar.

Background

Mammalian target of rapamycin inhibitors (mTORi) are antiproliferative agents with a wide spectrum of actions, used as immunosuppressant in solid organ transplantation (heart, lung, and kidney) and as anti-neoplastic agents. However, these drugs are associated with a great number of potential side effects that could involve almost all organ systems^{1,2}.

After SYMPHONY trial showed low-dose calcineurin inhibitors superiority, mTORi use as immunosuppressant decreased during the second decade of XXI century. However, recent evidence resuscitates mTORi role in kidney transplantation (KTx) immunosuppression, as an option in low-/moderate-risk patients^{3,4}. Despite this, mTORi remained essential in the setting of calcineurin inhibitors toxicity, Kaposi sarcoma, lymphomas including Epstein–Barr virus-related post-transplant lymphoproliferative disorders, and skin and kidney neoplasms^{5,6}. Furthermore, they are the favorite agents in the setting of viral diseases including cytomegalovirus^{7,8} and human polyomavirus^{9,10}. Finally, mTORi may replace mycophenolate due to its side effects, including neutropenia and gastrointestinal complaints.

Hypersensitivity pneumonitis (HP) is a rare adverse effect, initially described in patients under SRL, probably because this was the first approved mTORi, but more recently recognized as a class side effect^{11,12}. The lack of uniform diagnostic criteria led to wide reported incidence rates¹³.

The exact pathophysiology is unknown, with both immune-mediated and direct toxicity mechanisms already described. A dose-dependent mechanism is suspected, because HP rates are higher in the oncology setting, as higher doses are used when compared to solid organ transplantation^{12,13}. An immunological mechanism was suggested because of the lymphocytosis and eosinophilia is detected on bronchoalveolar lavage (BAL) (see ahead). Delayed T-cell-mediated hypersensitivity has also been described^{1,12-14}.

HP develops only in a minority of exposed individuals, suggesting either genetic predisposition or simultaneous exposure to another trigger. Risk factors include a late switch to mTORi and impaired kidney function^{13,15}. For SRL, male sex and a higher age are also considered risk factors. There is no association with a history of smoking, chronic obstructive pulmonary disease, or abnormal baseline pulmonary function test¹³.

mTORi-induced HP is mainly asymptomatic, or just mildly symptomatic with dry cough, dyspnea, hypoxia, occasionally with hemoptysis and systemic symptoms, such as fever and fatigue. Rarely, symptoms are severe and may progress to potentially life-threatening disease requiring mechanical ventilation^{1,12,13,16,17}. The reported time for HP onset is wide, from months to years^{12,13}.

The non-specific clinical features require exclusion of entities more common in these patients, namely, opportunistic infections, a much more common adverse effect of mTORi use. The diagnosis is also supported by laboratory and imaging studies^{12,13}.

A temporal association between drug exposure and HP onset may exist, but previous cases describe a wide temporal window, until up to 6 years after first exposure¹¹.

Drug withdrawal is the cornerstone of treatment, but some reports suggest improvement with dose reduction^{12,13,15,18}.

The purpose of this report was to describe the clinical features of mTORi pulmonary toxicity in KTx recipients.

Subjects and methods

We retrospectively reviewed all KTx recipients from our center, to whom immunosuppression with everolimus (EVR) or SRL was prescribed between 2013 and 2018. We identified 379 recipients under mTORi in that period (303 were under EVR and 158 under SRL; 86 of those patients were initially under SRL and were converted to EVR later).

We analyzed clinical, analytical, and image data of those recipients, to identify the ones with evidence of respiratory symptoms, with or without constitutional symptoms (fever and fatigue), after mTORi first prescription (in the absence of features to suggest a systemic rheumatic disease). HP diagnosis was established with the presence of typical chest CT findings, BAL lymphocytosis (>20%), and response to antigen avoidance. In the presence of the three criteria, histopathologic confirmation is not necessary¹⁹. Fourteen recipients presented evidence of HP, but two were excluded because we could not exclude pneumonitis due to another cause. Infectious process was excluded based on analytical evaluation (negative C-reactive protein and leukocytes blood count within normal range), BAL results, suggestive chest CT features, and clinical evolution, including improvement after drug withdrawal.

