

Interferon (IFN)- λ is a potential mediator in lupus nephritis

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ABSTRACT

Objectives: Interferon (IFN)- α is thought to be central in the pathogenesis for lupus nephritis (LN) and recent studies also indicate a role for IFN λ . Little is known about these cytokines in the context of treatment response. We studied levels of IFN α and IFN λ in patients with LN in association with clinical and histological response (HR) to treatment.

Methods: Fifty-six patients with active LN were included. Renal biopsies were performed at baseline and after immunosuppressive therapy. Serum levels of IFN α and IFN λ were analysed at both biopsy occasions and in 163 controls. The biopsies were evaluated according to the International Society of Nephrology/Renal Pathology Society classification. Clinical response was defined according to recent definitions. HR was defined as class I, II or III/IV-C on repeat biopsies. The expression of IFN λ in renal tissue was assessed by immunohistochemistry.

Results: At baseline, serum levels of both IFN α and IFN λ were higher in patients versus controls ($p=0.01$ and $p=0.03$, respectively). There was no correlation between IFN α and IFN λ . Overall, IFN α decreased after treatment ($p=0.003$) but IFN λ remained unchanged. However in patients with HR, IFN λ decreased ($p=0.01$). The highest levels of IFN λ were seen in patients with poor HR. Immunostaining of renal tissue revealed expression of IFN λ , particularly in crescent formations, inflammatory infiltrates and tubular cells.

Conclusions: The study supports a role for IFN λ in LN, both in circulation and at a tissue level. Levels of IFN α and IFN λ did not correlate and were affected differently by immunosuppression, indicating that they are differently involved in subgroups of LN. Persistent increased levels of IFN λ were associated to an unfavourable HR to treatment.

studies support that many of the typical immunological and pathological features of lupus are a consequence of a persistent self-directed immune reaction driven by IFN α . In addition, many patients with SLE have an increased expression of IFN α -regulated genes in mononuclear cells in the peripheral blood (the IFN signature).^{2 3}

Type III IFNs are the most recently described members of the IFN family and comprise IFN λ -1 (also called interleukin (IL)-29), IFN λ -2 (IL-28A) and IFN λ -3 (IL-28B). In infected individuals, both type I and III IFNs are important cytokines in anti-viral immune responses. Although IFN λ and IFN α share many biological activities, there are also important differences between these IFNs.⁴ While IFN α is mainly produced by plasmacytoid dendritic cells (pDCs), IFN λ can be produced by various cell types, mainly by antigen-presenting cells. Additionally, IFN α has a variety of target cells while IFN λ acts through a distinct receptor restricted to epithelial cells and some leucocytes (B cells and pDCs).^{5 6} Some recent studies indicate that IFN λ is involved in the pathogenesis of SLE. Increased levels of IFN λ have been demonstrated in patients with SLE, the highest levels were found in patients with renal involvement and arthritis and levels also correlated with disease activity.⁷ IFN λ was also expressed in skin lesions from patients with SLE.⁸

Although IFN α is considered central in SLE, and recent data support a role also for IFN λ , not much is known about how these cytokines correlate or how they are affected by immunosuppressive treatment in LN. We aimed to study serum levels of IFN α and IFN λ in patients with LN, both at active disease and after induction immunosuppressive treatment, in association with routine laboratory and histopathological findings as well as in relation to treatment response. As a pilot, we also performed immunohistochemistry staining of IFN λ in renal tissue from nine patients with LN.

INTRODUCTION

Lupus nephritis (LN) is a severe manifestation of SLE, affecting up to 60% of the patients at some point of the disease.¹ The pathogenesis for LN is not completely understood and involves multiple components of both the innate and adaptive immune systems. Interferon (IFN)- α is claimed to be central in the pathogenesis and several



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METHODS

Patients

Fifty-six patients with biopsy-proven active LN who were followed at the department of rheumatology at the Karolinska University Hospital between 1996 and 2011 were included. All patients met at least four of the 1982 American College of Rheumatology classification criteria for SLE.⁹ The patients were treated in accordance with the standard therapy for LN, corticosteroids combined with intravenous cyclophosphamide (CYC) (n=40), mycophenolate mofetil (n=9) or rituximab (n=6). One patient was treated with azathioprine. The treatment regimen for CYC was 0.5–1 g/m² monthly as modified from the National Institutes of Health protocol¹⁰ or the low-dose CYC regimen according to the EURO-lupus protocol.¹¹ As part of the clinical routine at our unit, all patients except one underwent a second renal biopsy after induction therapy. Repeated renal biopsies were performed after a median time of 7 months (range 5–15). Clinical data, blood and urinary samples were collected on both biopsy occasions. Serum samples were stored at –80°C.

