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Clinical significance of soluble interleukin-2 receptor measurement in patients with idiopathic retroperitoneal fibrosis

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Abstract

Background Idiopathic retroperitoneal fibrosis (iRPF) is a rare chronic fibro-inflammatory disorder of unknown etiology. Activated T-helper cells, which shed soluble interleukin-2 receptor (sIL-2R) into the circulation, may play a pathogenetic role. Hence, measuring sIL-2R may be of value in monitoring disease activity and treatment response in iRPF patients.

Methods We performed a prospective inception cohort study of 82 patients with untreated (re)active iRPF stratified by elevated (> 623 U/mL) or normal sIL-2R level at baseline and compared disease characteristics among these groups. Baseline and changes in sIL-2R levels following treatment with tamoxifen (TMX) or prednisone (PDN) were analyzed and related to treatment response.

Results Median sIL-2R level was 668 U/mL (IQR 502.8–827.5); 48 patients (59%) had elevated baseline sIL-2R levels. Patients with elevated sIL-2R presented with higher CRP ($P = 0.049$) and serum creatinine (sCr) levels ($P < 0.001$) and more often had hydroureteronephrosis ($P = 0.01$). There was an age and sex adjusted linear association between baseline sIL-2R and both CRP ($P = 0.02$) and sCr ($P < 0.001$). Baseline and serial levels of sIL-2R were predictive and concordant, respectively, with clinical response in patients treated with PDN. ROC curve analyses of sIL-2R on a continuous scale and PDN treatment success showed an AUC of 0.84. A serum sIL-2R cut-off value for PDN treatment success of ≤ 703 U/mL was found with a sensitivity of 100% and specificity of 72%.

Conclusion Serial measurement of sIL-2R may be of value in monitoring disease activity and PDN treatment response in iRPF patients.

Keywords Retroperitoneal fibrosis · Soluble interleukin 2 receptor · Disease activity · Treatment response

Introduction

Idiopathic retroperitoneal fibrosis (iRPF) is a rare disorder characterized by chronic nonspecific inflammation of the retroperitoneum leading to fibrosis [1]. If unrecognized or left untreated, progressive fibrosis may lead to obstruction of adjacent organs, notably the ureters [2].

Although its exact pathogenesis is unclear, T-helper (CD4+) cells are thought to play an important role in the immunopathophysiology of iRPF [3]. We previously observed a predominant T-cell infiltrate in RPF tissue material, largely consisting of T-helper cells expressing the IL-2 receptor (IL-2R) α-chain (aka CD25) [4]. The IL-2R α-chain is part of the high-affinity, trimeric IL-2 receptor complex together with a β-chain (CD122) and the common cytokine receptor γ-chain (CD132). Upon T-cell activation, the α-chain is being shed from the cell surface into the circulation as soluble IL-2R(α) (sIL-2R) [5].

Elevated serum levels of sIL-2R have been found in various pathological conditions characterized by significant T-cell activation, such as autoimmune diseases, infectious diseases, transplant rejection, malignancies, and more recently in IgG4-related disease (IgG4-RD), a systemic

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chronic fibro-inflammatory disorder, which can also present as iRPF [6, 7].

In patients with IgG4-RD, sIL-2R levels might represent a marker for disease activity and treatment response [8–10]. In a small case series, elevated serum sIL-2R levels were observed in patients with iRPF at disease presentation [11].

In this study, we prospectively analyzed serum sIL-2R levels in patients with iRPF at the time of disease presentation and compared disease characteristics of patients presenting with normal and elevated levels. In addition, serum sIL-2R levels at baseline and during follow-up (FU) were analyzed in relation to treatment response.

Patients and methods

Patients

From September 2010 through June 2021, 82 patients with a diagnosis of iRPF who started tamoxifen (TMX) or prednisone (PDN) for first or recurrent presentation who were seen at our tertiary care referral center were included in this prospective inception cohort study. Patients without active disease or patients who already received medical treatment for active disease at the time of referral to our center were excluded from this study. After careful exclusion of malignancy, the diagnosis of iRPF was based on the typical clinical picture and the presence of characteristic contrast-enhanced computed tomography (CT) findings. There was no history of infection or drugs (notably ergot-derivatives) that could have been associated with RPF. There were no signs of IgG4-related disease or Erdheim-Chester disease. In case of diagnostic doubt, histologic examination of biopsy material was performed.

Patients typically received fixed-dose tamoxifen (TMX) 20 mg b.i.d. as primary treatment ($n = 65$, 79%). The prescribed duration of TMX treatment was two years. Seventeen (21%) patients were primarily treated with initial high-dose PDN (60 mg/day) because of extensive disease or recurrent active disease. If indicated, (emergency) renal drainage was performed, either with placement of a percutaneous nephrostomy tube (PCN) or a double-J splint (DJ), sometimes in sequence. Ureteral stents were changed every 4–6 months until definitive removal. In addition to specific baseline examination, the prescribed FU included periodic clinical and laboratory examination at 6 weeks, 4 months and 8 months, respectively and repeated contrast-enhanced CT scanning at 4 and 8 months of treatment with TMX or PDN. In case of TMX treatment failure, patients were converted to initial high-dose PDN. In case of unsatisfactory response to primary or second-line treatment with PDN, mycophenolate mofetil (MMF, 750–1000 mg b.i.d.) or methotrexate (MTX, 15 mg, once weekly) was added. In some cases of unresponsive disease to combined immunosuppressive treatment, cyclic rituximab 500–1000 mg i.v. was prescribed.

