# Changes in the Diffusion Capacity for Carbon Monoxide and the Development of Non-infectious Pneumonitis in Patients with Metastatic Renal Cell Carcinoma Treated with Everolimus

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**Abstract**. *Aim: The aim of the present study was to evaluate how treatment with everolimus changes readouts of the pulmonary function test (PFT) in patients with metastatic renal cell carcinoma (mRCC). We also attempted to determine whether changes of PFT or everolimus-associated non-infectious pneumonitis (NIP) might affect the efficacy of everolimus. Materials and Methods: The results of PFTs, radiological reports and medical records of 36 mRCC patients treated with everolimus after failure to vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) were reviewed. Results: Whereas 9 patients (30%) developed radiological changes consistent with everolimus-associated NIP (pneumonitis group), 27 were included in the non-pneumonitis group. The baseline value of the diffusing capacity for carbon monoxide divided by the alveolar volume (DLco/VA) was 90%. It decreased significantly as the duration of treatment increased (p<0.01). There was no significant difference in DLco/VA values between patients with and without NIP either at baseline (p=0.28) and 6 weeks after the initiation of everolimus therapy (p=0.18). The changes in DLco/VA between baseline and 6 weeks did not differ between the two groups (p=0.55). Time-dependent covariate Cox analysis, indicated that the decrease in DLco/VA was not correlated with the efficacy of everolimus in terms of progression-free survival (PFS; HR=1.0, p=0.94) and overall survival (OS; HR=0.98, p=0.18), whereas development of NIP was associated with worse PFS (HR=4.60, p=0.01). Conclusion: Patients with mRCC who are receiving everolimus therapy display a reduction in DLco/VA over time. However, neither the baseline DLco/VA nor the change in DLco/VA over time can help predict either development of NIP or the efficacy of everolimus.*

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Considerable evidence of the therapeutic potential of everolimus, a selective inhibitor of the mammalian target of rapamycin (mTOR) pathway, has led to its approval to treat metastatic renal cell carcinoma (mRCC) patients refractory to vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs) (1, 2). The mTOR inhibitors have been shown to be associated with characteristic adverse events, such as hyperglycemia and hyperlipidemia, which are not typically seen with the VEGFR-TKIs (1, 3, 4). Non-infectious pneumonitis (NIP) is one of the most important classes of toxicity associated with mTOR inhibitors. Although the incidence of everolimus-associated NIP varies betweeng different reports, NIP is one of the most common adverse events associated with everolimus therapy, with an incidence as high as 30-40% (5-7). Moreover, a few reports across multiple tumor types have indicated that high-grade toxicity or worsening of quality of life might cause unfavorable outcomes associated with interruption of anticancer treatment (6, 8, 9), although previous reports showed mTOR inhibitors to be relatively unaggressive and that any side-effects of their use could be reversed upon discontinuation of their administration (10-12).

The relatively high incidence of everolimus-associated NIP and the severity of the condition underscore two important considerations in the clinical practice of mRCC patients treated with everolimus. The first is whether there is a predictive marker of NIP development that permits early detection. Given our prediction that changes in outcomes of the pulmonary function test (PFT) are related to everolimus-associated NIP, we predicted that PFT could be a predictive marker of pneumonitis. The second consideration is whether the development of pneumonitis is correlated with improved efficacy of everolimus.

The aim of the present study was to evaluate the changes of PFT during everolimus treatment and to assess whether the change of PFT is associated with the development of NIP in patients with mRCC. We also attempted to determine whether a change of pulmonary function or NIP was associated with the efficacy of everolimus.

## Materials and Methods

*Patient population*. The study involved 100 patients at the Asan Medical Center (AMC) between April 2006 and July 2012. All had been treated with VEGFR-TKIs (sunitinib, sorafenib or pazopanib) for mRCC progression. Out of these 100 patients, 36 patients who underwent baseline PFT with regular follow-up constitute a separate cohort.