At the time point for the first renal biopsy, 38/56 (68%) of the patients were treated with prednisolone, median dose 20 mg/day (range 2.5–60). At the start of immunosuppressive therapy, all but one (98%) were treated with prednisolone, median dose 40 mg/day, doses ranging from 2.5 to 80 mg/day as decided by the treating physician, and were thereafter successively tapered. At repeat biopsies, 98% of the patients were still treated with prednisolone, median dose 10 mg/day (range 2.5–30). The clinical characteristics of patients and nephritis data at baseline and follow-up are presented in table 1.

One hundred and sixty-three healthy controls were used as a control group for the IFN analyses. The controls were recruited as population controls for our other larger cohort study in SLE described elsewhere.¹² Informed consent was obtained from all subjects and the regional ethics committees in Stockholm approved the study protocol (KI Forskningsetikkommitte Nord, Karolinska sjukhuset; Regionala etikprövningsnämnden i Stockholm).

Table 1 Clinical, laboratory and histopathological characteristics at the first and second biopsies

	First biopsy	Second biopsy	p Value
Gender, n (%)			
Female	48 (86)		
Male	8 (14)		
Age (years)	32 (18–61)		
Creatinine, µmol/L	82.5 (49–284)	76.0 (48–306)	0.003
Albuminuria, g/day	1.4 (0–8.4)	0.5 (0–3.8)	<0.001
C3, g/L	0.5 (0.2–1.13)	0.79 (0.38–1.41)	<0.001
C4, g/L	0.10 (0.02–0.51)	0.14 (0.02–0.45)	<0.001
Anti-DNA AB IU/mL	86.0 (<5–300)	20.5 (<5–300)	<0.001
Renal histology (ISN/RPS), n			
I–II	–	15	
III–C	–	5	
III–A or III–A/C	13	8	
IV–C	–	1	
IV–A or IV–A/C	26	6	
III–IV/V	6	3	
V	11	16	
Vasculitis	–	1	
Activity index	5 (0–13)	2 (0–12)	<0.001
Chronicity index	1 (0–6)	1 (0–8)	<0.001
Prednisolone at			
Biopsy*, %	68	98	
Dose, mg/day	20 (2.5–60)	10 (2.5–30)	
Induction treatment, n			
Cyclophosphamide	40		
Mycophenolate mofetil	9		
Rituximab	6		
Azathioprine	1		
IFN α (ng/mL)	0.08 (0–1.2)	0.03 (0–0.68)	0.003
IFN λ (ng/mL)	0 (0–5.32)	0 (0–4.02)	0.14

Values are presented as a median (range) unless otherwise indicated.

*Percentage of patients treated with prednisolone.

C3, complement component 3; C4, complement component 4; IFN, interferon; ISN/RPS, International Society of Nephrology/Renal Pathology Society; n, number of patients.

Evaluation of renal function, histopathology and renal activity

Renal evaluation at the time of both biopsies included urine analyses (dip-slide procedure and urinary sediment) and investigation of 24-hour urine albumin excretion. Renal function was determined by serum creatinine levels ($\mu\text{mol/L}$).

Renal biopsies were evaluated by light microscopy, immunofluorescence microscopy and electron microscopy. The biopsies were classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification,¹³ and scored for activity and chronicity indices.¹⁴

Renal response was defined according to a consensus statement by Gordon *et al.*¹⁵ A complete clinical response (CR) was defined as inactive urinary sediment, proteinuria ≤ 0.2 g/day and normal glomerular filtration rate >90 mL/min or stable (within 10% of normal if previously abnormal) renal function. Partial response (PR) was defined by inactive sediment, proteinuria ≤ 0.5 g/day and normal or stable ($<10\%$ deterioration from baseline if previously abnormal) renal function. Patients not reaching these criteria were regarded as clinical non-responders (NR).

