Renal diseases secondary to interferon-β treatment: a multicentre clinico-pathological study and systematic literature review

Maxime Dauvergne, David Buob, Cédric Rafat, Marie-Flore Hennino, Mathilde Lemoine, Vincent Audard, Dominique Chauveau, David Ribes, Emilie Cornec-Le Gall, Eric Daugas, et al.

Clinical Kidney Journal, 2021, vol. 14, no. 12, 2563–2572

doi: 10.1093/ckj/sfab114
Advance Access Publication Date: 6 July 2021
Original Article

ORIGINAL ARTICLE

Renal diseases secondary to interferon-β treatment: a multicentre clinico-pathological study and systematic literature review

Maxime Dauvergne[1,2], David Buob[2,3,4], Cédric Rafat[5], Marie-Flore Hennino[6], Mathilde Lemoine[7], Vincent Audard[8,9], Dominique Chauveau[10,11], David Ribes[10,11], Emilie Cornec-Le Gall[12], Eric Daugas[13], Evangéline Pillebout[14], Vincent Vuiblet[15] and Jean-Jacques Boffa[1,2,3]; French Nephropathology Group

[1]Assistance Publique des Hôpitaux de Paris, Hôpital Tenon, Service de Néphrologie et Dialyses, Paris, France, [2]Institut National de la Santé et de la Recherche Médicale, Paris, France, [3]Unité Mixte de Recherche 1155, Sorbonne Université, Paris, France, [4]Assistance Publique des Hôpitaux de Paris, Hôpital Tenon, Service D'anatomie et Cytologie Pathologiques, Paris, France, [5]Assistance Publique des Hôpitaux de Paris, Hôpital Tenon, Urgences Néphrologiques et Transplantation Rénale, Paris, France, [6]Centre Hospitalier de Valenciennes, Service de Néphrologie, Valenciennes, France, [7]CHU de Rouen, Service de Néphrologie, Dialyse et Transplantation, Rouen, France, [8]Assistance Publique des Hôpitaux de Paris, Hôpitaux Universitaires Henri Mondor, Service de Néphrologie et Transplantation, Centre de Référence Maladie Rare Syndrome Néphrotique Idiopathique, Fédération Hospitalo-Universitaire Innovative Therapy for Immune Disorders, Créteil, France, [9]Université Paris-Est Créteil, Institut National de la Santé et de la Recherche Médicale U955, Institut Mondor de Recherche Biomédicale, Créteil, France, [10]CHU Rangueil, Département de Néphrologie et Transplantation d'Organes et Centre de Référence Maladies Rénales Rares SORARE, Toulouse, France, [11]INSERM U1048, Toulouse, France, [12]Brest University, CHRU Brest, UMR 1078, Brest, France, [13]Assistance Publique des Hôpitaux de Paris, Hôpital Bichat, Service de Néphrologie, Paris, France, [14]Assistance Publique des Hôpitaux de Paris, Hôpital Saint-Louis, Service de Néphrologie, Paris, France and [15]Département de Néphro-Pathologie, Unité de Pathologie, CHU Reims, Reims, France

Correspondence to: Maxime Dauvergne; E-mail: maxime.dauvergne@gmail.com

ABSTRACT

Background. The spectrum of interferon-β (IFN-β)-associated nephropathy remains poorly described and the potential features of this uncommon association remain to be determined.

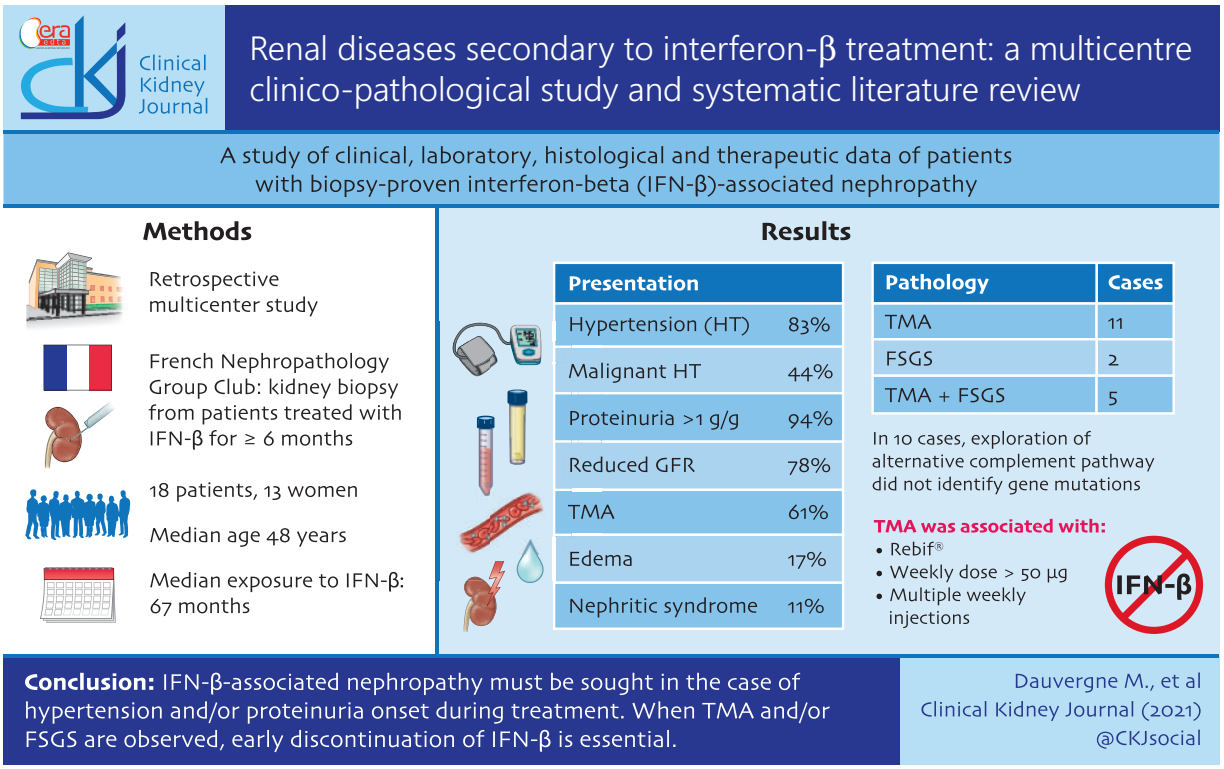
Methods. In this study we retrospectively analysed the clinical, laboratory, histological and therapeutic data of patients with biopsy-proven renal disease in a context of IFN-β treatment administered for at least 6 months.

