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Discrepant elevation of sIL-2R levels in sarcoidosis patients with renal insufficiency

To the Editor:

Sarcoidosis is a systemic, granulomatous disease that can manifest in multiple organs [1]. Several biomarkers are used to assess disease activity and monitor response to therapy, including soluble interleukin-2 receptor (sIL-2R) and angiotensin-converting enzyme (ACE) [2]. sIL-2R was previously shown to correlate with the amount of CD4⁺ T-lymphocytes in bronchoalveolar lavage fluid [3]. Furthermore, it was shown that sIL-2R >4000 pg·mL⁻¹ was a significant predictor of relapse after discontinuation of infliximab therapy and that sIL-2R is a suitable prognostic marker for disease progression [4, 5]. We observed, however, that in a small number of patients with co-existing renal insufficiency, sIL-2R can be disproportionately high without marked signs of disease activity based on ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET), ACE and the clinical presentation. The aim of this pilot study is therefore to evaluate the influence of renal function on sIL-2R levels to determine if and how the marker can be used in sarcoidosis patients with renal insufficiency. In order to further illustrate the discrepancy, we first describe two cases.

The first case concerns a 56-year-old woman with pulmonary sarcoidosis, and a history of nephrotic syndrome and membranous glomerulonephritis resulting in moderate renal insufficiency (estimated glomerular filtration rate (eGFR) 50 mL·min⁻¹ per 1.73 m²). ACE levels were repeatedly normal over a period of >2 years and no signs of sarcoidosis disease activity were present on the latest FDG-PET scan. However, sIL-2R levels remained highly elevated (>9000 pg·mL⁻¹; normal reference value <3000 pg·mL⁻¹) despite treatment with infliximab.

The second case involves a 50-year-old man with sarcoidosis and a complicated history of stage V diabetic nephropathy, heart failure and various infections. The patient was treated with peritoneal dialysis. ACE was normal but sIL-2R levels were repeatedly extraordinarily high (>50 000 pg·mL⁻¹) despite immunosuppressive

treatment. FDG-PET scans showed only moderately active sarcoidosis in the pulmonary parenchyma and mediastinal and hilar lymph nodes. Although this patient still had fairly active sarcoidosis, potentially leading to an elevation in sIL-2R, the exceptionally high levels measured in this patient are rarely observed.

Both patients showed a higher than expected level of sIL-2R in concurrence with more or less severely impaired renal function. The observation of these and similar cases over the past few years led to the question of whether renal insufficiency results in elevated sIL-2R levels in sarcoidosis patients.

It has been described that sIL-2R is cleared by the kidneys [6], and an association between sIL-2R and renal function has been reported in a few small studies in other diseases [7, 8]. However, the implications for clinical use of sIL-2R as a disease activity marker in sarcoidosis patients with renal insufficiency remain unknown. Renal insufficiency in sarcoidosis patients may occur in cases of disease-associated hypercalcaemia or renal sarcoidosis, or result from comorbid conditions such as hypertension or diabetic nephropathy, as illustrated here.

To investigate the relation between serum sIL-2R levels and renal function, we performed a retrospective analysis in a cohort that was previously described by VORSELAARS *et al.* [9]. This cohort consists of patients treated with methotrexate at St Antonius Hospital, Nieuwegein, which is a tertiary referral centre for interstitial lung disease in The Netherlands. All patients were treated between June 2004 and September 2011. Medical records were retrospectively reviewed for relevant demographic data, treatment and disease activity parameters. eGFR, calculated using the Modification of Diet in Renal Disease formula [10], was used as a marker for renal function. It was split into the following categories: insufficient, <60; sufficient-normal, 60–90; and sufficient-high, >90 mL min⁻¹ per 1.73 m². Importantly, sIL-2R levels are highly variable between patients depending on the amount of disease activity present, as described above. Hence, in order to be able to measure the pure effect of renal function on sIL-2R levels, we attempted to eliminate the factor of disease activity as much as possible by collecting all disease parameters after a period of 6 months of methotrexate treatment. Levels of sIL-2R were determined with DIACLONE ELISA Kit Human sIL-2R/sCD25 (Sanquin, Amsterdam, The Netherlands) according to manufacturer's instructions. Values >3000 pg·mL⁻¹ are considered increased.