Measurements

Age, sex, duration of symptoms, specific laboratory parameters and CT scan findings were documented at baseline. Laboratory parameters, obtained before start of treatment, included acute-phase reactant (APR) levels [i.e., erythrocyte sedimentation rate (ESR), mm/h; C-reactive protein (CRP), mg/L], serum creatinine (sCr, µmol/L), serum immunoglobulin G4 level (sIgG4, g/L) and serum sIL-2R level (U/mL). Serum sIgG4 subclass levels were measured by nephelometry (Siemens Healthcare Diagnostics, the Siemens BN™ II System) with 1.4 g/L being the upper limit of normal sIgG4 concentration [12]. Serum sIL-2R levels were measured by chemiluminescence enzyme immunoassay (Immulite, Siemens Healthcare, Germany), with a reference range of 158–623 U/mL. All baseline CT scans were evaluated for the presence or absence of hydroureteronephrosis. In addition, RPF mass thickness was measured in transversal direction (mm). FU measurements included changes in laboratory parameters and radiological findings on repeat CT scanning. Treatment success was defined as the aggregate of 3 criteria: significant clinical improvement within 6 weeks of treatment; documented stable or decreasing mass size on the prescribed FU CT scan at 4 months; and documented definitive decrease in mass size on the prescribed FU CT scan at 8 months. All three criteria had to be met. Of note, in case of treatment failure and subsequent initiation of second-line treatment, last values before initiation of this second-line therapy were used as baseline values with values obtained thereafter as follow-up measurements. Treatment outcome was analyzed in study patients who had at least 8 months of FU after initiation of primary treatment with TMX or PDN. Patients who were converted to PDN after failed TMX treatment were included in treatment outcome analysis of patients who received PDN as primary treatment. Other treatment regimens, prescribed at later stages of disease because of unsatisfactory response to primary or second-line treatment with PDN, were not subject to this study.

Statistical analyses

Because of non-Gaussian distribution of several study variables, all continuous variables were reported as median with interquartile range (25th to 75th percentile) for consistency. In addition, all analysis were done with non-parametric tests. Differences between continuous variables were analyzed by using the Mann–Whitney or Wilcoxon signed rank test, where appropriate. Categorical variables were reported as number and percentage and compared by the Chi-Square

test. Correlations were analyzed using Spearman's rank correlation coefficient. Scatterplots were graphed to examine possible linearity between variables. We performed linear regression analyses to study the relation between baseline sIL-2R, sCr and CRP levels. In order to meet the assumption of linearity, normality and homoscedasticity of residuals, we log-transformed these variables by natural logarithm. The association between sIL-2R levels and treatment success with TMX or PDN was determined using univariate and multivariate binary logistic regression. Because of the wide range of sIL-2R levels in our study population and the limited clinical significance of a small increase on treatment outcome, we categorized baseline sIL-2R levels into intervals of 100 U/mL. The independent variables in the multivariate regression model were chosen because of their clinical relevance and included ESR, CRP and sCr level at baseline. Variance inflation factors were calculated to assess the degree of multicollinearity among these independent variables in the multivariate logistic regression model. Receiver operating characteristic (ROC) analysis was performed to visualize the utility of serum sIL-2R levels in predicting treatment success and to determine the threshold for predicting treatment success. All reported *P* values are two-sided. A *P* value less than 0.05 was considered significant. Statistical analyses were performed using SPSS software, version 24.0 (IBM).

Results

Baseline characteristics

Demographic and clinical characteristics of the 82 study patients according to the serum sIL-2R levels at presentation are depicted in Table 1. Median sIL-2R level was 668 U/mL (IQR 502.8–827.5); 48 patients (59%) presented with an elevated sIL-2R level. Groups with normal range or elevated sIL-2R levels had similar duration of symptoms. Median CRP levels were higher in patients presenting with an elevated sIL-2R level. Baseline sIL-2R levels correlated significantly with CRP levels at baseline (ρ 0.25; $P=0.03$). A significant linear association was found between logarithmic transformed sIL-2R and CRP levels [β 0.27, (95% CI 0.02–0.20); $P=0.02$] (Fig. 1A). After adjusting for age and

Table 1 Demographic, clinical and radiological characteristics of study patients at presentation