For the 12 recipients with evidence of mTORi-induced HP, we collected demographic and clinical data, namely, comorbidities (including previous respiratory infections/disease), kidney graft function, history of immunosuppression and other medications with recognized pulmonary toxicity (e.g., amiodarone), diagnostic tests, treatments, and outcomes. Until December 2019, all serum creatinine and blood mTORi measurements were performed in the same laboratory.

Data are presented as medians and interquartile range (IQR) or frequencies and proportions whenever appropriate. Data were analyzed using IBM® SPSS version 23.0 (SPSS, Inc., Chicago, IL) statistical software.

Results

From a pool of 379 KTx recipients, 12 presented evidence of mTORi-induced HP (3.2%). Table 1 summarizes the patient characteristics (Table 1).

The median age at HP onset was 62.8 (IQR 51.5-68.9) years. Eleven patients were male, and 10 patients were Caucasian. At the time of HP onset, most patients (n = 11) had chronic graft dysfunction, with a median serum creatinine of 1.9 (IQR 1.5-2.3) mg/dL.

At the time of HP diagnosis, nine patients were under EVR and three under SRL. Four of the patients currently under EVR have been on SRL previously.

Three patients presented at least two lower respiratory infections in the previous year of HP diagnosis. One other patient had two consecutive episodes 3 years before diagnosis. Other three patients had a previous pulmonary disease and two were currently

taking another drug with recognized pulmonary toxicity (amiodarone).

All patients had chronic treatment with prednisone and were previously under immunosuppression with calcineurin inhibitors (three with ciclosporin and the remaining with tacrolimus). After KTx, patients were converted to mTORi after a median time of 12.2 (IQR 8.4-34.6) months.

At the time of HP diagnosis, all patients were under mTORi for at least 2 years (median time since mTORi initiation of 85.0 [IQR 44.5-100.4] months). At diagnosis, the median trough level for EVR was 5.7 (IQR 5.3-6.7) µg/L and for SRL 3.5 (3.3-3.8) µg/L. Six months before, the median trough levels were slightly superior: EVR 7.6 (IQR 4.9-8.4) µg/L and SRL 6.2 (5.0-11.8) µg/L. However, no trough level was in a toxic range.

The most common symptoms were dry cough (n = 8) and low-grade fever (n = 5). Three patients presented hemoptysis and two referred dyspnea. Chest CT¹¹ revealed ground-glass opacities in all patients and a micronodular pattern in two of them. Lower lobe was involved in all patients and bilateral pulmonary involvement was observed in the majority (n = 10). BAL was performed in four patients: three unveiled evidence of lymphocytic alveolitis and the fourth presented no changes. Only two patients performed functional pulmonary tests [FPT], describing a restrictive pattern.

Two patients required mechanical ventilation, and one of them eventually died during intensive care unit (ICU) admission (the only death in this series). All but one patient had clinical improvement after withdrawal of mTORi and reversion to calcineurin inhibitors. We present the radiographic evolution of patient number 5 (Figs. 1 and 2), unveiling a dramatic improvement of the detected changes within 3 months of mTORi withdrawal, with simultaneous clinical improvement. Two patients were additionally treated with increased doses of systemic corticoid.

Seven patients repeated the chest CT scan, showing radiologic improvement, within a median time of 3.4 (IQR 2.7-10.7) months.

Discussion

Initial reports of HP related with mTORi were attributed to SRL, the first of this class to be approved^{14,15,17}, and subsequently reports showed a great number of cases related to EVR¹¹. In our study, there were more cases related to EVR due to its greater current use.

Several risk factors already described in the literature^{13,15}, such as male sex and impaired kidney