*Assessment of non-infectious pneumonitis and response to everolimus*. Everolimus (10 mg) was administered orally once daily. Patients were treated until evident progression of disease, occurrence of unacceptable toxic effects, refusal to continue therapy, concomitant disease precluding the use of everolimus or death. Comprehensive clinical, laboratory and radiological data were collected and reviewed to optimize accuracy and completeness after initiation of everolimus therapy. Patients were followed during visits to an outpatient clinic every 2-4 weeks. Computed tomography (CT) scans of the chest, abdomen and pelvis were obtained before treatment and at 6-8 week intervals during treatment. Baseline and sequential chest CT images and chest X-rays were reviewed in consensus by two investigators (P. K and L. J-L). Radiological abnormalities were reviewed with the corresponding clinical data to assess whether the radiologic abnormalities likely arose from everolimus-induced pneumonitis, pneumonia or tumor progression. Tumor responses were also reassessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. (13).

This study was approved by the Institutional review board of Asan Medical Center, which waived the requirement for informed consent given the retrospective design of this study.

*Pulmonary function test*. The PFT involved a standard protocol and included spirometry (Vmax 22, SensorMedics, Yorba Linda, CA, USA; PFDX, MedGraphics, St Paul, MN, USA), determination of lung volumes by body plethysmography (V6200, SensorMedics or PFDX) and measurement of the transfer factor by determining the single-breath diffusing capacity (Vmax 22 or PFDX) (14). All PFTs were performed at baseline and repeated every 6 weeks after the start of everolimus. PFT was not followed-up after everolimus treatment was terminated. We focused on the diffusing capacity for carbon monoxide divided by the alveolar volume (DLco/VA), which was identified as the most sensitive indicator of pulmonary toxicities following treatment with mTOR inhibitor (7, 12, 15). The rationale for including PFTs up to 24 weeks after the initiation of everolimus therapy was that the median progression-free survival of patients with mRCC treated with salvage everolimus was less than 24 weeks and the median time to onset of radiographically diagnosed pneumonitis was 15 weeks, while the majority of cases occurred within the first 24 weeks of everolimus treatment (1, 16). Data for complete PFT follow-up over 24 weeks was collected from 13 patients. Data collection from 23 patients was discontinued before 24 weeks due to disease progression or indications of intolerability including NIP.

*Statistical analysis*. Descriptive statistics used to summarize characteristics of the study population were reported as proportions and medians. The change in DLco/VA over time was analyzed using repeated-measures ANOVA. The Student's *t*-test or the Mann-Whitney *U*-test were used to analyze the differences in DLco/VA values between patients with NIP and those without NIP. The Kaplan–Meier product-limit method was used to estimate progression-free survival (PFS) and overall survival (OS) distribution. A Cox proportional hazard model considering the onset of pneumonitis and changes of DLco/VA as a time-dependent covariate was used to evaluate the association with PFS or OS. All statistical analyses were two sided and $p<0.05$ was considered to be significant. Statistical analyses were performed using the SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

*Baseline characteristics and treatment administration*. The baseline characteristics of the 36 patients are presented in Table I. The median age was 58 years (range=30-83 years) and 83% of the subjects had undergone nephrectomy. Four patients were favorable, 28 were intermediate and 4 were poor-risk, according to Heng's criteria (17). The majority of patients initially received sunitinib (n=26), followed by those initially treated with sorafenib (n=5) and pazopanib (n=5). At the time of analysis (October 2012), where 12 patients were still receiving everolimus, the remaining 24 patients had terminated everolimus treatment with a median treatment duration of 4.5 months (range=1.4-12.8 months). Whereas 21 patients discontinued the treatment due to disease progression, treatment of 3 patients with everolimus was terminated due to adverse events (AEs). Patients with NIP were younger than those without NIP. Nonetheless, there were no differences between patients with NIP or those without NIP in gender, histology, previous VEGFR-TKI type, existence of lung metastasis or Heng's criteria.

*Features of everolimus-associated pneumonitis*. Whereas 9 patients (30%) showed radiographic evidence of NIP (pneumonitis group), 27 were included in the non-pneumonitis group. Of the members of the pneumonitis group, 5 patients were symptomatic. The median time to the onset of pneumonitis was 52 days (range=34-259 days). Of the patients with symptomatic NIP, the most common presenting symptoms were cough (100%) and dyspnea (80%). Whereas patients with asymptomatic radiographic pneumonitis received everolimus cotinuously without additional management, 4 patients with symptomatic pneumonitis stopped the treatment and received steroid intervention. The two patients for whom everolimus thrapy was interrupted resumed everolimus treatment after the acute episode.