	All patients	Serum sIL-2R level at presentation		*P* value
		Normal range	Elevated*	
No of patients, *n* (%)	82	34 (41)	48 (59)	
Age, *y*	64 (55–71)	61.0 (53.5–69.0)	66.0 (58.0–71.8)	0.23
Male sex, *n* (%)	54/82 (66)	19/34 (56)	35/48 (73)	0.11
Duration of symptoms, *mo*	6 (3–12)	7 (4–15)	5.5 (2.0–12.0)	0.57
Blood markers				
ESR, mm/h	35.0 (18.3–66.5)	31.5 (14.5–54.0)	37.5 (18.8–72.3)	0.32
CRP, mg/L	11.5 (5.0–26.3)	9.0 (5.0–19.8)	16.0 (7.0–34.8)	0.049
IgG4, g/L	0.8 (0.3–1.6)	0.9 (0.6–1.7)	0.7 (0.3–1.5)	0.16
sIL-2R, U/mL	668 (502.8–827.5)	481.0 (398.0–518.5)	792.5 (689.5–1101.3)	< 0.001
Renal function				
Creatinine, mg/dL	92 (74–132)	81.0 (60.3–95.3)	109.5 (86.5–150.5)	< 0.001
HUN, *n* (%)	38/80 (48)	10/33 (30)	28/47 (60)	0.01
DJ splint or PCN, *n* (%)	22/80 (28)	8/33 (24)	14/47 (30)	0.56
RPF mass thickness, mm	36.0 (24.7–48.0)	37.0 (24.3–47.0)	35.0 (26.0–48.5)	0.72
Outcome				
Treatment success†, *n* (%)				
Overall	41/70 (59)‡	21/31 (68)	20/39 (51)	0.17
Tamoxifen	29/56 (52)	15/25 (60)	14/31 (45)	0.27
Prednisolone	12/14 (86)	6/6 (100)	6/8 (75)	0.19
Recurrence rate, *n* (%)	5/34 (15)	1/17 (6)	4/17 (24)	0.15

Values are median and interquartile ranges (25th to 75th percentile) or numbers and percentages

sIL2R soluble interleukin 2 receptor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *HUN* hydroureteronephrosis, *DJ* double J, *PCN* percutaneous nephrostomy

*Defined as serum sIL2R level > 623 U/mL

†Treatment success was analyzed in study patients with at least 8 months of follow-up

‡In 12 patients there was insufficient follow-up time for analyzing treatment success, hence $n=70$

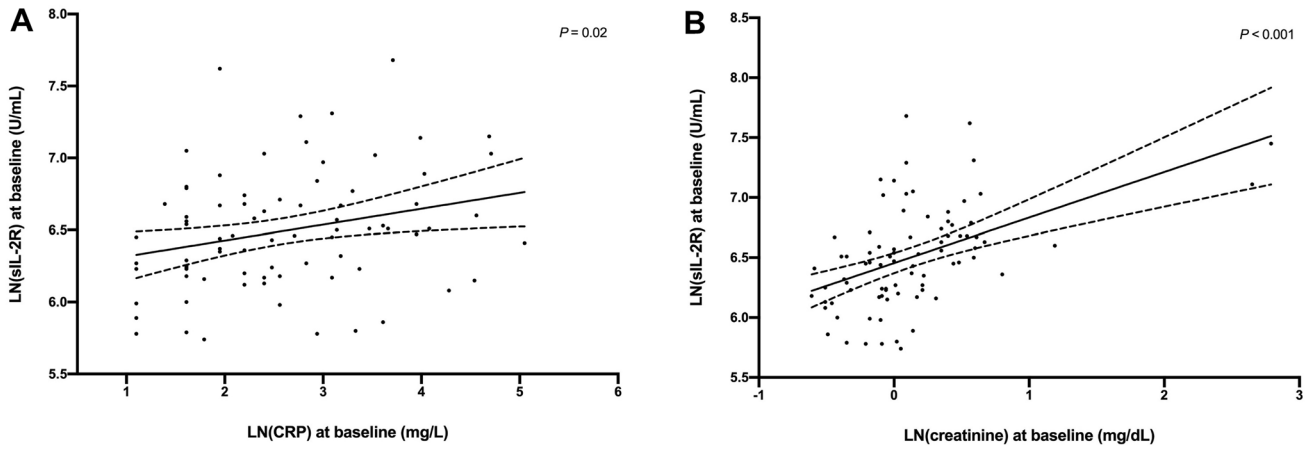

Fig. 1 Linear regression analyses of the logarithmic transformed sIL-2R and CRP levels (**A**) and sIL-2R and serum creatinine (sCr) levels (**B**). A significant linear association was found between sIL-2R and both CRP and sCr levels

sex, this association remained significant [β 0.25, (95% CI 0.01–0.19); $P = 0.02$]. ESR and sIgG4 levels did not differ between patients with normal range or elevated sIL-2R levels (Table 1), nor was there a correlation between sIL-2R levels and ESR or sIgG4 levels (both $P = 0.11$). In patients presenting with an elevated serum sIL-2R level, higher sCr levels were observed and the presence of hydroureteronephrosis was more common (Table 1). Baseline sIL-2R levels correlated significantly with sCr levels (ρ 0.53; $P < 0.001$) and with the presence of hydroureteronephrosis (ρ 0.27; $P = 0.02$). In addition, a significant linear association was observed between logarithmic transformed sIL-2R and sCr levels [β 0.49, (95% CI 0.23–0.53); $P < 0.001$] (Fig. 1B). After adjusting for age and sex, this association remained significant [β 0.49, (95% CI 0.22–0.54); $P < 0.001$]. CT-documented retroperitoneal mass thickness did not differ between groups (Table 1), nor did retroperitoneal mass thickness correlate with baseline sIL-2R levels (ρ 0.12, $P = 0.37$). Median sIL-2R levels did not differ between patients primarily treated with TMX or PDN [672 U/mL (IQR 495.0–859.5) vs. 664 U/mL (IQR 500.5–808.0); $P = 0.95$].