Table 1. Patient's characteristics

	Patients											
	1	2	3	4	5	6	7	8	9	10	11	12
mTORi	EVR	EVR	(SRL) EVR	EVR	(SRL) EVR	EVR	(SRL) EVR	EVR	(SRL) EVR	SRL	SRL	SRL
Age, years	63	66	78	59	70	63	71	51	45	54	63	53
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Female
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Black	Black	Caucasian	Caucasian
Nephropathy	ADPKD	ADPKD	Analgesic NP	Unknown	Diabetic NP	ADPKD	Hypertensive NP	Unknown	Hypertensive NP	Hypertensive NP	ANCA vasculitis	FSGS
Basal SCr, mg/dL	2.3	1.5	2.5	1.7	1.3	1.0	1.5	2.0	2.5	2.2	2.0	1.8
Smoking status	No	No	No	No	No	Previous	No	No	No	No	No	No
Previous respiratory infections	Yes Last year	Yes Last year	No	Yes Last year	No	No	No	No	Yes	No	No	No
Underlying respiratory disease	No	Bronchiectasis	No	No	No	Neoplasm	No	No	No	No	No	Asthma
Concomitant pulmonary toxic medication	No	No	Amiodarone	No	No	No	No	Amiodarone	No	No	No	No
Previous IS (other classes)	FK	CsA	CsA	FK	FK	FK	FK	FK	FK	FK	CsA	FK
Concomitant IS	CTS MP	CTS MP	CTS MA	CTS MP	CTS MA	CTS MP	CTS MP	CTS MP	CTS MP	CTS MP	CTS MP	CTS MP
Time from KTx to mTORi initiation, months	4.8	10.1	7.8	12.0	41.7	64.9	12.4	13.1	11.9	87.5	4.6	12.6
Total time from mTORi initiation to HP onset, months	40.8	55.5	86.8	63.2	133.8	100.0	100.5	34.8	94.4	83.2	38.6	178.1

(continues)

Table 1. (continuación)

	Patients											
	1	2	3	4	5	6	7	8	9	10	11	12
Drug through level 6 months before the onset, µg/L	7.8	5.8	6.1	5.3	7.6	9.0	8.2	4.0	5.0	11.8	6.2	6.1
Drug through level at onset, µg/L	5.5	5.2	5.9	5.1	6.2	5.8	8.0	5.4	3.5	4.7	3.3	5.7
Dry cough	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
Fever	Yes	No	No	Yes	No	No	Yes	No	No	No	Yes	Yes
Hemoptysis	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No
Dyspnea	No	Yes	Yes	No	No	No	No	No	No	No	No	No
Chest CT	GGO; Inferior lobe; Bilateral	GGO; Micronodular pattern; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Unilateral	GGO; Inferior lobe; Bilateral	GGO; Inferior lobe; Bilateral	GGO; Micronodular pattern; Inferior lobe; Unilateral
BAL	Lymphocytosis >60%	-	-	-	-	Lymphocytosis >20%	-	-	-	Lymphocytosis >80%	-	No changes
PFT	-	Restrictive pattern	-	-	-	Restrictive pattern	-	-	-	-	-	-
MV	No	No	No	No	No	No	No	No	No	No	Yes	Yes
Treatment	Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal; SC	Withdrawal	Withdrawal; SC	Withdrawal
IS conversion	CsA	FK	FK	FK	FK	FK	CsA	FK	-	CsA	CsA	FK
Clinical improvement	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Death	Yes	No	Yes
Chest CT – after withdrawal	Improvement	Improvement	-	Improvement	Improvement	-	Improvement	-	-	Improvement	Acute and chronic changes	Improvement

(-) Represents the previous mTOR inhibitor; ADPKD: autosomal dominant polycystic kidney disease; ANCA: antineutrophil cytoplasmic antibody; BAL: bronchoalveolar lavage; CsA: ciclosporin; CT: computerized tomography; CTS: corticosteroids; EVR: everolimus; FK: tacrolimus; FPT: functional pulmonary tests; FSGS: focal segmental glomerulosclerosis; HP: hypersensitive pneumonitis; IS: immunosuppression; KT: kidney transplantation; mTORi: mammalian target of rapamycin inhibitors; MV: mechanical ventilation; NP: nephropathy; RRI: recurrent respiratory infections; SCr: serum creatinine; SRL: sirolimus.

Figure 1. Chest CT from patient number 5, upper and lower views, before mTORi withdraw, showing bilateral ground glass opacities.

Figure 2. Chest CT from patient number 5, upper and lower views, 3 months after mTORi withdraw, showing a dramatic improvement of the affected areas.

function, were also observed in our group of patients. However, there is neither a clear predominance of older patients nor evidence for a later switch to mTORi. All patients were under mTORi for at least 2 years (median time of exposition of 85.0 months), suggesting a tendency to a longer exposure time and cumulative dose before the pneumonitis diagnosis.