We also assessed histopathological response; transformation into class I, II or III/IV-C was considered HR whereas persistent class III/IV-A or III/IV-A/C and persistent, or transformation into, class V was considered as histopathological non-response (HNR).

Serology and complement measures

Anti-double-stranded DNA antibodies were analysed using Luminex Bioplex 2200 (Bio-Rad Laboratories, California, USA) according to the routines of the laboratory, cut-off <5 IU/mL. The complement components C3 and C4 were determined by nephelometry. Antibodies against complement component C1q were analysed by ELISA (Alegria, Orgentec Diagnostika GmbH, Germany), cut-off <14 IU/L.

The detection of IFN α and IFN λ

ELISA was performed as indicated by the manufacturer, IFN α was measured by a pan IFN α ELISA detecting kit and the detected IFN α subtypes were 1/13, 2, 4, 5, 6, 7, 8, 10, 14, 16 and 17 (product code 3425-1A-20, Mabtech AB, Nacka, Sweden). IFN λ was measured using a monoclonal mouse IgG2A capture antibody that recognises IFN λ -1 (catalogue number MAB15981, R&D Systems, Minneapolis, Minnesota, USA). For the detection of affinity, purified goat polyclonal anti-IFN λ -1 IgG antibodies were used (catalogue number BAF1598, R&D Systems). In short, high-binding 96 well plates (Nunc) were coated with capture antibody at a concentration of 4 and 8 $\mu\text{g/mL}$, respectively, for IFN α and IFN λ in a carbonate buffer, pH 9.6 and kept in $+4^\circ\text{C}$ overnight. The plates were blocked with 5% (w/v) fat-free milk in Tween for 60 min, washed and incubated with patient sera, diluted $\times 2$ for the detection of IFN α and $\times 4$ for the detection of IFN λ in a dilution buffer (catalogue

number 3652-D2, Mabtech AB) and were kept overnight at $+4^\circ\text{C}$. For the derivation of standard curve for IFN α , a standard reagent included in the kit was used; for IFN λ , a recombinant human IL-IFN λ -1 was purchased (R&D Systems, catalogue number 1598-IL). Ten serial dilutions were performed and negative controls were obtained by adding only buffer. All samples were run in duplicates. After washing, biotinylated detection antibodies were diluted in the dilution buffer at a concentration of 1 and 0.4 $\mu\text{g/mL}$ for IFN α and IFN λ , respectively, and incubated for 1 hour at room temperature (RT). After washing, streptavidine-alkaline phosphatase diluted at a ratio of 1:1000 was added and incubated for 1 hour at RT. Afterwards, a substrate solution was added and optical density was measured after 1 hour, 2 hours and overnight, at 405 nm. The detection levels were set according to the manufacturer's recommendation: 0.036 ng/mL for IFN α and 0.3 ng/mL for IFN λ .

Immunohistochemistry

Immunohistochemical (IHC) stainings were performed on formaldehyde-fixed paraffin-embedded serial sections of nine renal biopsies from patients with LN. Six of the renal biopsies were baseline biopsies and three were from repeated biopsies after treatment. All steps were performed at RT, unless otherwise stated. The slides were deparaffinised in xylene and rehydrated to water with ethanol in decreasing concentrations. Antigen retrieval was achieved by microwave irradiation in 10 mM Tris (KEBO) buffer containing 0.5 mM EDTA (Sigma), pH 9.0. Endogenous peroxidase activity was blocked with 3% H_2O_2 in 0.05 M tris-buffered saline (TBS), pH 7.6. Sections were subsequently treated with an avidin-biotin blocking system (DakoCytomation) to block endogenous biotin-binding sites followed by a 60 min serum block with 3% skim-milk, 7% donkey sera, 3% human AB sera, 3.2 mg/mL poly-L-lysine hydrobromide (Sigma) in TBS. The slides were thereafter incubated overnight at 4°C with primary antibodies (1 $\mu\text{g/mL}$ rabbit anti-IL29, Santa Cruz Biotechnology, or 0.5 $\mu\text{g/mL}$ rabbit anti-CD3, Thermo Fisher Scientific) and isotype controls (rabbit mAb Ig, cell signalling) diluted in TBS supplemented with 0.5% skim-milk and species-specific serum. After washing, a biotinylated donkey anti-rabbit antibody (Jackson ImmunoResearch Laboratories) diluted in TBS with 0.5% skim-milk and species-specific serum was used for detection of the corresponding primary antibody and isotype controls. For signal amplification, the slides were treated with Vectastain ABC complex (Vector Laboratories, Burlingame, California, USA), diluted in 0.1 M Tris buffer containing 0.15 M NaCl and 0.5% (w/v) Du Pont blocking reagent. After washing, biotinylated tyramide (TSA indirect; NEL 700) diluted at a ratio of 1:50 in an amplification buffer (NEN; PerkinElmer Life Sciences, Boston, Massachusetts, USA) was added followed by a second treatment with the Vectastain ABC complex. The stainings were developed using 3,3'-diaminobenzidine tetrahydrochloride (Sigma) dissolved in TBS and counterstained