Follow-up

Twelve patients had insufficient FU time to analyze treatment success or failure (i.e., 9 patients who received TMX treatment and 3 patients who received PDN treatment). Overall, percentage of patients who had treatment success did not differ between groups with normal range or elevated serum sIL-2R levels at presentation (Table 1). Patients treated with PDN more often experienced treatment success than patients treated with TMX (86% vs. 52%; $P = 0.02$).

In patients receiving primary TMX treatment, median baseline sIL-2R levels did not differ between patients who had treatment failure and patients who had treatment success ($P = 0.79$). In patients who had TMX treatment success, serum sIL-2R levels did not decrease during FU.

ESR, CRP and sIgG4 levels decreased during FU in patients who had TMX treatment success (Table 2). The odds ratio (OR) of ordinal baseline serum sIL-2R level for TMX treatment success was 0.96 (95% CI 0.83–1.10; $P = 0.54$). Adjusted for APRs and sCr, the OR was 0.97 (95% CI 0.83–1.13; $P = 0.69$). ROC curve analyses of serum sIL-2R levels and TMX treatment outcome showed an AUC of 0.52 (Fig. 2A).

Twenty-four patients who had treatment failure with TMX were converted to PDN-based second-line treatment. Median time interval between start of TMX and subsequent conversion to this second-line treatment was 4.6 months (IQR 2.1–8.0). Median serum sIL-2R level at the time of treatment switch in patients who had TMX treatment failure was 618 U/mL (IQR 470.0–738.8), which did not differ from their initial level at presentation [638 U/mL (IQR 474.3–829.3); $P = 0.85$]. No difference was found in baseline sIL-2R levels between patients receiving primary TMX treatment vs. cumulative patients receiving primary PDN treatment or second-line PDN treatment following TMX failure [691 U/mL (IQR 508.0–883.0) vs. 642 U/mL (IQR 485.5–808.0); $P = 0.71$]. In patients who were converted to PDN following TMX treatment failure, 20 of 24 patients (83%) eventually had treatment success (Table 3).

In patients treated with PDN as either first or second-line treatment, median baseline sIL-2R levels were significantly higher in patients who had treatment failure compared to that in patients who had treatment success (Fig. 3). In patients with PDN treatment success, serum sIL-2R levels decreased significantly during FU. ESR, CRP and sIgG4 levels also decreased significantly. Conversely, in patients with PDN treatment failure, neither sIL-2R nor APR levels decreased significantly during FU (Table 3). The OR of ordinal baseline

Table 2 Changes in APR, serum IgG4 and serum sIL-2R levels during tamoxifen therapy

	Presentation	Follow-up		
		6 weeks	4 months	8 months
Success tamoxifen, *n*	29	29	29	29
ESR, mm/h	28.0 (15.5–48.0)	15.0 (5.3–28.0)†	10 (2–21)†	8 (2–17)†
CRP, mg/L	7 (5–20)	5.0 (3.0–7.5)†	5.0 (3.0–5.8)†	5 (3–5)†
IgG4, g/L	0.8 (0.4–1.5)	0.9 (0.5–1.4)	0.8 (0.4–1.4)	0.7 (0.4–1.0)†
sIL-2R, U/mL	609.0 (508.0–845.5)	684.0 (530.8–848.8)	561 (455–848)	641.5 (491.0–883.8)
Failure tamoxifen, *n*	27	23	16	8
ESR, mm/h	38 (21–65)	26 (7–37)†	28.0 (5.3–39.5)*	28.0 (9.5–40.5)*
CRP, mg/L	13 (6–28)	5 (4–15)†	9.0 (5.0–15.8)	8.5 (5.0–27.3)
IgG4, g/L	0.6 (0.3–1.5)	0.7 (0.4–1.5)	0.5 (0.2–0.9)*	0.4 (0.2–0.5)
sIL-2R, U/mL	641 (473–984)	672.0 (468.5–923.0)	778.5 (504.3–1156.8)	742.5 (417.5–1598.0)

Values are median and interquartile range (25th–75th percentile)

Depicted values are number of patients (*n*) and laboratory values while on active tamoxifen treatment