*Relationship between DLco/VA and everolimus treatment*. The baseline DLco/VA of patients was 90±4.9%. It decreased to 80±5.1%, 76±4.8%, 76±5.1% and 72±4.0% at

Table I. *Characteristics of metastatic renal cell carcinoma patients treated with everolimus.*

| Characteristics | Total (N=36) | Pneumonitis (N=9) | Non-pneumonitis (N=27) | *p*-Value |
|---|---|---|---|---|
| Age (year, range) | 58 (30-83) | 56 | 65 | 0.003 |
| Gender | | | | |
| Male | 25 (69%) | 6 (67%) | 19 (70%) | 1.000 |
| Female | 11 (31%) | 3 (33%) | 8 (30%) | |
| Histology | | | | |
| Clear cell type | 33 (89%) | 7 (78%) | 26 (96%) | 0.148 |
| Non-clear cell type | 3 (11%) | 2 (22%) | 1 (4%) | |
| Initial VEGFR-TKI | | | | |
| Sunitinib | 26 (72%) | 6 (67%) | 20 (74%) | 0.825 |
| Sorafenib | 5 (14%) | 2 (22%) | 3 (11%) | |
| Pazopanib | 5 (14%) | 1 (11%) | 4 (15%) | |
| Number of previous VEGFR-TKI | | | | |
| 1 | 28 (78%) | 7 (78%) | 21 (78%) | 1.000 |
| ≥2 | 8 (22%) | 2 (22%) | 6 (22%) | |
| Prior nephrectomy | | | | |
| Yes | 30 (83%) | 7 (78%) | 23 (85%) | 0.627 |
| No | 6 (17%) | 2 (22%) | 4 (15%) | |
| Prior immunotherapy | | | | |
| Yes | 8 (22%) | 1 (11%) | 7 (26%) | 0.648 |
| No | 28 (78%) | 8 (89%) | 20 (74%) | |
| Number of metastatic sites[a] | | | | |
| ≤1 | 28 (78%) | 7 (78%) | 21 (78%) | 1.000 |
| ≥2 | 8 (22%) | 2 (22%) | 6 (22%) | |
| Lung metastatic lesions[a] | | | | |
| Yes | 30 (83%) | 8 (89%) | 22 (82%) | 1.000 |
| None | 6 (17%) | 1 (11%) | 5 (18%) | |
| Heng's criteria[a] | | | | |
| Favourable | 4 (11%) | 0 | 4 (15%) | 0.343 |
| Intermediate | 28 (78%) | 7 (78%) | 21 (78%) | |
| Poor | 4 (11%) | 2 (22%) | 2 (7%) | |

VEGFR-TKI: Vascular endothelial growth factor receptor-tyrosine kinase inhibitor. [a]Determined at the start of everolimus therapy.

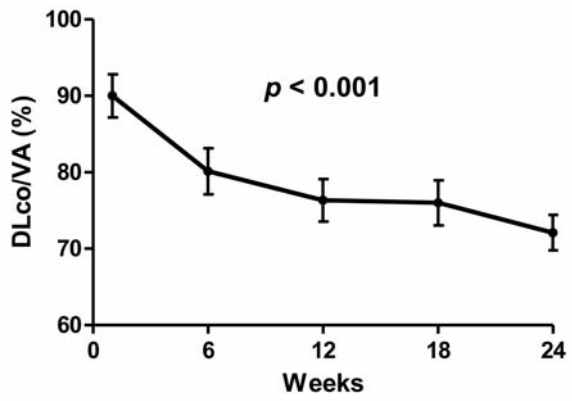


Figure 1. *Significant decline in DLco/VA with prolonged treatment (p<0.001)[a]. [a]This significant result was drawn from analysis based on 13 patients who completed a 24-week PFT follow-up data.*

6, 12, 18, 24 weeks after everolimus treatment, respectively (mean±standard deviation). The DLco/VA declined significantly as the treatment duration became longer ($p<0.01$) (Figure 1). Although the result shown in Figure 1 was from 13 patients for whom complete follow-up PFT data was available until 24 weeks after the initiation of everolimus therapy, there were also significant declines of DLco/VA in 27 patients who underwent a 12-week follow-up ($p<0.01$) and 21 patients who underwent an 18-week follow-up ($p<0.01$).