with haematoxylin. The sections were dehydrated and mounted in Pertex (Histolab AB, Sweden).

Statistics

The levels of IFNs were calculated as a ratio from the standard curve. The distribution of values was not normal (D'Agostino-Pearson omnibus normality test), therefore respective non-parametric tests were used when calculating associations with levels of IFNs. We performed the Wilcoxon matched pair test to compare variables at baseline and follow-up. We used the Mann-Whitney U test for comparisons between the two groups. For categorical variables, the χ^2 test was used. Correlations were calculated using Spearman's rank correlation. Statistical significance was set at the level of $p < 0.05$. The statistical evaluation was performed using STATISTICA V.9, StatSoft, Tulsa, Oklahoma, USA.

RESULTS

Histopathology and renal activity

All patients had an active nephritis at baseline, 45/56 had proliferative nephritis (PN), class III-A or III-A/C (n=13), class IV-A or IV-A/C (n=26) and class III-IV/V (n=6), and 11/56 had class V membranous nephritis (MN). Follow-up biopsies revealed class I (n=1), class II (n=14), class III-C (n=5), class IV-C (n=1), class III-A or III-A/C (n=8), class IV-A or IV-A/C (n=6), class III-IV/V (n=3) or class V (n=16). One patient developed a renal vasculitis.

There was a decrease in proteinuria at follow-up ($p < 0.001$) whereas no overall difference in creatinine levels was found (data presented in [table 1](#)).

CR or PR was observed in 33/56 (59%) patients at the time of repeated biopsies. Nineteen patients had CR (34%), 14 had PR (25%) and 23 had NR (41%).

Twenty-one patients (38%) were regarded as HRs and 34 (62%) as HNRs according to the definition used. The renal activity index decreased significantly (< 0.001) whereas there was an increase in the chronicity index ($p < 0.001$).

Serology and complement

At the time point of follow-up biopsies, anti-DNA antibodies had decreased ($p < 0.001$). Anti C1q antibodies also decreased ($p < 0.001$), whereas levels of C3 and C4 increased ($p < 0.001$) ([table 1](#)).

Table 2 Baseline levels of interferon (IFN)- α and IFN λ in patients versus controls

	Patients	Controls	p Value
IFN α (ng/mL)	0.08 (0–1.2)	0.03 (0–0.67)	0.01
IFN λ (ng/mL)	0 (0–5.32)	0 (0–4.27)	0.03

Values are presented as a median (range).

Levels of IFNs in patients and controls

Thirty-seven of 56 (66%) patients had detectable levels of IFN α and 17/56 (30%) had detectable levels of IFN λ .

At baseline, serum levels of both IFN α and IFN λ were higher in patients versus controls ($p = 0.01$ and 0.03 , respectively) ([table 2](#), [figure 1](#)). At follow-up, the levels of IFN α had decreased ($p = 0.003$) but the levels of IFN λ remained unchanged ([table 1](#), [figure 1](#)).

There was no correlation between the levels of IFN α and IFN λ either at baseline or at follow-up (data not shown).