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein

*$p < 0.05$ vs. similar variable at presentation

†$p < 0.01$ vs. similar variable at presentation

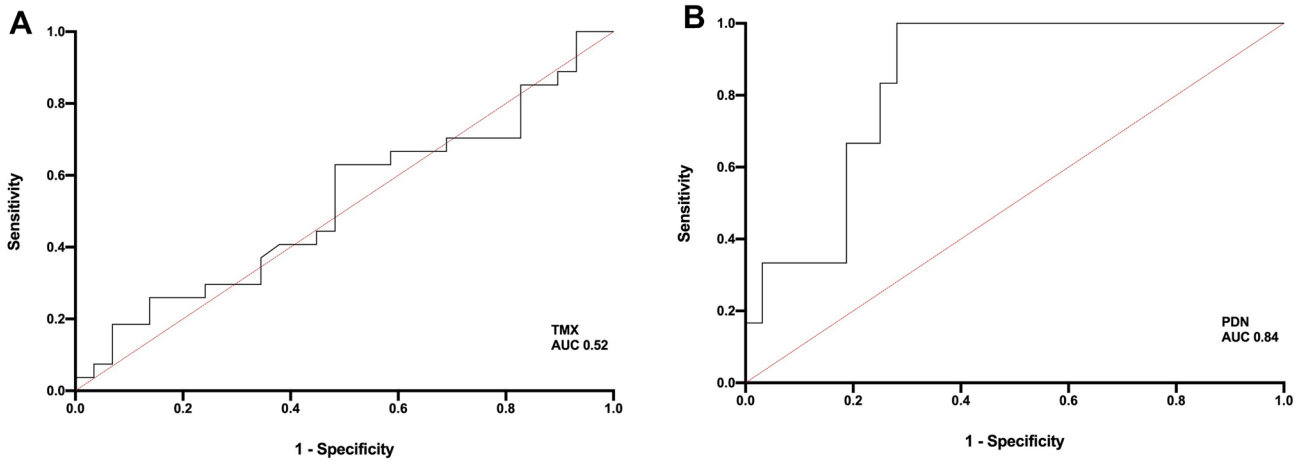

Fig. 2 ROC curve analyses of sIL-2R levels on a continuous scale and treatment success in patient treated with tamoxifen (TMX) (**A**) and prednisone (PDN) (**B**). The ROC curve of PDN shows a cut-off value of 703 U/mL with a sensitivity of 100% and specificity of 72%

serum sIL-2R level for PDN treatment success was 0.68 (95% CI 0.46–0.996; $P = 0.047$). Adjusted for APRs and sCr, the OR was 0.72 (95% CI 0.47–1.11; $P = 0.13$). ROC curve analyses of baseline serum sIL-2R levels and PDN treatment outcome showed an AUC of 0.84 (Fig. 2B). A serum sIL-2R cut-off value for PDN treatment success of ≤ 703 U/mL was found with a sensitivity of 100% and specificity of 72%.

Discussion

In this study, we demonstrate that serum sIL-2R levels are elevated in up to 60% of patients with active iRPF at presentation. In addition, the change in sIL-2R level over time was concordant with the clinical course of patients

Table 3 Changes in APR, serum IgG4 and serum sIL-2R levels during prednisone therapy

	Presentation	Follow-up[†]	
		First follow-up	Second follow-up
Success prednisolone, *n*	32	32	31
ESR, mm/h	36.0 (11.0–65.3)	8.0 (2.0–23.8)[§]	8 (5–17)[§]
CRP, mg/L	10.0 (5.0–23.8)	5.0 (3.0–7.5)[§]	4 (3–5)[§]
IgG4, g/L	1.1 (0.5–2.1)	0.7 (0.3–1.2)[§]	0.4 (0.2–0.7)[§]
sIL-2R, U/mL	563.5 (470.0–758.3)	480 (338–633)[‡]	397 (336–610)[§]
Failure prednisolone, *n*	6	6	6
ESR, mm/h	35.5 (16.5–64.3)	22.5 (10.3–38.0)	27.0 (17.0–62.5)
CRP, mg/L	25.0 (3.0–66.8)	7.0 (4.5–27.8)	6.0 (3.8–54.8)
IgG4, g/L	0.3 (0.2–0.8)	0.2 (0.1–1.5)[‡]	0.2 (0.1–0.4)[‡]
sIL-2R, U/mL	791.5 (728.8–1403.0)	813 (697.0–1086.3)	664.5 (509.3–987.5)

This analysis was performed in cumulative patients who received primary treatment with prednisolone and patients who were converted to prednisolone following tamoxifen treatment failure with at least 8 months FU after initiation of this treatment

Values are median and interquartile range (25th–75th percentile)

Depicted values are number of patients (*n*) and laboratory values while on active prednisolone treatment

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein

[†]Median time interval between start of or switch to prednisolone therapy to first follow-up was 1.5 months (IQR 1.0–1.5) and to end of follow-up 7.4 months (IQR 4.4–8.0)

[‡]$p < 0.05$ vs. similar variable at presentation

[§]$p < 0.01$ vs. similar variable at presentation

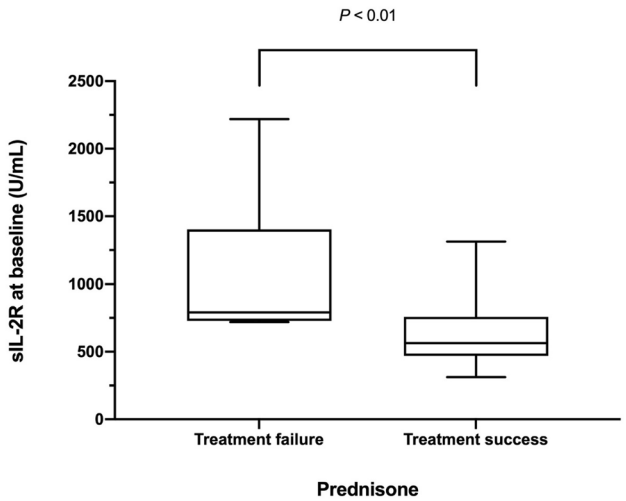

Fig. 3 Box-and-Whisker plot showing baseline sIL-2R levels according to treatment success in patients treated with prednisone (PDN). Patients who experienced treatment failure had significantly higher sIL-2R levels at baseline compared to patients who experienced treatment success. Values are expressed as median with quartiles and range

treated with PDN. Furthermore, baseline serum sIL-2R levels were able to predict treatment response in PDN-treated patients.