Received: 24.2.2021; Editorial decision: 28.5.2021

Results. Eighteen patients (13 women, median age 48 years) with biopsy-proven renal disease occurring during IFN-β therapy were included. The median exposure to IFN-β (14 patients were treated with IFN-β1a and 4 patients with IFN-β1b) was 67 months (range 23–165 months). The clinical presentation consists in hypertension (HT; 83%), malignant HT (44%), proteinuria (protU) >1 g/g (94%), reduced renal function (78%), biological hallmark suggesting thrombotic microangiopathy (TMA; 61%), oedematous syndrome (17%) or nephritic syndrome (11%). The pathological findings included typical features of isolated TMAs in 11 cases, isolated focal segmental glomerulosclerosis (FSGS) lesions in 2 cases and 5 cases with concomitant TMA and FSGS lesions. An exploration of the alternative complement pathway performed in 10 cases (63%) did not identify mutations in genes that regulate the complement system. The statistical analysis highlighted that the occurrence of IFN-β-associated TMA was significantly associated with Rebif , with a weekly dose >50 μg and with multiple weekly injections. In all cases, IFN-β therapy was discontinued. Patients with TMA lesions received other therapies, including corticosteroids (44%), eculizumab (13%) and plasma exchanges (25%). At the end of a 36-month median follow-up, persistent HT and persistent protU were observed in 61% and 22% of patients, respectively. Estimated glomerular filtration rate <60 mL/min/1.73 m^2 was present in 61% of patients.

Conclusions. IFN-β-associated nephropathy must be sought in the case of HT and/or protU onset during treatment. When TMA and/or FSGS are observed on renal biopsy, early discontinuation of IFN-β is essential.

GRAPHICAL ABSTRACT



Keywords: drug nephrotoxicity, focal segmental glomerulosclerosis (FSGS), interferon (IFN), nephrotic syndrome, thrombotic microangiopathy (TMA)

INTRODUCTION

Interferon-β (IFN-β) has been the cornerstone of multiple sclerosis (MS) treatment for >20 years [1]. IFN-β is believed to be effective in MS by modifying the pro- and anti-inflammatory cytokine balance and decreasing the T-helper 17 response [2].

IFN-β therapies have been associated with the development of renal injury, with two predominant underlying renal lesions: thrombotic microangiopathy (TMA) [3–26] and focal segmental glomerulosclerosis (FSGS) [27–31]. The occurrence of TMA or

nephrotic syndrome (NS) during IFN-β therapy is considered to be rare, with an estimated rate of 1/10 000–1/1000. The number of reported TMA and FSGS cases has dramatically increased during the last decade (Supplementary data, Tables S1 and S2). Even though a recent study unravelled the involvement of the anti-angiogenic effect of type 1 IFNs in the development of TMA [32], risk factors and pathophysiological mechanisms involved in IFN-β-mediated nephropathy remain poorly understood. Type I IFNs are known to inhibit vascular endothelial growth factor (VEGF) [33] and could promote the development of TMA, as observed in patients receiving anti-VEGF therapies [34].

The aim of this national retrospective multicentre study was to revisit the clinico-biological characteristics, pathological features and prognosis of IFN-β-associated nephropathies. We evaluated the existence of risk factors contributing to the occurrence of these renal diseases.

MATERIALS AND METHODS

Inclusion criteria

To identify patients who presented with nephropathy during IFN-β treatment we contacted all French nephrology and pathology departments through the French Nephropathology Group (Club Francophone de Pathologie Rénale). Criteria of inclusion consisted of patients treated with IFN-β for at least 6 months with biopsy-proven renal disease.

Clinico-biological definitions

Acute kidney injury (AKI) was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [35]. Reduced renal function was defined as a decrease in the estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease formula. The severity of chronic kidney disease (CKD) was classified according to the KDIGO criteria [36]. Proteinuria (protU) was defined as a urine protein:creatinine ratio (UPCR) >0.15 g/g. NS was defined as a UPCR >3 g/g associated with an albumin level <30 g/L. Complete remission of protU was defined as protU <0.5 g/g after a 6-month follow-up. Patients with protU between 0.5 and 3 g/g and with at least a 50% reduction in protU, with an albumin level >30 g/L, were considered in partial remission. Clinical signs of TMA were anaemia <10 g/dL, thrombocytopaenia <150 G/L, increased lactate dehydrogenase (LDH) , reduced haptoglobin, the presence of circulating schizocytes, normal coagulation parameters and a negative Coombs test. Hypertension (HT) was defined as blood pressure ≥140/90 mmHg and malignant HT if diastolic blood pressure was ≥110 mmHg with organ dysfunction.

Pathological analysis

All kidney biopsies were centralized and reviewed by a senior renal pathologist (D.B.). Immunofluorescence data were collected from the initial kidney biopsy reports. For a TMA diagnosis, the following lesions were registered: endothelial swelling (arteriolar and glomerular), fibrin thrombi (arteriolar and glomerular), glomerular congestion, arteriolar subendothelial oedema, fibrinoid necrosis of arteriolar walls, 'onion-skin' concentric thickening of arteriolar walls, fibrous arteriolar occlusion, remodelling of glomerular capillary walls with double contours, ischaemic wrinkling of the glomerular tuft and mesangiolysis. The changes were classified as either focal [changes in <50% of glomeruli and arterioles] or diffuse (changes in ≥50% of glomeruli or arterioles or both). The presence of fibrin thrombi or fibrinoid necrosis of arteriolar walls was defined as 'active' TMA [37]. The Columbia classification criteria were applied when FSGS changes were observed [38]. The severity of interstitial fibrosis (IF) and tubular atrophy was semi-quantitatively scored on a scale of 0 to 3+ (0: 0–5%; 1: 6–25%; 2: 26–50%; 3: >50%).

Statistical analysis

Continuous variables were given as median and interquartile range (IQR), while categorical variables were given as number and percentage. The categorical variables were analysed using Fisher's exact statistical test. The significance level used was $P < 0.05$. The Médic'AM database lists the number of medicine boxes supported by the French health insurance system [39]. This database was used to estimate the market share of each IFN-β in France, assuming that all patients treated with this expensive therapy were covered by the French health insurance system. The average number of patients treated between 2012 and 2017 was used to determine the number of 'patient-years' treated over this period (Supplementary data, Table S3).