Associations between IFN levels, laboratory findings and CR

At baseline, IFN α was positively correlated with anti-DNA ($r = 0.6$) and anti-C1q antibodies ($r = 0.3$, $p < 0.05$ for both) and inversely correlated with C3 and C4 ($r = -0.4$ for both, $p < 0.05$). No correlations were seen between IFN λ and antibodies or complement levels. Neither IFN α nor IFN λ correlated with proteinuria or creatinine at either baseline or follow-up, and there was no clear association with CR (data not shown).

Associations between IFN levels and HR

At baseline biopsies, there was a trend, although not significant, towards higher levels of IFN α in patients with PN versus patients with MN ($p = 0.06$) and higher levels of IFN λ in patients with MN versus patients with PN ($p = 0.052$). In PN, 73% of the patients had detectable IFN α versus 36% in MN ($p = 0.02$). In PN, 27% of the patients had detectable IFN λ versus 45% in MN (NS).

Overall, the levels of IFN λ had not decreased at follow-up. However, in the subgroup of patients with an HR, the levels of IFN λ decreased after treatment ($p = 0.01$), while those remained unchanged in the subgroup of patients with a HNR ([figure 2](#)). No difference in IFN α levels was seen in HR versus HNR. Increasing levels of IFN λ after treatment were only seen in HNR.

IFN λ expression in renal tissue

Immunostaining revealed expression of IFN λ in all the examined renal biopsies from patients with LN. The staining was most pronounced in glomeruli with cellular crescent formations and was also expressed in areas of inflammatory infiltrates of CD3+ T cells and in tubular cells ([figures 3](#) and [4](#)).

The sample size was too small to perform any statistical analysis, but the presence of IFN λ was observed in all nephritis classes (class III, IV or V) at baseline biopsies. In the renal biopsy specimens obtained at follow-up, the patients with HR (both class II) had no clear glomerular staining although the tubular staining was still present ([figure 5](#)).

DISCUSSION

We report that levels of IFN λ declined after treatment in patients with LN with a favourable HR, while remained unchanged in HNRs. In renal tissue, IFN λ was expressed

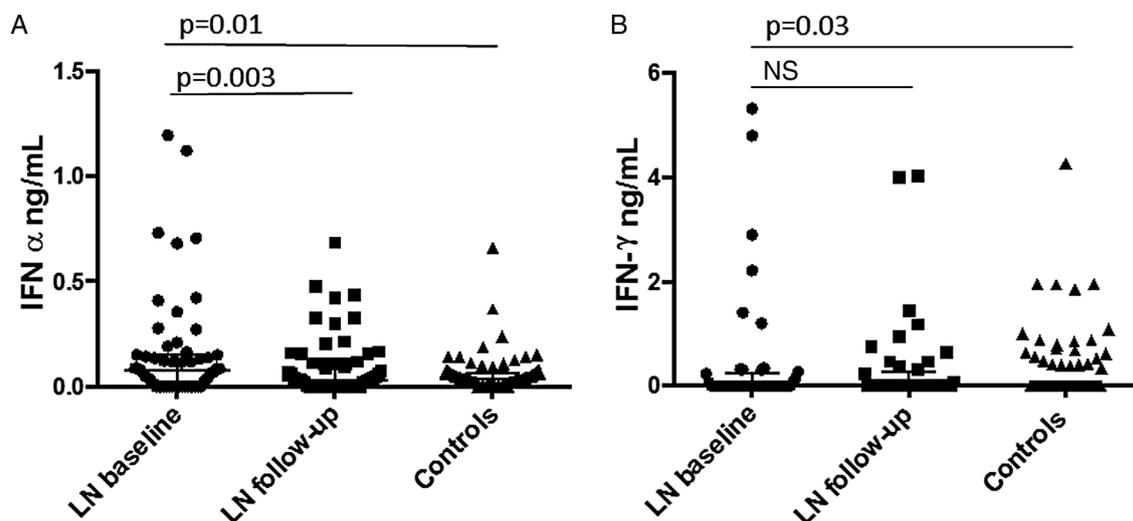


Figure 1 Serum levels of (A) interferon (IFN)- α and (B) IFN λ , at baseline and follow-up, in patients and controls. LN, lupus nephritis; NS, not significant.