Median baseline sIL-2R levels in our study population was 668 U/mL. This finding of increased sIL-2R levels in the majority of patients lend further support for the hypothesis that T-lymphocytes are involved in the pathogenesis of iRPF [1, 4, 13]. Histologically, iRPF is characterized by the proliferation of fibrous and inflammatory tissue consisting of various immune cells, such as macrophages, lymphocytes, plasma cells and occasional eosinophils and neutrophils [1, 13]. The lymphocytic population is mainly comprised of CD4 + T cells [4, 13]. Different T-cell subsets are probably involved in the immunopathogenesis of iRPF. A T-helper 2 (Th2)-skewed immune response, which is known to promote fibrocyte differentiation, is suggested by the observed increased serum levels of the Th2 cytokines interleukin-10 [IL-10] and IL-13 and dominant infiltration of GATA-3 + cells in iRPF biopsy samples [14]. In addition, T cells locally produce IL-6, which can activate B cells and fibroblasts [15]. Increased serum levels of the Th2-response related chemokine eotaxin/CCL11 and of the chemokine CXCL12 were also observed, both of which are involved in promoting fibrosis [14, 16]. In another study, increased serum levels of the Th2-response related chemokine CCL18, which plays an important role in the stimulation of collagen production, was observed in iRPF patients and correlated with disease extent and activity [17]. By analogy to IgG4-RD, overproduction of CD4 + CD25 + cells, which are part of a naturally occurring population of regulatory T cells (Tregs), may also play a role [4, 13].

The IL-2R α-chain is secreted by activated T-cells as sIL-2R into the circulation and is generally regarded as a

marker of T-cell activation [18]. Indeed, elevated sIL-2R levels have been found in various other pathological conditions characterized by significant T-cell activation, such as rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis and IgG4-RD [6]. The specific role of sIL-2R in the interplay of the IL2—IL2R pathway in immunity and tolerance, however, is still controversial and depends on which cell type (i.e., antigen presenting cell, conventional T-cell or Treg is being (mostly) affected [6, 19]. If increased levels of sIL2R indeed reflect ongoing disease activity, sIL2R may be involved by activating effector cells. Alternatively, extensive shedding of the IL2R may be a (ineffective) attempt to restore immune homeostasis by reducing bioavailability of IL2 for effector cells, while maintaining it for Tregs [19]. It is also possible that sIL-2R does not exert any major biological effects and might only be useful as a biomarker [6, 19].

To date, only limited data is available on serum sIL-2R levels in patients with iRPF. In one small case series, increased sIL-2R levels were observed in 5 out of 6 (83%) patients with iRPF with a median of 970 U/mL [11]. It would be of great interest if serum sIL-2R could serve as a marker of disease activity and, more notably, of treatment response in iRPF disease. Because sIL-2R is a non-disease specific T-cell activation marker, it will probably not suit as a diagnostic tool [19]. Elevated ESR and CRP levels are typically thought to represent active inflammation and hence, indicative of a potential response to medical treatment [20]. However, although iRPF patients with elevated APR levels may be more symptomatic, APR levels at baseline nor their respective changes following initiation of treatment were predictive for treatment success [20–22]. Recent data suggest that sIL-2R levels may correlate with disease activity, number of affected organs and possibly predict disease relapse in various autoimmune and inflammatory diseases [6, 9, 10]. In the present study, patients with normal range or elevated baseline sIL-2R levels had comparable duration of symptoms and CT-documented RPF mass thickness. However, patients with elevated baseline sIL-2R levels presented with higher CRP and sCr levels. Moreover, a positive linear association was found between baseline sIL2-R and both CRP and sCr levels. In addition, patients with elevated sIL2-R levels more often presented with hydroureteronephrosis compared to patients with normal range sIL-2R levels.

Combined data suggest that sIL-2R levels may correlate with disease intensity in patients with iRPF. However, the observed association between baseline sIL-2R levels and sCr should be interpreted with caution as it may also reflect renal impairment, since sIL-2R is cleared by the kidneys [23]. Indeed, in patients with sarcoidosis, it has been suggested that elevated sIL-2R levels may not only reflect disease activity but also accumulation through impaired renal clearance [24]. Therefore, assessment of renal function when interpreting sIL-2R levels is warranted.

In a subset of patients, iRPF may be a manifestation of IgG4-RD [7]. Elevated levels of sIL-2R have been described in 53% to 100% of patients with IgG4-RD with median levels varying from 568 to 959 U/mL [8–10]. No correlation was observed between sIL2R and sIgG4 levels in patients with IgG4-RD [8]. We also observed no correlation between sIL2R and sIgG4 levels in iRPF patients. Albeit measured in only a few patients, no correlation was found between sIL2R and sIgG4 levels in another study involving iRPF patients [11]. However, previous data suggest that sIgG4 may be of added value in monitoring disease activity in iRPF disease, although not discriminative for predicting treatment success [22]. Possibly, sIL-2R and sIgG4 have value independent from each other, but this should be investigated further in larger studies.