RESULTS

Clinical, biological and pathological data

Nineteen adult patients from the nephrology departments of 12 French hospitals were identified. One patient who developed a complete biological TMA syndrome with AKI was excluded since no renal biopsy was performed because of a single kidney. Eighteen patients with biopsy-proven IFN-β-associated nephropathy occurring between 2002 and 2017 were included in the study (Table 1).

All patients received IFN-β for MS treatment. Their clinical and biological settings at the time of diagnosis are summarized in Table 2. There was a predominance of women (13 women and 5 men) consistent with MS epidemiology. The age span ranged from 28 to 65 years (median 48). The exposure duration to IFN-β ranged from 23 to 165 months (median 67). Fourteen patients (78%) were treated with IFN-β1a (all with Rebif, EMD Serono, Rockland, MA, USA). Four patients were treated with IFN-β1b (all with Betaferon, Bayer AG, Leverkusen, Germany). No patient had a known underlying renal disease at the time of IFN-β initiation. Two patients (11%) had an additional autoimmune disease associated with MS—Graves' disease in one case and idiopathic thrombocytopenic purpura in one case. The most common renal finding is an increased protU level, with UPCR ≥1 g/g in 17 cases (94%) and ≥3 g/g in 8 cases (44%), but only 2 patients exhibited NS (11%). The median UPCR value was 2.9 g/g (IQR 1.7–3.6). HT was present in 15 patients (83%) and was malignant in 8 (44%). Biological TMAs were present in 11 patients (61%), with full-blown TMA in 9 cases and partial clinical features in 2 cases. AKI was present in 14 patients (78%): 1 Stage 1 (6%), 8 Stage 2 (44%) and 5 Stage 3 (28%). The evolution of creatinine level during the follow-up is summarized in Figure 1.

Data from the pathological review are summarized in Table 3. Isolated TMA lesions were found in 11 cases (61%), isolated FSGS lesions in two cases (11%) and TMA lesions associated with FSGS lesions in five cases (28%).

Patients with TMA

Sixteen patients (89%) presented with TMA. The median duration of exposure to IFN-β was 72 months. The IFN-β used at the

Table 1. Presentation and outcome of the 18 patients with IFN-β-associated nephropathies

No.	Sex, age (years)	Year of diagnosis	IFN-β	IFN-β duration (months)	Presentation	Biopsy findings	Initial RRT	Specific treatment	eGFR[a] (follow-up, months)	Outcome
1	F, 53	2002	Betaferon	NA	HT, protU, ARF, bioTMA	TMA	No	CS	20 (131)	Persistent HT, death
2	F, 58	2004	Betaferon	96	HT, protU, ARF	TMA	No	No	34 (47)	
3	F, 39	2008	Rebif	72	protU, ARF, bioTMA	TMA	Yes	PE	31 (133)	Persistent HT
4	F, 29	2008	Rebif	24	protU, NS	FSGS	No	CS, cyclosporine	84 (99)	Persistent HT
5	M, 65	2009	Rebif	84	HT, ARF, bioTMA	TMA	No	No	82 (86)	
6	F, 37	2009	Rebif	154	HT, protU, ARF, bioTMA	TMA	No	CS, PE	60 (53)	Persistent HT
7	M, 52	2010	Rebif	58	HT, protU,	TMA	No	No	59 (24)	
8	M, 47	2011	Rebif	48	HT, protU, ARF, bioTMA	TMA + FSGS	No	Eculizumab	37 (72)	Persistent HT
9	M, 61	2012	Betaferon	149	HT, protU, ARF	TMA	No	No	22 (24)	Persistent HT
10	F, 37	2012	Rebif	89	HT, protU,	TMA + FSGS	No	No	94 (18)	Persistent protU
11	F, 48	2012	Rebif	24	HT, protU, ARF, bioTMA	TMA	No	CS, PE	38 (37)	
12	F, 38	2014	Rebif	23	HT, protU,	TMA + FSGS	No	No	81 (39)	Persistent HT
13	M, 42	2014	Rebif	49	HT, protU, ARF, bioTMA	TMA + FSGS	Yes	CS, PE, eculizumab	43 (34)	Persistent HT, persistent protU
14	F, 28	2015	Rebif	78	HT, protU, ARF, bioTMA	TMA	No	No	73 (31)	Persistent protU
15	F, 52	2016	Rebif	47	HT, protU, ARF, bioTMA	TMA	Yes	No	30 (18)	Persistent HT
16	F, 56	2016	Rebif	67	HT, protU, ARF, bioTMA	TMA	No	CS	26 (21)	Persistent HT, persistent protU
17	F, 32	2016	Rebif	36	protU, NS, ARF	FSGS	No	CS, rituximab	79 (12)	
18	F, 56	2017	Betaferon	165	HT, protU, ARF, BioTMA	TMA + FSGS	No	No	46 (12)	Persistent HT

ARF, acute renal failure; BioTMA, biological thrombotic microangiopathy; CS, corticosteroid; NA, not available; PE, plasma exchange.
[a]eGFR determined by the Modification of Diet in Renal Disease equation, in mL/min/1.73 m^2.

Table 2. Demographic, clinical and laboratory characteristics of the 18 patients with IFN-β-associated nephropathy

Characteristics	Values
Age at diagnosis (years), median (IQR) 25th–75th percentiles	48 (37–55)
Ethnicity, *n* (%)	
Caucasian	13 (72)
African	2 (11)
Maghreb	3 (17)
Medical background, *n* (%)	
NSAIDs	5 (28)
Nephrotoxic drugs	0 (0)
High blood pressure	3 (17)
Diabetes	0 (0)
Obesity	0 (0)
Autoimmune disease (other than MS)	2 (11)
MS	18 (100)
IFN-β received, *n* (%)	
IFN-β1a (Rebif)	14 (78)
IFN-β1b (Betaferon)	4 (21)
Duration (months), median (IQR) 25th–75th percentiles	67 (47–89)
Clinical and laboratory features, *n* (%)	
De novo HT or worsening of a known HT	15 (83)
Malignant HT	8 (44)
UPCR $\geq$1 g/g	17 (94)
UPCR $\geq$3 g/g	8 (44)
UPCR level (g/g), median (IQR) 25th–75th percentiles	2.9 (1.7–3.6)
NS	2 (11)
Oedemas	3 (17)
AKI	14 (78)
Serum creatinine level (µmol/L), median (IQR) 25th–75th percentiles	191 (145–345)
Biological TMA, *n* (%)	11 (61)
Neurological signs (headaches, focal sign and confusion), *n* (%)	7 (39)
Abdominal signs (nauseas, vomiting and diarrhoea), *n* (%)	3 (17)
Asthaenia, *n* (%)	2 (11)
Asymptomatic, *n* (%)	2 (11)

NSAIDs, non-steroidal anti-inflammatory drugs.

time of the TMA diagnosis was IFN-β1a (Rebif) for 12 patients (75%) and IFN-β1b (Betaferon) for 4 patients (25%).