Examination of how the DLco/VA was affected by the development of NIP failed to indicate any statistically significant differences in DLco/VA at baseline and 6 weeks between the non-pneumonitis group (85.2% at baseline; 76.7% at 6weeks) and the pneumonitis group (77.6% at baseline; 68.2% at 6 weeks) ($p=0.278$ at baseline; $p=0.18$ at 6weeks). Changes in DLco/VA between baseline and 6 weeks after the onset of NIP were similar between the two groups with an 8.4% decrease in the non-pneumonitis group, 9.3% decrease in pneumonitis group, $p=0.55$).

*Correlation between pneumonitis and antitumor efficacy.* Out of the 36 patients, 1 (3%) achieved a confirmed partial response and 30 (83%) had stable disease. Five (14%) patients had progressive disease (PD) with no complete responses. With a median follow-up duration of 10.1 months (range=2.6-23.6 month), the PFS was 4.4 months (95% confidence interval (CI): 2.9-5.9) and the median OS was 11.9 months (95% CI=9.0-14.8). Cox analysis using a time-dependent variable indicated that the development of pneumonitis was correlated with poor PFS (hazard ratio (HR)=4.60, $p=0.01$), although this effect was not statistically significant for OS (HR=2.30, $p=0.17$, Table II). Cox analysis using a time-dependent variable indicated that the decrease of DLco/VA was not correlated with the efficacy of everolimus (PFS: HR=1.00, $p=0.94$; OS: HR=0.98, $p=0.17$, Table III).

## Discussion

NIP, which is a class effect of rapamycin analogues, is one of the most important adverse events observed in patients with mRCC who are receiving everolimus therapy. Notwithstanding the extensive data published on mTOR inhibitor-induced lung toxicity, the pathogenesis associated with these drugs is not well-understood and there is very limited published information about the effects of these drugs on pulmonary function and clinical implications of NIP.

Table II. *A Cox proportional hazard model using onset of pneumonitis as a time-dependent variable.*

| Variable | Progression-free survival | | Overall survival | |
|---|---|---|---|---|
| | Hazard ratio | *p*-Value | Hazard ratio | *p*-Value |
| Age (≥60 *vs.* <60 years) | 0.97 | 0.96 (0.33-2.83) | 0.64 | 0.48 (0.18-2.22) |
| Gender (female *vs.* male) | 0.45 | 0.21 (0.13-1.59) | 0.31 | 0.09 (0.09-1.20) |
| Heng's criteria | | | | |
| (favor *vs.* poor) | 1.19 | 0.87 (0.14-10.05) | 0.73 | 0.77 (0.09-6.10) |
| (intermediate *vs.* poor) | 2.99 | 0.36 (0.28-32.00) | 3.17 | 0.35 (0.28-35.47) |
| NIP (Yes *vs.* None) | 4.60 | 0.01 (1.58-13.40) | 2.30 | 0.17 (0.70-7.55) |

NIP: Non-infectious pneumonitis.

Table III. *A Cox proportional hazard model using changes of DLco/VA as a time-dependent variable.*

| Variable | Progression-free survival | | Overall survival | |
|---|---|---|---|---|
| | Hazard ratio | *p*-Value | Hazard ratio | *p*-Value |
| Age (≥60 *vs.* < 60years) | 1.04 | 0.12 (0.99-1.09) | 0.93 | 0.91 (0.28-3.08) |
| Gender (female *vs.* male) | 0.66 | 0.51 (0.19-2.26) | 0.40 | 0.16 (0.11-1.42) |
| Heng's criteria | | | | |
| (favor *vs.* poor) | 1.84 | 0.57 (0.22-15.15) | 0.67 | 0.720 (0.08-5.85) |
| (intermediate *vs.* poor) | 3.54 | 0.28 (0.35-36.10) | 2.90 | 0.39 (0.26-32.24) |
| DLco/VA | 1.00 | 0.94 (0.97-1.03) | 0.98 | 0.17 (0.94-1.01) |

DLco/VA: Diffusing capacity for carbon monoxide divided by the alveolar volume.