Patients primarily treated with PDN more often experienced treatment success than patients treated with TMX in our study and the majority of patients who switched to second-line PDN treatment after TMX failure subsequently had treatment success. Baseline sIL-2R levels of patients who had treatment failure with PDN were significantly higher compared to that in patients who had treatment success with PDN. During FU, sIL-2R levels decreased significantly in patients who had treatment success with PDN, but not in patients who had treatment failure with PDN. Previous studies in patients with IgG4-RD also demonstrated decreasing sIL-2R levels following corticosteroid (CS) therapy.8–10 In addition, in patients with rheumatoid arthritis treated with infliximab, low baseline sIL-2R levels were able to predict rapid clinical response [25]. In the present study, ROC curve analysis of baseline serum sIL-2R levels and PDN treatment outcome showed a high AUC of 0.84. Moreover, a baseline (i.e., pre-treatment) sIL-2R cut-off value of $\leq$ 703 U/mL was able to predict PDN treatment success with satisfying sensitivity (100%) and specificity (72%).

In TMX-treated patients, baseline sIL-2R levels between patients with treatment success and failure did not differ nor did we observe a decline in serum sIL-2R levels during FU. Given that TMX is less effective than PDN in iRPF disease [26, 27], one might speculate that TMX has less anti-inflammatory activity compared to CSs. Another explanation may be that TMX has no effect on serum sIL-2R levels per se. No other data exist in the literature on the effect of TMX on sIL-2R levels. The present observation of a decline in ESR and CRP levels following TMX treatment is consistent with our earlier observations [20, 28]. However, as is the case for baseline sIL-2R levels, it has been shown previously that baseline APR levels are also not able to predict treatment outcome in patients treated with TMX [20].

Our observation of declining sIL-2R serum levels upon clinical improvement in PDN-treated patients supports the pathological role of excessive T-cell activity in iRPF and further indicates that serum sIL-2R levels might reflect disease

activity in patients with iRPF. CSs are generally considered first-line treatment for patients with iRPF [26, 27], but TMX has been shown to be a viable therapeutic option [28, 29]. While recognizing the superiority of CS therapy, we—and many of our patients—prefer TMX as primary treatment, particularly in cases of less extensive disease (e.g., limited fibrotic mass with no hydronephrosis or venous compression) and/or in cases of (relative) contraindications to long-term CS use. Given the success rate with TMX [28, 29], a substantial number of patients will not need prolonged CS treatment with its potentially hazardous complications and most non-responders to TMX will respond to subsequent PDN treatment. However, our study does not indicate a role of baseline sIL-2R levels in determining choice of primary treatment as baseline sIL2R levels between patients primarily treated with TMX or PDN did not differ.

The present study has some limitations. Although this is the first prospective study to date in investigating the role of sIL-2R levels in a relatively large cohort of patients with iRPF, the number of patients is still small. This can be explained by the rarity of the disease with an estimated incidence of 1.3 per 100.000 inhabitants [2]. We included patients who received second-line PDN in our treatment outcome analysis of PDN-treated patients. Time interval for measurements of blood markers varied in patients treated with second-line PDN compared to that in patients primarily with PDN, which were according to the standardized FU protocol. However, median time interval to first and end of FU in patients who received second-line PDN treatment (i.e., 1.5 months and 7.4 months, respectively) approximated those for patients who received primary treatment with PDN (i.e., 6 weeks and 8 months, respectively).

In conclusion, serum sIL-2R level is elevated in the majority of patients with iRPF and showed positive association with CRP and sCr level and the presence of hydroureteronephrosis. Baseline sIL2R level predicted treatment success in patients treated with PDN. The change in sIL-2R level over time was concordant with the clinical course of patients treated with PDN. Data suggest that serial measurement of serum sIL-2R may be of added value in monitoring disease activity and PDN treatment response in iRPF patients, but larger studies are required to substantiate this potential role.

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Data availability Data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study involving human participants was in accordance with the 1964 Helsinki Declaration. The study protocol was approved by the institutional review board of the Albert Schweitzer hospital.

Consent to participate Informed consent was obtained from all patients included in the study.

References

1. van Bommel EF (2002) Retroperitoneal fibrosis. Neth J Med 60(6):231–242
2. van Bommel EFH, Jansen I, Hendriksz TR et al (2009) Idiopathic retroperitoneal fibrosis: prospective evaluation of incidence and clinicoradiologic presentation. Medicine (Baltimore). https://doi.org/10.1097/MD.0b013e3181afc420
3. Parums DV, Choudhury RP, Shields SA et al (1991) Characterisation of inflammatory cells associated with "idiopathic retroperitoneal fibrosis." Br J Urol. https://doi.org/10.1111/j.1464-410x.1991.tb15216.x
4. van Bommel EF, de Mol M, Langerak AW et al (2011) Idiopathic retroperitoneal fibrosis mimicking malignant lymphoma. Pathol Int. https://doi.org/10.1111/j.1440-1827.2011.02718.x
5. Rubin LA, Nelson DL (1990) The soluble interleukin-2 receptor: biology, function, and clinical application. Ann Intern Med. https://doi.org/10.7326/0003-4819-113-8-619
6. Dik WA, Heron M (2020) Clinical significance of soluble interleukin-2 receptor measurement in immune-mediated diseases. Neth J Med 78(5):220–231
7. Stone JH, Zen Y, Deshpande V (2012) IgG4-related disease. N Engl J Med. https://doi.org/10.1056/NEJMra1104650
8. Karim F, Eurelings LEM, Bansie R et al (2018) Soluble interleukin-2 receptor: a potential marker for monitoring disease activity in IgG4-related disease. Mediators Inflamm. https://doi.org/10.1155/2018/6103064
9. Handa T, Matsui S, Yoshifuji H et al (2018) Serum soluble interleukin-2 receptor as a biomarker in immunoglobulin G4-related disease. Mod Rheumatol. https://doi.org/10.1080/14397595.2017.1416739
10. Akiyama M, Sasaki T, Kaneko Y et al (2018) Serum soluble interleukin-2 receptor is a useful biomarker for disease activity but not for differential diagnosis in IgG4-related disease and primary Sjögren's syndrome adults from a defined population. Clin Exp Rheumatol 36(3):157–164
11. Sakamoto A, Nagai R, Saito K et al (2012) Idiopathic retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pericarditis–retrospective analysis of 11 case histories. J Cardiol. https://doi.org/10.1016/j.jjcc.2011.07.014