Most patients (94%) had *de novo* HT or worsening of pre-existing HT that was malignant in eight subjects (50%). All patients displayed at least one abnormal renal clinical feature, including AKI (81%) and/or protU $\geq$1 g/g (88%), often $\geq$3 g/g (38%). The median UPCR value was 2.7 g/g (IQR 1.5–3.0). AKI was Stage 2 in eight cases (50%) and Stage 3 in five cases (31%). The median serum creatinine level was 210 μmol/L (158–358). Fourteen patients (88%) presented with anaemia, with a median haemoglobin of 8.5 g/dL (IQR 7.6–9.3), while thrombocytopaenia occurred in nine patients (56%), with a median platelet count of 133 10^9/L (IQR 70–213). The median LDH level was 555 U/L (IQR 226–1551). Biological TMAs were observed in 11 patients (69%), with full-blown TMA in 9 cases and partial clinical features in 2 cases. Five patients (31%) presented with headache. Further neurological involvement (confusional state or focal sign) was present in five patients (31%). On brain imaging, none of the patients had any signs of posterior reversible encephalopathy syndrome or ischaemic stroke. Cardiac involvement was observed in five patients (31%), with documented myocardial ischaemia in three (19%) and an isolated decrease in the left ventricular ejection fraction in two (13%). Three of these patients (19%) displayed acute pulmonary oedema.

A pathological review was performed for all renal biopsies ($n = 16$) with TMA lesions (Table 3 and Figure 2). Fifteen patients (94%) had glomerular TMA lesions and 13 patients (81%) had arteriolar TMA. Fibrin thrombi were inconsistent (38%). TMA changes were superimposed on FSGS in five cases (31%) with different FSGS lesions: one 'not otherwise specified (NOS)', two 'collapsing' and two 'Tip lesion'. Acute tubular necrosis (TN) was associated in 69% of the cases. Immunofluorescence revealed no significant deposits. Electron microscopy examination was performed in only one patient in whom we did not observe typical tubuloreticular endothelial inclusion.

An in-depth diagnostic workup ruled out other causes of TMA. Shiga toxin stoolpolymerase chain reaction was performed and was negative in three patients (19%). Four patients (25%) had anti-nuclear antibody, without specificity. Two patients (11%) had an anti-cardiolipin antibody, later confirmed

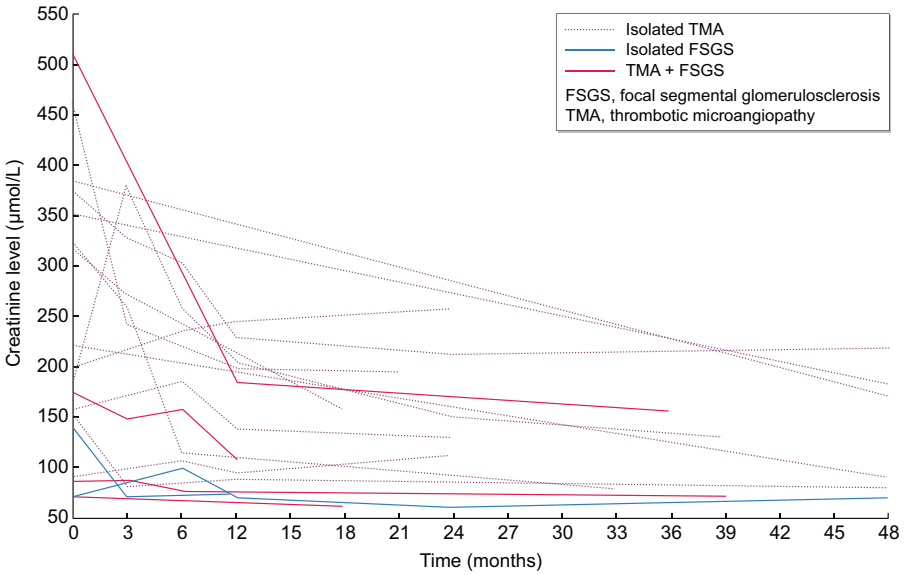


FIGURE 1: Evolution of creatinine level during the follow-up.

Table 3. Diagnosis and biopsy findings of the 18 patients with IFN-β-associated nephropathy

Patient	Diagnosis	Glom (+ OG), *n*	IF[a]	TN[b]	TMA				FSGS[c]
					Localization	Arteriolar TMA	Glomerular TMA	Fibrin thrombi	
1	TMA	27 (7)	3	0	Mixt	Diffuse	Focal	–	–
2	TMA	13 (1)	2	0	Glomerular	–	Focal	–	–
3	TMA	24 (2)	2	++	Mixt	Diffuse	Focal	Mixt	–
4	FSGS	20 (8)	2	+	–	–	–	–	NOS
5	TMA	11 (1)	2	+	Arteriolar	Diffuse	–	–	–
6	TMA	8 (0)	2	+++	Mixt	Focal	Focal	–	–
7	TMA	15 (0)	0	0	Glomerular	–	Focal	–	–
8	TMA+FSGS	11 (2)	2	++	Mixt	Diffuse	Focal	Arteriolar	Collapsing
9	TMA	18 (2)	3	0	Glomerular	–	Focal	–	–
10	TMA+FSGS	15 (0)	1	+	Mixt	Focal	Diffuse	–	Collapsing
11	TMA	12 (2)	1	+	Mixt	Diffuse	Diffuse	Mixt	–
12	TMA+FSGS	30 (2)	1	0	Mixt	Focal	Diffuse	–	Tip lesion
13	TMA+FSGS	30 (0)	1	+	Mixt	Diffuse	Diffuse	Mixt	NOS
14	TMA	12 (2)	2	0	Mixt	Diffuse	Diffuse	Arteriolar	–
15	TMA	6 (1)	0	+	Mixt	Focal	Diffuse	–	–
16	TMA	27 (1)	2	+	Mixt	Diffuse	Focal	Mixt	–
17	FSGS	14 (0)	0	+	–	–	–	–	Tip lesion
18	TMA+FSGS	14 (3)	1	+	Mixt	Focal	Diffuse	–	Tip lesion

OG, obsolete Glom.
[a]IF quantification: 0, 0–5%; 1, 6–25%; 2, 26–50%; 3, >50%.
[b]TN quantification: 0, 0–5%; +, 6–25%; ++, 26–50%; +++, >50%.
[c]Columbia classification.