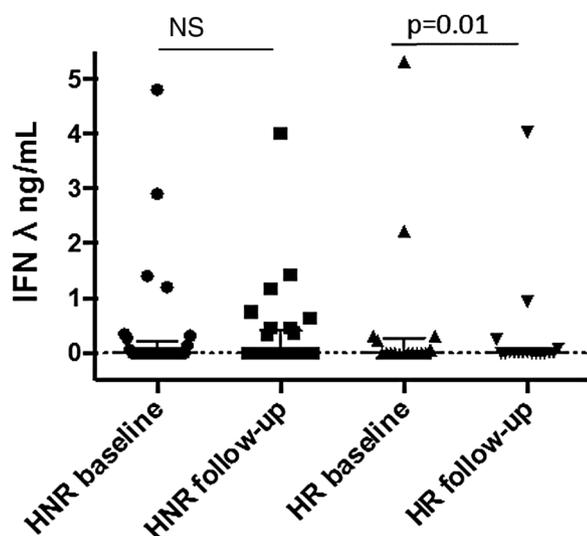


Figure 2 Serum levels of interferon λ , at baseline and follow-up, in patients with histological response and histological non-response. HNR, histological non-response; HR, histological non-response; IFN, interferon; NS, not significant.

in crescent formations within the glomeruli, and also in inflammatory infiltrates, which indicates that IFN λ may be involved in the inflammatory process in LN.

IFN α and IFN λ were both increased in patients with LN but did not correlate with each other and levels were affected differently by an immunosuppressive treatment. Thus, our study supports a role for IFN λ and confirms previous findings regarding the importance of IFN α , in LN.

The lack of correlation between levels of IFN α and IFN λ indicates differences between these cytokines regarding both regulation and involvement in the subgroups of LN. While IFN α correlated with routine LN biomarkers, such as anti-DNA antibodies and

complement levels, no such correlations were seen for IFN λ . In addition, IFN α decreased after immunosuppressive treatment while the overall levels of IFN λ remained unchanged. Interestingly, in patients with LN with HR, levels of IFN λ decreased after treatment while in patients with LN with HNR the levels were unchanged or even increased. Our results thus indicate that unaffected levels of IFN λ are associated with a more severe LN, which does not respond to currently used immunosuppressives.

Current available biomarkers for clinical assessment of renal disease activity and treatment response in lupus are insufficient and patients with LN may have inflammatory activity in the renal tissue without clinical signs of renal involvement, or despite good CR to therapy.^{16–19} Thus, new biomarkers to assess treatment response in LN are needed. Our findings on persisting levels of IFN λ in patients with an active nephritis after immunosuppression indicate that it may be a potential biomarker for treatment response in LN.

The observation that IFN λ was expressed in all the examined renal biopsies further supports a role for IFN λ in LN. The staining was most pronounced in glomeruli and in areas of inflammatory infiltrates but was also expressed in tubuli. Interestingly, there was no glomerular expression in the biopsies from the repeated biopsies with a favourable histological outcome after treatment (class II nephritis). The increased expression in glomerular crescents may be of special importance. The crescent formation mainly consists of proliferating epithelial cells that originate from the Bowman's capsula²⁰ and is a feature of severe nephritis and renal vasculitis. The pronounced staining of IFN λ in the crescent formations thus supports that IFN λ receptors are mainly located on epithelial cells.⁵ One previous study on mice found that epithelial cells were the only cells within the kidney that responded to IFN λ .²¹ However,