12. Vlug A, Nieuwenhuys EJ, van Eijk RV et al (1994) Nephelometric measurements of human IgG subclasses and their reference ranges. Ann Biol Clin (Paris) 52(7–8):561–567
13. Raglianti V, Rossi GM, Vaglio A (2020) Idiopathic retroperitoneal fibrosis: an update for nephrologists. Nephrol Dial Transplant. https://doi.org/10.1093/ndt/gfaa083
14. Nicastro M, Vescovini R, Maritati F et al (2019) Fibrocytes in chronic periaortitis: a novel mechanism linking inflammation and fibrosis. Arthritis Rheumatol. https://doi.org/10.1002/art.41024
15. Vaglio A, Catanoso MG, Spaggiari L et al (2013) Interleukin-6 as an inflammatory mediator and target of therapy in chronic periaortitis. Arthritis Rheum. https://doi.org/10.1002/art.38032
16. Mangieri D, Corradi D, Martorana D et al (2012) Eotaxin/CCL11 in idiopathic retroperitoneal fibrosis. Nephrol Dial Transplant. https://doi.org/10.1093/ndt/gfs408
17. Kollert F, Binder M, Probst C et al (2012) CCL18—potential biomarker of fibroinflammatory activity in chronic periaortitis. J Rheumatol. https://doi.org/10.3899/jrheum.111143
18. Boyman O, Sprent J (2012) The role of interleukin-2 during homeostasis and activation of the immune system. Nat Rev Immunol. https://doi.org/10.1038/nri3156
19. Damoiseaux J (2020) The IL-2—IL-2 receptor pathway in health and disease: the role of the soluble IL-2 receptor. Clin Immunol. https://doi.org/10.1016/j.clim.2020.108515
20. Pelkmans LG, Aarnoudse AJ, Hendriksz TR et al (2012) Value of acute-phase reactants in monitoring disease activity and treatment response in idiopathic retroperitoneal fibrosis. Nephrol Dial Transplant. https://doi.org/10.1093/ndt/gfr779
21. Magrey MN, Husni ME, Kushner I et al (2009) Do acute-phase reactants predict response to glucocorticoid therapy in retroperitoneal fibrosis? Arthritis Rheum. https://doi.org/10.1002/art.24461
22. Pelkmans LG, Hendriksz TR, Westenend PJ et al (2017) Elevated serum IgG4 levels in diagnosis and treatment response in patients with idiopathic retroperitoneal fibrosis. Clin Rheumatol. https://doi.org/10.1007/s10067-017-3542-8
23. Nässberger L, Sturfelt G, Thysell H (1992) Serum levels of the soluble interleukin-2 receptor are dependent on the kidney function. Am J Nephrol. https://doi.org/10.1159/000168489
24. Verwoerd A, Vorselaars ADM, Moorsel V, Coline HM et al (2015) Discrepant elevation of sIL-2R levels in sarcoidosis patients with renal insufficiency. Eur Respir J. https://doi.org/10.1183/09031936.00005315
25. Kuuliala A, Nissinen R, Kautiainen H et al (2006) Low circulating soluble interleukin 2 receptor level predicts rapid response in patients with refractory rheumatoid arthritis treated with infliximab. Ann Rheum Dis. https://doi.org/10.1136/ard.2004.034728
26. van der Bilt FE, Hendriksz TR, van der Meijden WA et al (2016) Outcome in patients with idiopathic retroperitoneal fibrosis treated with corticosteroid or tamoxifen monotherapy. Clin Kidney J. https://doi.org/10.1093/ckj/sfv148
27. Vaglio A, Palmisano A, Alberici F et al (2011) Prednisone versus tamoxifen in patients with idiopathic retroperitoneal fibrosis: an open-label randomised controlled trial. Lancet. https://doi.org/10.1016/S0140-6736(11)60934-3
28. van Bommel EF, Hendriksz TR, Huiskes AW et al (2006) Brief communication: tamoxifen therapy for nonmalignant retroperitoneal fibrosis. Ann Intern Med. https://doi.org/10.7326/0003-4819-144-2-200601170-00007
29. van Bommel EF, Pelkmans LG, van Damme H et al (2013) Long-term safety and efficacy of a tamoxifen-based treatment strategy for idiopathic retroperitoneal fibrosis. Eur J Intern Med. https://doi.org/10.1016/j.ejim.2012.11.010