To evaluate the effect of renal function on sIL-2R levels, a multiple linear regression analysis was performed. Independent variables in the analysis included eGFR and ACE. As eGFR was divided into categories, it was recoded into the dummy variables eGFR <60 and 60–90 mL·min⁻¹ per 1.73 m², where eGFR >90 mL·min⁻¹ per 1.73 m² was used as a reference category. ACE (divided into normal (<70 U·L⁻¹) and high (>70 U·L⁻¹)) was merely introduced into the model as another activity marker to adjust for remaining disease activity, for reasons described earlier. The study was approved by the local institutional review board (St Antonius Hospital, Nieuwegein, The Netherlands) with registration number LTME/Z-12.05 and acronym METHVERAZ.

In 86 patients out of the initial 145, data on renal function and disease activity markers at corresponding time-points were available. Of these, 63% were male and the treatment indication was related to pulmonary involvement in 66% of patients. In total, seven patients were classified as having renal insufficiency by an eGFR <60 mL·min⁻¹ per 1.73 m².

A significant association was found between sIL-2R and insufficient eGFR of <60 (p=0.001) relative to sufficient-high eGFR of >90 mL·min⁻¹ per 1.73 m². Importantly, no association was found between sIL-2R and sufficient-normal eGFR of 60–90 relative to a sufficient-high eGFR of >90 mL·min⁻¹ per 1.73 m² (p=0.992). Both results were adjusted for disease activity by ACE. Because of the small sample size of the eGFR <60 mL·min⁻¹ per 1.73 m² group and the resulting imperfect normal distribution, we also performed a nonparametric Kruskal-Wallis test, which gave similar results. Results are shown in figure 1.

These findings suggest that renal function impairment may indeed have a significant influence on sIL-2R levels in patients with sarcoidosis. Importantly, it also shows that sIL-2R levels do not correlate with normal renal function. Thus, in patients with renal insufficiency, sIL-2R levels may rise and probably also reflect accumulation through impaired renal clearance, instead of just sarcoidosis disease activity. This may lead to an overestimation of actual disease activity in this specific patient group. Therefore, we suggest caution regarding the interpretation of sIL-2R levels when renal function is impaired.

Theoretically, not only impaired clearance of sIL-2R but also increased production may lead to a higher than expected level of sIL-2R [11]. In patients with end-stage renal disease, T-cells appear to be pre-activated and, therefore, express more interleukin-2 receptor on their membrane. As a result, more shed sIL-2R appears in the blood. High sIL-2R levels in patients with stage V renal failure could thus be both the result of impaired clearance and increased production. In addition, it is worth mentioning that patients with chronic renal failure who are on maintenance dialysis show higher sIL-2R levels than undialysed patients [11, 12].

This study is limited by the small sample size and the retrospective design. In addition, this was a pilot study in an existing cohort. However, since renal insufficiency is a contraindication to the prescription of

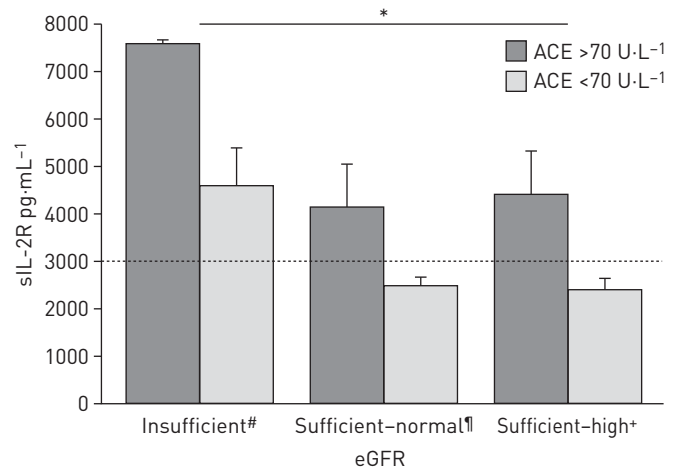


FIGURE 1 Mean \pm SEM levels of soluble interleukin-2 receptor (sIL-2R) are displayed per category of estimated glomerular filtration rate (eGFR). These categories were subsequently split into normal angiotension-converting enzyme (ACE) (<70 U·L⁻¹), representing low disease activity, and high ACE (>70 U·L⁻¹), representing high disease activity. The mean levels of sIL-2R are considerably higher in the patient group with insufficient eGFR, reflecting accumulation. The dotted line indicates the normal reference value of sIL-2R (<3000 pg·mL⁻¹). [#]: <60 mL·min⁻¹ per 1.73 m²; [¶]: 60–90 mL·min⁻¹ per 1.73 m²; ⁺: >90 mL·min⁻¹ per 1.73 m².

methotrexate, this cohort might underestimate the occurrence of renal insufficiency in the general sarcoidosis patient population. The effect will possibly be more substantial when a larger, more representative cohort is evaluated.