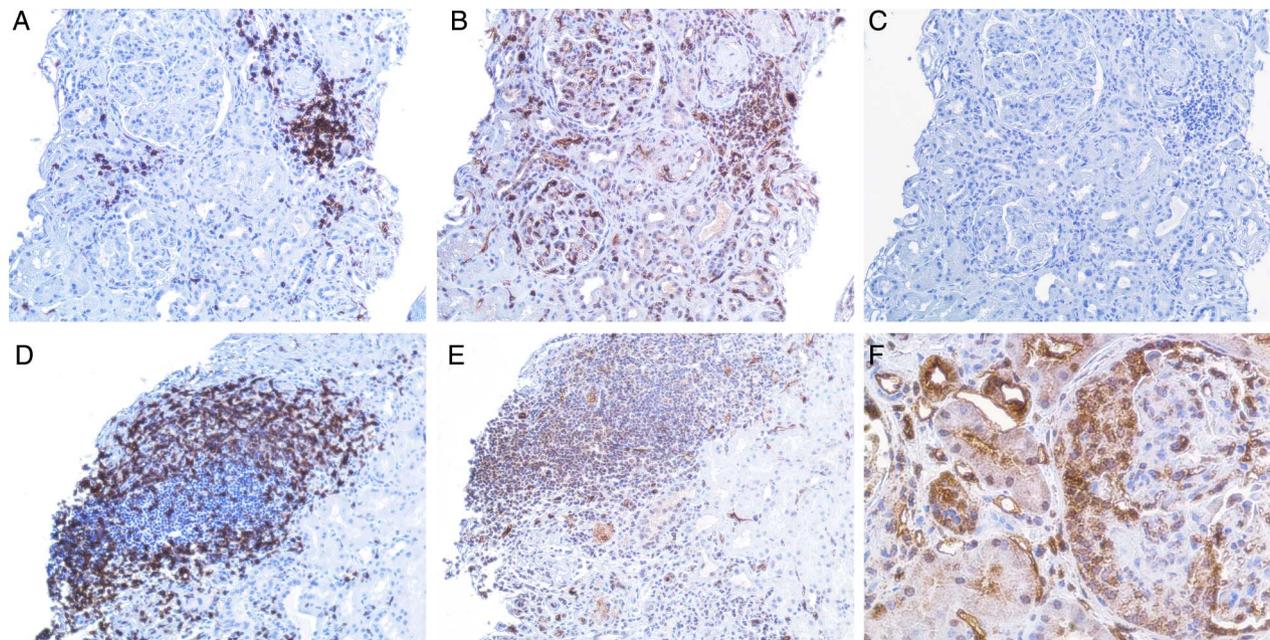


Figure 3 (A–E) demonstrate a kidney biopsy from a patient with lupus nephritis (LN) class V. Representative micrographs: (A), an inflammatory infiltrate with T cells as demonstrated by a positive CD3 staining. (B), demonstration of interferon (IFN)- λ staining, predominantly found in the inflammatory infiltrate shown in (A) but also present in the glomeruli. (C), the same infiltrate from a consecutive section, stained with irrelevant isotype control antibody. (D), another part of the biopsy from the same patient, showing an inflammatory infiltrate with T cells as demonstrated by positive CD3 staining. (E), demonstration of IFN λ staining in that infiltrate. Original magnifications: $\times 20$. (F), predominant expression of IFN λ in a cellular crescent formation in the glomeruli (original magnifications: $\times 40$) in a kidney biopsy from a patient with LN class IV.

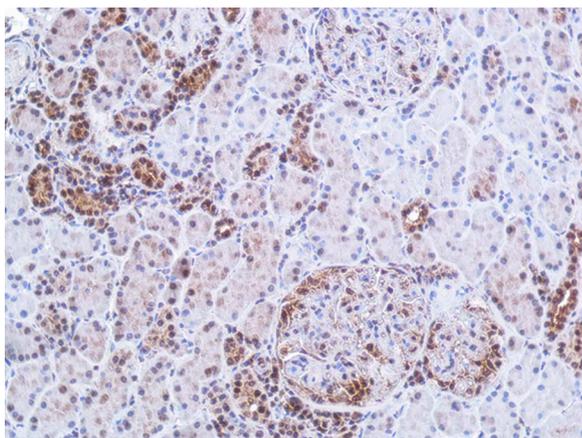


Figure 4 Immunohistochemistry staining of interferon (IFN)- λ in renal tissue. The figure demonstrates a kidney biopsy from a patient with lupus nephritis class IV. The representative micrograph displays IFN λ staining predominantly found in tubular cells and in an incipient cellular crescent in the glomeruli. In the glomeruli without crescent, the staining is sparse. Original magnifications: $\times 20$.