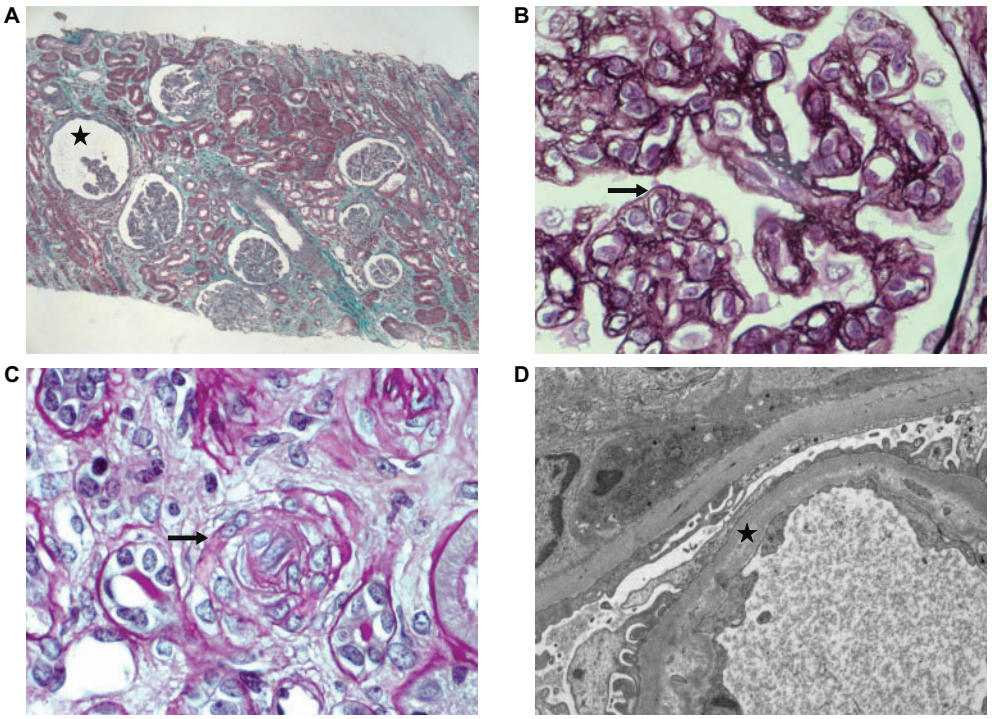


FIGURE 2: Thrombotic microangiopathy lesions. (**A**) Glomerular ischaemia at low magnification (Masson's trichrome). (**B**) Glomerular thrombotic microangiopathy at high magnification. (**C**) Arteriolar thrombotic microangiopathy at high magnification. (**D**) Glomerular thrombotic microangiopathy with electron microscopy.

as negative, excluding an anti-phospholipid syndrome. ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity was measured in eight patients (50%), but none of these had <5% ADAMTS13 activity, excluding thrombotic thrombocytopenic purpura (TTP). No patients had C3, C4 or CH50 hypocomplementaemia. In renal tissue, C3 and C1q deposits were observed by immunofluorescence in 3 (19%) and 1 (6%) cases, respectively. An exploration of the alternative complement pathway including factor H, factor I,membrane cofactor protein (MCP) and anti-factor H measurements was performed in 10 patients (63%) and yielded normal results in every case. In one patient, the genetic study found two rare variants of undetermined significance in the *CFI* gene, associated with a homozygous deletion of *CFHR1*

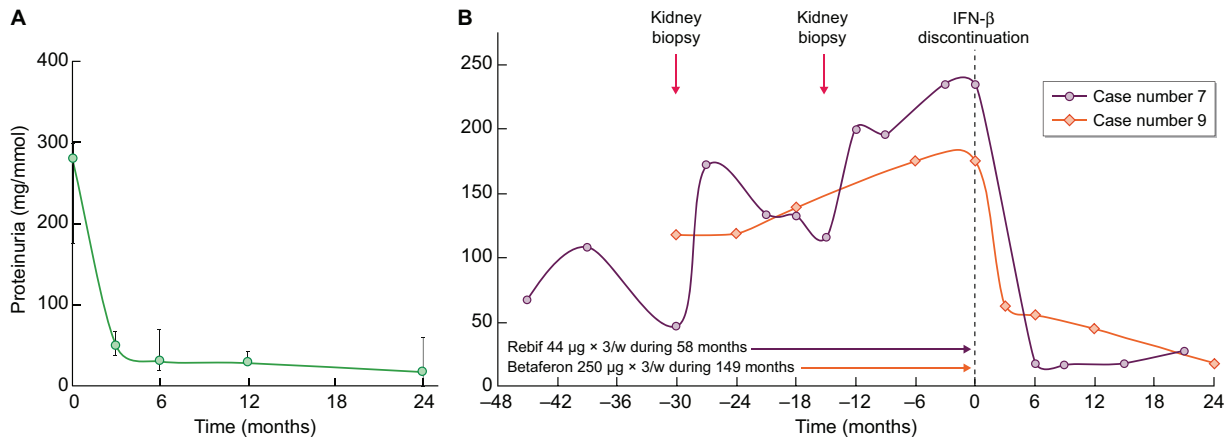


FIGURE 3: Evolution of protU after IFN-β discontinuation in thrombotic microangiopathy cases. (**A**) Evolution of protU after IFN-β discontinuation in the first 24 months for patients with TMA [median (IQR) 25th–75th percentiles]. (**B**) Evolution of protU for two patients with TMA before and after IFN-β discontinuation.

without anti-factor H antibodies. Three other patients had a heterozygous deletion of *CFHR1* without anti-factor H antibodies. No patient had a CFH or MCP haplotype, usually increased in atypical haemolytic uraemic syndrome (HUS).

