

M-TOR INHIBITORS-INDUCED PNEUMONITIS IN RENAL TRANSPLANTED PATIENTS: A SINGLE CENTER EXPERIENCE

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OBJECTIVES

- The **mTOR inhibitors drugs (mTORi)**, sirolimus and everolimus, are both associated with **pulmonary toxicity**.
- **Radiological images** of mTORi-induced pneumonitis are characterized either by **interstitial damage (NSIP)** or by **organizing damage (OP)**¹ (Figure 1).
- The overall experience in Literature with mTORi-induced pneumonitis incidence, clinical relevance, risk factors and outcomes in renal transplanted patients is limited.¹⁻⁵(Figure 2)

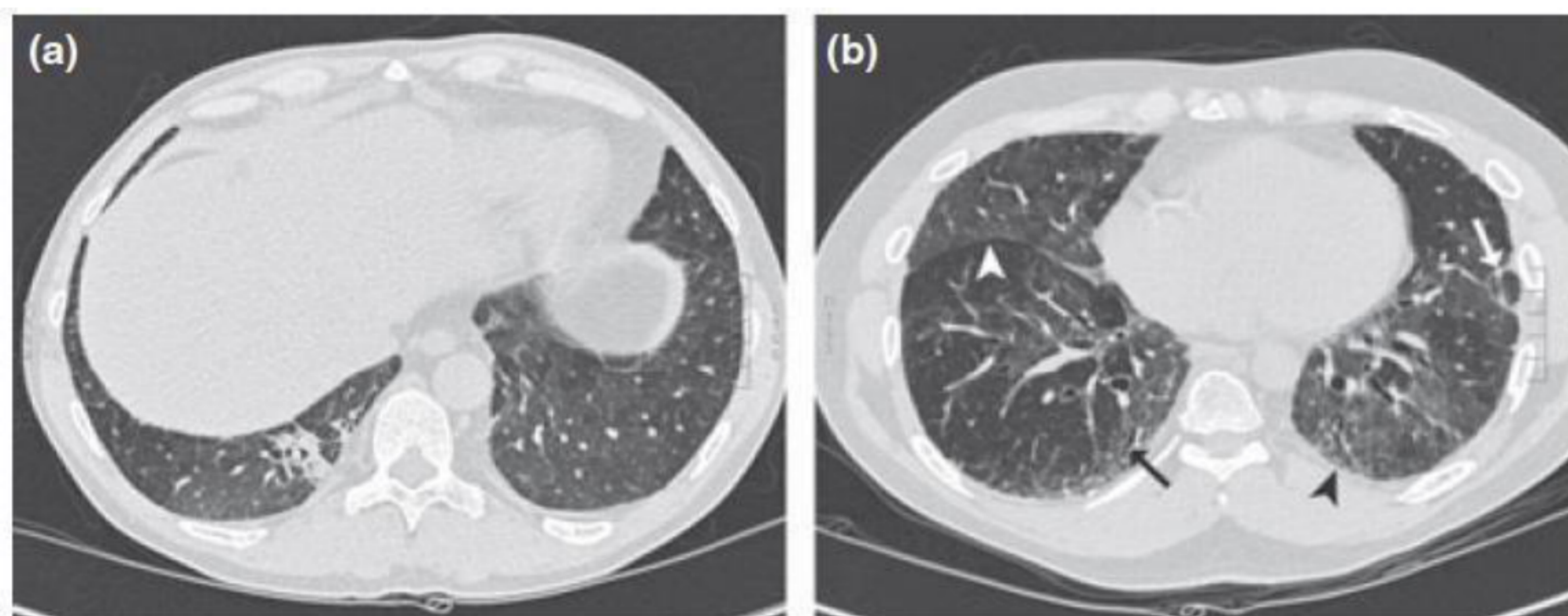


Figure 1. mTORi-induced pneumonitis on TC-scan a) organizing pattern b) interstitial pattern (adapted from Baas et al Transpl Int 2014)

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|---|--|
| Incidence | 4-16.7% |
| Time between mTORi introduction and radiological demonstration of mTORi-induced pneumonitis | 30-1530 days |
| Symptoms | Fever+cough+dyspnoea (classic presentation) Mild/severe respiratory impairment |
| mTOR threshold level associated with mTORi-induced pneumonitis | No |
| Radiological data | Non specific interstitial pneumonia (NSIP) Organising pneumonia (OP) Mixed pattern |
| BAL data | Lymphocytic alveolitis Eosinophilic alveolitis (possible) Foamy macrophages (not specific) |
| Treatment | Drug Interruption Steroids (in case of severe pulmonary impairment) mTORi dose reduction? Conversion to other mTORi drug? |

Figure 2. mTORi-induced pneumonitis characteristics (based on Literature data)

CONCLUSIONS

- In the AA's experience mTORi-induced pneumonitis is not such a rare adverse event as initially reported in literature data (incidence 3,9%)
- **An early diagnosis, a multidisciplinary approach and a defined diagnostic pathway** (CT scan, PFTs and bronchoalveolar lavage) are the baseline cornerstones for a possible positive outcome.

On the basis of their favorable experience the AA's suggest:

- a) to adopt a **steroid based therapeutic regimen** in patients with **severe pulmonary impairment**.
- b) to **withdraw mTORi** after a diagnosis of mTORi-induced pneumonitis **if not elsewhere contraindicated** (i.e. cancer in the patient)
- c) to **consider the mTORi-induced pneumonitis diagnosis also without classic symptoms or sovranormal mTORi serum levels**

METHODS

We performed a retrospective analysis among the **434/1052 mTORi-treated** (in continuous or intermittent protocols) renal transplanted patients in our Center between 01/01/1997-12/31/2011.

RESULTS

- **mTORi-induced pneumonitis** was observed in **17/434** (incidence **3,9%**)

Characteristics of mTORi-induced pneumonitis group:

- **7/17** patients mTORi treated **ab-initio**
- Ratio M/F 8/1; median age **58 years** (min-max 35-70)
- **Risk factors** (smoke, a pre-existant pneumopathy, post-transplant CMV infection) in **5/17**
- **Classic symptoms** (fever+cough+dyspnoea) in **6/17**.
- **Median time between mTORi introduction and radiological demonstration** of mTORi-induced pneumonitis **716 days** (min-max 66-3176)
- **Median mTORi serum levels** detected respectively 6, 3, 1 months before pneumonitis onset and at diagnosis: **similar** (7 ng/mL, 8 ng/mL, 7.6 ng/mL and 7.3 ng/mL; p= NS). Only in **2/17 cases**, serum mTORi levels were **beyond the prescribed target**.

Diagnosis

- **CT scan** in **16/17** patients (10 OP, 6 NSIP); in one case radiological images were inconclusive.
- **All patients** presented altered pulmonary functional tests (PFTs) intended as reduction in carbon monoxide diffusing capacity
- A **lymphocytic alveolitis** on bronchoalveolar lavage was found in **5/11** patients.

Treatment

- The mTORi drug was **withdrawn** at different times after mTORi-induced pneumonitis onset in **all patients**; in **3/17** a **steroid therapy** was associated.

Outcomes

- **Symptoms resolution** was observed in **9/17** at **≤3 months**, **7/17** at **≤6 months**, **1/17** at **≤12 months**. No deaths were recorded.
- Renal function tests remained unchanged after mTORi interruption at a one year f/up.

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