In conclusion, this pilot study shows that renal insufficiency has a significant influence on sIL-2R levels in sarcoidosis patients. Assessment of renal function when interpreting sIL-2R values is therefore warranted. Although this study only involved sarcoidosis patients, the results may likely be extended to other diseases in which sIL-2R is used as a biomarker for disease evaluation.



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Levels of soluble IL-2 receptor can be discrepantly elevated in sarcoidosis patients with renal insufficiency <http://ow.ly/ICVrY>

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10-year long-term survival of a metastatic *EGFR*-mutated nonsmall cell lung cancer patient



To the Editor:

10 years ago, the US Food and Drug Administration approved erlotinib in the second and third line settings for unselected advanced nonsmall cell lung cancer (NSCLC) patients. Activating *EGFR* mutations were discovered by analysing patient subgroups who responded to oral, first-generation, single-target reversible *EGFR* tyrosine kinase inhibitor (TKI). Nine randomised phase III chemotherapy-controlled trials in *EGFR*-mutant NSCLC naive patients showed the superiority of gefitinib, erlotinib and afatinib, respectively, in terms of response rate and progression-free survival. Response rate is in the range of 70% and progression-free survival about 1 year. Exon 19 in-frame deletions represent about 45% of overall *EGFR* mutations and half of the sensitising ones [1]. New generation targeted therapies are currently under clinical development. However, treatment sequence is still debated after a first line of *EGFR* TKI regimen in these molecularly selected patients. We herein report a case of a metastatic *EGFR*-mutated lung adenocarcinoma patient who achieved a prolonged survival of 10 years through multiple surgical and medical treatments (fig. 1).

Our female patient was 60 years old when a chronic cough led to the diagnosis of a right lower lobe adenocarcinoma in January 2005. She had smoked five to six cigarillos per day from the age of 53 to 58 years, was treated for hypertension and had undergone a hysterectomy in 1999 for personal convenience. She presented an initial pericardial effusion with a positive cytology. The tumour was then classified as stage IV (cT4N1pM1a), according to the current seventh TNM classification. Thus, she was treated with a six-cycle platinum-based chemotherapy doublet. The tumour progressed in November 2006 and new biopsies revealed an E746 A750 deletion in exon 19 of the *EGFR* gene. Neratinib was then unsuccessfully administered for 3 months with grade 2 diarrhoea and grade 1 skin ulceration of the index finger. The tumour progressed through three cycles of pemetrexed. It was proposed that our patient join a phase 1 trial testing an oral signal-transduction inhibitor with both anti-angiogenic (VEGFR1–3 inhibition) and anti-HER functions (HER1, HER2, HER4): BMS690514 [2]. She presented grade 1 facial folliculitis, grade 2 diarrhoea and grade 3 hypertension, despite an association of angiotensin-converting enzyme inhibitor and thiazide diuretic. Therefore, the drug dose was decreased by 25%. BMS690514 was interrupted after 1 month because of a Tako-Tsubo cardiomyopathy and restarted with half a dose. After 15 months of treatment, the patient underwent an extended surgical procedure in a context of remarkable partial response. Tumour residues were found in mediastinal adenopathies which led to local irradiation. BMS690514 was discontinued after a 5-month adjuvant therapy. Interestingly, post-operative molecular analyses did not reveal any *EGFR* mutation but a chromosome 7 polysomy. 1 year later the tumour relapsed in all lung parenchyma. Gefitinib was unsuccessfully administered for 1 month and switched for a sixth line prescription of 85% full-dose erlotinib (because of grade 2 skin toxicity). The disease remained stable for 3 years in a context of manageable grade 2 skin toxicities and one resected skin basal cell carcinoma. In October 2013, the patient was enrolled on the AZD 9291 phase 1 trial testing this oral daily irreversible *EGFR* inhibitor. After 1 year, she still presents an excellent partial response with excellent physical condition and normal daily activities.