Five patients (31%) were admitted to an intensive care unit. Renal replacement therapy (RRT) was required for three patients (19%). IFN-β was discontinued in all cases and was followed by a rapid decrease of UPCR level (Figure 3A). IFN-β discontinuation was delayed in two patients whose course had been remarkable for a gradual increase in protU until ultimate drug discontinuation, after which a prompt and complete reduction of protU was observed (Figure 3B). Fifteen patients (94%) received a renin–angiotensin–aldosterone system (RAAS) inhibitor. Other therapies included steroids in seven (44%) patients, plasma exchanges in four (25%) or eculizumab in two (13%). Biological TMA resolved in all patients after 1 week of IFN-β withdrawal. At the 36-month median follow-up (IQR 23–58) after IFN-β discontinuation, persistent HT and protU were observed in 10 (63%) and 5 (31%) patients, respectively. The median UPCR value was 0.3 g/g (IQR 0–0.6). The median serum creatinine level was 134 μmol/L (IQR 88–172), equating with a median eGFR of 44 mL/min/1.73 m^2 (IQR 32–73). CKD was observed in 11 patients (69%): Stage 3A in 2 (13%), Stage 3B in 6 (38%) and Stage 4 in 3 (19%). No patient required RRT. No patient died during the inaugural clinical phase. A 64-year-old woman with Stage 4 CKD died of an unknown cause after a 131-month follow-up.

We next investigated potential risk factors of TMA development under IFN-β: the statistical analysis using the Médic'AM database is summarized in Table 4. The occurrence of IFN-β-associated TMA was significantly associated with Rebif, with a weekly dose >50 µg and with multiple weekly injections. Avonex(Biogen, Cambridge, MA, USA) was the most prescribed IFN-β, but none of our patients received this treatment.

Patients with isolated FSGS

Only two patients (11%) presented with FSGS lesions without TMA lesions. These were two non-obese women in their 30s who had been treated with IFN-β1a (Rebif) for 24 and 36 months, respectively. One was of African ancestry, with an unknown apolipoprotein L1 status and a medical history of Graves' disease. Both women developed sudden-onset NS with protU >5 g/g and albuminaemia <15 g/L, without HT and with an eGFR of 110 and 48 mL/min/1.73 m^2, respectively. The kidney biopsies showed typical lesions of FSGS with an NOS variant in one case and a Tip lesion variant in the other. The extensive investigations revealed no other cause of FSGS. Despite an immediate discontinuation of IFN-β and introduction of RAAS inhibitors, NS persisted in both patients after 1- and 3-month follow-ups, respectively. Each patient required steroids (1 mg/kg/day for one and 0.5 mg/kg/day for the other) in combination with an immunosuppressive drug, cyclosporine for one and rituximab (4 infusions of 600 mg by week for 1 month) for the other, to obtain complete remission of NS at 24- and 12-months follow-up, respectively. None of the patients showed reduced kidney function at the end of follow-up.

Table 4. Comparison of the type and dosage of IFN-β in patients with TMA and in all patients treated in France

Treatment information	Patients with TMA ($N = 16$), n (%)	Patient-years[a] ($N = 15\,801$), n (%)	P-value
Type of IFN-β			
IFN-β1a	12 (75)	13 607 (86)	0.28
Avonex	0 (0)	8538 (54)	<0.001
Rebif	12 (75)	3975 (25)	<0.001
IFN-β1b			
Betaferon	4 (25)	1847 (12)	0.13
Dosage			
>1 injection/week	16 (100)	6169 (39)	<0.001
>50 µg/week	16 (100)	6156 (39)	<0.001

[a]Treated in France, estimated with the Médic'AM database from 2012 to 2017.

DISCUSSION

We report here, to our knowledge, the largest series to date of 18 cases of biopsy-proven IFN-β-associated nephropathy. The occurrence of nephropathy during IFN-β therapy is a rare event, as only 14 cases have been reported to the French pharmacovigilance database (Supplementary data, Table S4). The onset of HT and/or protU >1 g/g was a near-constant feature shared by all patients. Other salient clinical manifestations included reduced renal function, biological TMA and malignant HT. Remarkably, the pathological features were restricted to two patterns: arteriolar and/or glomerular TMA and FSGS. In some patients ($n = 5$) we observed concomitant TMA and FSGS lesions.

A renal biopsy allows for the characterization of unsuspected lesions based on the clinico-biological presentation. Indeed, typical biological hallmarks of TMA were not systematically observed in patients with TMA lesions, which were ultimately ascertained by pathological examination ($n = 5$). As observed in patients with TMA occurring under anti-VEGF therapy [34] in our cohort, a protU ≥3 g/g was not associated with the presence of FSGS lesions. We found that 75% of patients with protU ≥3 g/g exhibited TMA lesions on renal biopsy examination.

A dose-dependent effect of IFN-β has been suggested as a key factor associated with renal disease development [18, 40]. Consistent with this hypothesis, in our study, all patients developing an IFN-β-associated nephropathy received a dose ≥50 µg/week over ≥2 years, with a maximum of 15 years for one patient. In addition, data on type I IFN-associated TMA suggest that the duration of exposure before TMA is significantly longer with IFN-β therapy compared with IFN-α therapy [40].

Early discontinuation of IFN-β seems to be essential. Sustained therapy results in a gradual increase of the protU level and worsening of renal function, as observed in two patients. In contrast, IFN-β discontinuation was associated with a rapid decrease of protU and resolution of biological TMA. Specific treatments were used depending on the context. Plasma exchanges and eculizumab were commonly used in patients with severe TMA and organ involvement, whereas immunosuppressive agents were used in patients with isolated FSGS. We could not determine the effects of these specific treatments because of the retrospective design of our series and the limited sample size of treated patients.