Despite a dose-related effect has been suggested, published cases showed both association with supra-therapeutic and therapeutic levels^{15,17}. In our series, drug through levels were within therapeutic range at HP onset, although slightly elevated 6 months earlier, but never in a toxic range.

The clinical and radiological features of our patients were similar to the ones observed in previous reports. The most prevalent symptoms were dry cough and dyspnea. Half of our patients suffered from recurrent respiratory infections during the time of immunosuppression with mTORi.

Chest radiography is usually the first step in the evaluation, but it either is normal or reveals nonspecific features. Chest CT may reveal ground-glass opacities, the most common feature, compatible with diffuse alveolar hemorrhage. Although characteristic, this finding may be seen in other disorders, namely, in opportunistic infections, pulmonary edema, and cellular non-specific interstitial pneumonia. A reticular micronodular pattern and focal areas of consolidations are also common. These features were described on high-resolution CT in asymptomatic patients, probably representing the initial pulmonary changes. However, the clinical implications of those changes in the absence of symptoms remain unknown. Usually, the pulmonary abnormalities on CT are bilateral and in the lower lobes^{1,13,18}.

BAL is considered the most sensitive diagnostic tool. The typical pattern is lymphocytic alveolitis (lymphocytosis > 20%), mainly CD4⁺ cells, with or without eosinophilia. It may also show evidence of alveolar

hemorrhage, with macrophage hemosiderosis^{14,17,18}. As suggested by Mayo Clinic investigators²⁰, these findings suggest two possible HP phenotypes, what probably explains the wide spectrum of symptoms and prognosis: a lymphocytic pneumonitis without alveolar hemorrhage or alveolar hemorrhage without lymphocytic pneumonitis. All things considered, probably, the most specific way to diagnose this entity is to do a thorough diagnostic workup with all the aforementioned studies.

Considering the current pandemic situation, one additional point needs to be highlighted. The possibility of COVID-19 should be considered primarily in immunosuppressed patients with respiratory tract symptoms or severe lower respiratory tract illness with no other apparent cause. Some CT findings of mTORi-induced HP may be similar to features observed in COVID-19, namely, bilateral ground-glass opacities^{21,22}. It is essential to compare the current radiological findings with previous chest radiographies or CTs in infected patients under mTORi. It is still uncertain whether infected patients previously under mTORi should have this therapy replaced, particularly in the setting of hypoxemia.

All patients in our series presented typical CT findings. The diagnosis was confirmed by BAL findings in three patients (lymphocytosis) and in the remaining ones, by clinical and radiological improvement with drug withdrawal. In two patients, HP diagnosis was assumed as “probable:” one died short term after the diagnosis; the other patient presented ANCA vasculitis with pulmonary involvement, and chest CT showed acute features suggestive of both diagnosis and chronic characteristics of mTORi pneumonitis (fibrosis in the previous affected lobes).

Drug withdrawal is the cornerstone of treatment, and it should be permanently discontinued in cases of life-threatening HP. Symptoms usually improve after cessation, but certain individuals may develop pulmonary fibrosis by a mechanism not completely understood. In patients with progressive disease, a restrictive pulmonary disease sets in, and FPT may be useful to determine HP severity and to follow clinical evolution¹³.

Treatment with corticosteroids is not widely accepted due to lack of evidence, but it should be considered in selected patients. On the other hand, in certain circumstances, a watchful waiting could be an accepted approach^{1,12,13,15-18}.

In our series, all patients interrupted the drug and were reconverted to calcineurin inhibitors and/or mycophenolate. Two patients underwent a course of higher doses of corticosteroids, one during ICU admission (the only death in this series) and the other with a favorable outcome.

The remaining patients evolved favorably, except the one with associated ANCA vasculitis.

Conclusions

The size of this sample does not allow inferring about risk factors or predictors of prognosis. However, most patients were male, with chronic graft dysfunction and exposure to the drug for at least 2 years. Chest CT was the most relevant complementary means for the identification of this pathology.

In conclusion, mTORi-induced pneumonitis is rare but should not be underestimated, because it can lead to respiratory insufficiency (acutely and chronically) and even death. Therefore, it should be included in the differential diagnosis of pulmonary conditions in these patients because early recognition and treatment are essential.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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