The results of our current study show that diffusion capacity decreased significantly over time in patients with mRCC after treatment with everolimus. The decrease of diffusion capacity is a generalized event; it occurs in the majority of patients regardless of radiographic alteration(s). This suggests that a direct toxic effect of everolimus or a metabolite of everolimus might contribute to the observed decrease in DLco/VA. Although diffusion capacity decreases substantially during the first 12 weeks after the initiation of everolimus therapy (Δ18%), the rate of decrease tends to reach a plateau by 24 weeks in patients who have received everolimus therapy and who have not developed NIP. Although exploratory analysis of reversibility to the baseline levels and the duration of impairment in DLco/VA were attempted, this was hampered by the retrospective nature of this study. PFT was not followed-up after everolimus treatment had been terminated.

Neither the baseline value of DLco/VA nor the extent of decrease in DLco/VA over 6 weeks was associated with the development of NIP. Initially, serial PFTs were performed to identify the DLco/VA value less than 40% that was predicted to hold everolimus temporarily. Nonetheless, there were no patients for whom DLco was 40% or less either with or without clinical NIP. These observations suggest that periodic PFTs is of limited value for the prediction or early detection of NIP before clinical symptoms or radiologic alterations become apparent.

A reliable biomarker for everolimus has not yet been identified for mRCC. Hypertension has been proposed as a potential biomarker for side-effects associated with VEGFR-TKIs (18), and the incidence of skin rash is related to the efficacy of EGFR-TKIs (19). Only a few reports have described the relationship between NIP and the anti-tumor efficacy of mTOR inhibitors with, however, contradictory results. Dabydeen *et al.* (5) reported that patients with NIP showed more favorable outcome in terms of both the proportion of patients achieving stable disease (86% *vs.* 44%) and extent of tumor shrinkage (–2.9% *vs.* +4.3%) than those without pneumonitis when treated with either everolimus or temsirolimus. While, other reports showed the development of NIP was not correlated with improved PFS (6, 20). However, these results should be interpreted with caution because they did not consider the onset of AEs or treatment duration. The correlation between NIP and the efficacy of mTOR inhibitors might be an epiphenomenon that resulted from the selection of patients who lived longer

and had a more prolonged exposure therapy and who thus had a greater likelihood of developing AEs. We used time-dependent co-variable Cox analysis to minimize bias in the current study. This enabled us to demonstrate that NIP is related with a worse outcome in terms of PFS, whereas the decrease in DLco/VA was not related to the efficacy of everolimus.

Management of NIP is empirical and should rely on combined radiographic and clinical assessments (6, 7, 21). Patients with radiographic NIP without symptoms might continue treatment with everolimus but should be monitored closely for respiratory symptoms. In contrast, treatment of patients with clinical NIP should be withheld until progression of a further evaluation with or without initiation of corticosteroid treatment. Depending on the clinical status of the patient, treatment with everolimus might then be resumed, either with or without a reduction in dose. In our current study, disease progression during the time when everolimus therapy was interrupted might account for inferior outcomes of patients with NIP compared to those that did not develop NIP. For patients with a critical tumor burden and rapid progression before everolimus therapy, other therapeutic options, such as alternative VEGFR-TKI, should be considered when everolimus is stopped due to clinical pneumonitis.

## Conclusion

Everolimus treatment decreased the diffusion capacity of patients with mRCC in a time-dependent manner. Neither the baseline DLco/VA nor the change in DLco/VA over time is of any help in predicting the development of NIP or the efficacy of everolimus. Although the development of NIP was associated with poor outcomes, these might be improved by bridging everolimus therapy with the use of other VEGFR-TKIs. Further prospective pulmonary investigations with a larger number of patients are needed to confirm these findings and to provide better insight into the pathogenesis and proper management of NIP.

## Conflicts of Interest

The Authors have declared no conflicts of interest.

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