In light of this study, IFN-β-associated nephropathies can be divided into two groups according to clinical, biological and histological data. TMAs ($n = 16$) with or without associated FSGS lesions represent the predominant pathological entity, as opposed to isolated FSGS, which involved only a minority of patients ($n = 2$). Patients with TMA with or without FSGS lesions had HT in the foreground, often severe or malignant. These patients usually presented with high protU, commonly ≥3 g/g without hypoalbuminaemia. In this group, the remissions of protU and TMA were rapid once IFN-β was discontinued. In contrast, patients with isolated FSGS were characterized by an oedematous syndrome of abrupt onset caused by marked NS with massive protU and severe hypoalbuminaemia. In addition to IFN-β therapy discontinuation, these patients required immunosuppressive therapy to obtain complete remission, which was observed after several months of follow-up.

These two distinct clinico-pathological pictures emphasize potential pathophysiological mechanisms, namely primary podocyte injury in isolated FSGS and primary endothelial involvement in TMA. In patients with overlapping TMA and FSGS lesions, it may be assumed that there is a common insult to both podocyte and endothelial cells. It has previously been shown that FSGS may be a complication of TMA itself, possibly via an ischaemic mechanism [41]. We therefore suspect that FSGS may in fact occur subsequent to endothelial injury in IFN-β-associated nephropathies, akin to other diseases causing TMA. Other drugs, such as calcineurin inhibitors, sirolimus and anti-VEGF molecules [34], have been shown to induce either TMA or FSGS.

The pathophysiological processes involved in TMA occurrence under IFN-β therapy remain unknown. An autoimmune phenomenon with the onset of auto-antibodies such as anti-phospholipid or anti-ADAMTS13 has been postulated [6, 12, 16]. However, in this study, no cases of anti-phospholipid antibody syndrome or thrombotic thrombocytopenic purpura were identified. The occurrence of a complement-dependent HUS triggered by IFN-β, revealing underlying genetic abnormalities affecting the complement system, has been reported in only one clinical case [21]. IFN-β may well be the triggering factor revealing genuine complement-dependent HUS, but such a scenario did not account for any of the cases described here.

It has been suggested that only some IFN-β formulations specifically favour the onset of TMA. We found that the new formulation of Rebif, marketed in 2007, coincides with an increase in reported TMAs [20, 42]. This hypothesis seems to be confirmed by our series since there was a significant association between the occurrence of TMA and treatment with Rebif.

A British team [18] has demonstrated the direct toxicity of type I IFNs on the endothelium using transgenic mice overexpressing type I IFN. Brain biopsies of these mice showed dose-dependent histological TMA. After invalidation of the IFN-α/β receptor (*IFNAR*) gene, such abnormalities were no longer found, suggesting the existence of direct IFN toxicity. However, these data do not explain the pathophysiological mechanisms involved in the genesis of TMA. One of these mechanisms may be mediated through the VEGF signalling pathway since type I IFNs are known to inhibit VEGF [12]. An *in vitro* study [32] showed that proliferation and survival of human umbilical vein endothelial cells were reduced with dose-dependent IFN-β. Taken together, these results argue for a direct effect of IFN-β on endothelial cells that could be mediated by inhibition of VEGF-induced angiogenesis, in turn eliciting TMA lesions.

The mechanisms leading to FSGS in patients exposed to IFN-β are unknown. However, podocytes are known to express IFNAR and its signalling pathway is activated in lupus and virus-induced nephropathies [43–45]. The majority of previously reported cases of IFN-β-induced FSGS occurred in African American patients. In this context, polymorphism of the *APOL1* gene, known to be a cause of FSGS, could be involved [28, 46]. In our series, we were unable to confirm this point.

CONCLUSION

Since HT and/or increased protU and/or renal function impairment seem to be the features of biopsy-proven IFN-β-associated nephropathy, blood pressure measurement and protU and creatinine assessment should be systematically monitored in the medical care of patients receiving IFN-β. Our data suggest that renal disease occurs after prolonged treatment, usually >12 months. Because the clinical manifestations may be disparate, renal biopsy remains crucial to determine underlying renal lesions: TMA is the predominant pathological finding, followed by FSGS, with overlapping patterns in some patients. Early IFN-β discontinuation seems to be essential and associated with a partially favourable renal outcome. IFN-β-associated kidney diseases display similar clinical features to anti-VEGF therapy-related kidney diseases, suggesting a common molecular mechanism that may involve inhibition of the VEGF signalling pathway.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

The authors also thank Dr S. Bouri (Hopital Erasme, Bruxelles, Belgium), Dr M. Colombat (Pathology Department, Toulouse, France) and Dr J. Verine (Pathology Department,

Saint-Louis, France). We would like to thank Prof. V. Fremeaux-Bacchi (CHU Paris IdF Ouest, Biological Immunology Department, Paris, France) for the exploration of the alternative complement pathway.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

D.M. was involved in the conception, design, data collection, analysis of data, writing the draft manuscript and final approval. B.D. was involved in pathological review and analysis, revising the manuscript and final approval. R.C., H.M.F., L.M., A.V., C.D., R.D., C.L.G.E., D.E., P.E. and the French Nephropathology Group participated in data collection and revising the manuscript. V.V. provided intellectual content and technical support. B.J.J. was responsible for the conception, design, analysis and interpretation of data, revising the manuscript and final approval.

CONFLICT OF INTEREST STATEMENT

There are no known conflicts of interest associated with this publication.

APPENDIX

The members of the French Nephropathology Group who participated in the study are Isabelle Brocheriou (Paris, France), David Buob (Paris, France), Laurent Daniel (Marseille, France), Laurent Doucet (Brest, France), Arnaud François (Rouen, France), Viviane Gnemmi (Lille, France), Anissa Moktefi (Créteil, France), and Vincent Vuiblet (Reims, France).