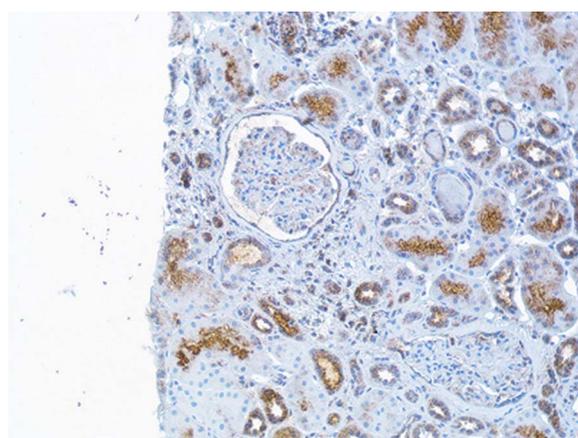


Figure 5 Immunohistochemistry (IHC) staining of interferon (IFN)- λ in renal tissue. The figure demonstrates a repeated renal biopsy obtained from a patient after immunosuppressive therapy and now lupus nephritis class II. The IHC staining for IFN λ is here sparse in tubular cells and not expressed in the glomeruli. Original magnifications: $\times 20$.

with the present staining method, we could not discriminate circulating from receptor-bound IFN λ .

It has been shown that Th17 cells are important local sources of IFN λ in psoriasis skin lesions.²² We observed renal expression of IFN λ in the CD3 positive cell infiltrates. In an earlier study, we demonstrated that IL-17 is

also expressed in renal infiltrates and associated with poor LN outcome.²³ Altogether, these findings may suggest that the infiltrating CD3+, possibly Th17 cells, are also the source of IFN λ in LN. Taken together, the results from the IHC-staining support a role for IFN λ in more severe LN. However, the number of tissue stainings in this study was limited and larger studies of renal

biopsies from different LN classes are needed to confirm our findings.

The prognosis of LN has improved but all patients do not respond to standard immunosuppressive treatment, side effects are a concern and renal relapses are common. Thus, there is a need for new therapies in LN. Treatment strategies targeting IFN α have been the focus of many studies on drug development for lupus in recent years.^{24 25} However, initial results from a study on the monoclonal antibody sifalimumab were somewhat disappointing. Although inhibition of the type I IFN gene signature was documented, no statistically significant differences in clinical activity between the sifalimumab and placebo groups were observed.²⁶ A more recent study reported promising data on sifalimumab, however patients with active nephritis were not included.²⁷

Recently, it was suggested that persistent disease activity despite inhibition of IFN α could be the result of IFN λ receptor signalling, and that drugs targeting IFN λ ought to be developed and tried in SLE.⁶ Our data support this view indicating that IFN λ could also be of interest as a drug target in LN.

Although patients with LN had overall higher levels of IFN λ as compared with controls, only one-third of the patients were positive for IFN λ according to the method used. The same ELISA assay was used by Zahn *et al*,⁸ who reported increased serum levels of IFN λ in patients with cutaneous SLE lesions. They observed IFN λ levels within a similar range as in the current study. Our study suggests that IFN λ may be important in a subgroup of patients with LN. Whether the finding that only a subgroup of patients had circulating levels of IFN λ is due to a genetic polymorphism, insensitive assays or other causes cannot be answered by the present study. Further studies on larger groups of patients are needed to address these issues.

The focus of this study was LN and non-renal manifestations have not been taken into consideration, but may also to some extent have influenced the serum IFN levels. Although this study is not able to define the pathogenic role of IFN λ in LN, the expression of IFN λ in the renal tissue clearly points to its involvement in LN.

In conclusion, our findings suggest that IFN λ and IFN α are involved in the pathogenesis for LN although the exact role of these cytokines remains to be elucidated. We report that IFN λ may drive LN independently of IFN α , and that persistent high levels of IFN λ were associated with poor response to the available treatment regimens. Based on our results and previous data, we suggest that IFN λ might be one of the driving molecules in severe LN. IFN λ signalling may thus also be of interest when tailoring new therapies for patients with LN.

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Contributors AZ: original idea, patient characterisation, acquisition of data, statistical analyses, interpretation of results and manuscript writing. VO: cytokine measurements, interpretation of results and manuscript writing. IP: patient characterisation and acquisition of data. ES: interpretation of results and manuscript writing. YS: Immunostaining of renal tissue and manuscript writing. IG: original idea, study design, interpretation of results and manuscript writing.

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Competing interests None.

Ethics approval KI Forskningsetikkommitte Nord, Karolinska sjukhuset; Regionala etikprövningsnämnden i Stockholm.

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Data sharing statement No additional data are available.

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