REFERENCES

1. Lublin F. History of modern multiple sclerosis therapy. *J Neurol* 2005; 252: iii3–iii9
2. Durelli L, Conti L, Clerico M *et al.* T-helper 17 cells expand in multiple sclerosis and are inhibited by interferon-β. *Ann Neurol* 2009; 65: 499–509
3. Ubara Y, Hara S, Takedatu H *et al.* Hemolytic uremic syndrome associated with β-interferon therapy for chronic hepatitis C. *Nephron* 1998; 80: 107–108
4. Herrera WG, Balizet LB, Harberts SW. Occurrence of a TTP-like syndrome in two women receiving beta interferon therapy for relapsing multiple sclerosis. *Neurology* 1999: 52(Suppl 2): A153
5. Serrano A, Xicoy B, Grifols JR *et al.* [Thrombotic thrombocytopenic purpura during treatment with interpheron]. *Med Clin (Barc)* 2007; 128: 276–277
6. Hansen T, New D, Reeve R *et al.* Acute renal failure, systemic lupus erythematosus and thrombotic microangiopathy following treatment with beta-interferon for multiple sclerosis: case report and review of the literature. *NDT Plus* 2009; 2: 466–468
7. Li Cavoli G, Bono L, Tortorici C *et al.* Renal thrombotic microangiopathy induced by β-interferon. *NDT Plus* 2011; 4: 80
8. Bensa C, Sohier E, Pillebout L *et al.* A case of thromboticmicroangiopathy associated with subcutaneous beta-1a-interferon therapy. *27th Congress of the European Committee for Treatment and Research in Multiple Sclerosis.*, abstract P526. https://doi.org/10.2165/00128415-201113800-00099
9. Broughton A, Cosyns JP, Jadoul M. Thrombotic microangiopathy induced by long-term interferon-β therapy for multiple sclerosis: a case report. *Clin Nephrol* 2011; 76: 396–400
10. Olea T, Díaz-Mancebo R, Picazo ML *et al.* Thrombotic microangiopathy associated with use of interferon-beta. *Int J Nephrol Renov Dis* 2012; 5: 97–100
11. Nerrant E, Charif M, Ramay AS *et al.* Hemolytic uremic syndrome: an unusual complication of interferon-β treatment in a MS patient. *J Neurol* 2013; 260: 1915–1916
12. Mahe J, Meurette A, Moreau A *et al.* Renal thrombotic microangiopathy caused by interferon beta-1a treatment for multiple sclerosis. *Drug Des Devel Ther* 2013; 7: 723–728
13. Hunt D, Kavanagh D, Drummond I *et al.* Thrombotic microangiopathy associated with interferon beta. *N Engl J Med* 2014; 370: 1270–1271
14. Vosoughi R, Marriott JJ. Thrombotic microangiopathy in Interferon Beta treated multiple sclerosis patients: review of literature and report of two new cases. *Mult Scler Relat Disord* 2014; 3: 321–325
15. Larochelle C, Grand'maison F, Bernier GP *et al.* Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in relapsing-remitting multiple sclerosis patients on high-dose interferon β. *Mult Scler* 2014; 20: 1783–1787
16. Orvain C, Augusto JF, Besson V *et al.* Thrombotic microangiopathy due to acquired ADAMTS13 deficiency in a patient receiving interferon-beta treatment for multiple sclerosis. *Int Urol Nephrol* 2014; 46: 239–242
17. Gerischer LM, Siebert E, Janke O *et al.* Favorable outcome of interferon-beta associated thrombotic microangiopathy following treatment with corticosteroids, plasma exchange and rituximab: a case report. *Mult Scler Relat Disord* 2016; 10: 63–65
18. Kavanagh D, McGlasson S, Jury A *et al.* Type I interferon causes thrombotic microangiopathy by a dose-dependent toxic effect on the microvasculature. *Blood* 2016; 128: 2824–2833
19. Nishio H, Tsukamoto T, Matsubara T *et al.* Thrombotic microangiopathy caused by interferon β-1b for multiple sclerosis: a case report. *CEN Case Rep* 2016; 5: 179–183
20. Azkune Calle I, Sánchez Menoyo JL, Ruiz Ojeda J *et al.* Case report of thrombotic microangiopathy associated with subcutaneous interferon beta-1a: an emerging complication? *Neurol Barc Spain* 2016; 31: 508–509
21. Milan Manani S, Virzì GM, Gastaldon F *et al.* Brief review and a clinical case of hemolytic uremic syndrome associated with interferon β treatment. *Blood Purif* 2017; 43: 136–143
22. Allinovi M, Cirami CL, Caroti L *et al.* Thrombotic microangiopathy induced by interferon beta in patients with multiple sclerosis: three cases treated with eculizumab. *Clin Kidney J* 2017; 10: 625–631
23. Pérez EP, Sánchez de la Nieta García MD, López LG, Hernández FR. Thrombotic microangiopathy and accelerated hypertension after treatment with interferon beta. *Nefrologia (Engl Ed)* 2018; 38: 564–565
24. Omoto S, Utsumi T, Matsuno H *et al.* Thrombotic microangiopathy presenting with intestinal involvement following

long-term interferon-β1b treatment for multiple sclerosis. *Intern Med* 2018; 57: 741–744
25. Baghbanian SM, Moghadasi AN. Thrombotic microangiopathy associated with interferon-beta treatment in patients with multiple sclerosis. *Iran J Neurol* 2018; 17: 89–90
26. Malekzadeh MM, Alizadeh R, Aghsaeifard Z *et al*. Thrombotic microangiopathy in interferon-beta-treated multiple sclerosis patient. *Clin Case Rep* 2020; 8: 1061–1064
27. Gotsman I, Elhallel-Darnitski M, Friedlander Z *et al*. Beta-interferon-induced nephrotic syndrome in a patient with multiple sclerosis. *Clin Nephrol* 2000; 54: 425–426
28. Markowitz GS, Nasr SH, Stokes MB *et al*. Treatment with IFN-α, -β, or -γ is associated with collapsing focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2010; 5: 607–615
29. Tornes L, Delgado S, Garcia-Buitrago M *et al*. Focal segmental glomerulosclerosis secondary to subcutaneous interferon β-1a treatment in a patient with multiple sclerosis. *Mult Scler Relat Disord* 2012; 1: 148–151
30. Evans R, Rudd P, Bass P *et al*. Tip variant focal segmental glomerulosclerosis associated with interferon-β treatment of multiple sclerosis. *BMJ Case Rep* 2014; 2014: bcr2013203077
31. Ozturk M, Basoglu F, Yilmaz M *et al*. Interferon β associated nephropathy in a multiple sclerosis patient: a case and review. *Mult Scler Relat Disord* 2016; 9: 50–53
32. Jia H, Thelwell C, Dilger P *et al*. Endothelial cell functions impaired by interferon in vitro: insights into the molecular mechanism of thrombotic microangiopathy associated with interferon therapy. *Thromb Res* 2018; 163: 105–116
33. Yıldırım C, Nieuwenhuis S, Teunissen PF *et al*. Interferon-beta, a decisive factor in angiogenesis and arteriogenesis. *J Interferon Cytokine Res* 2015; 35: 411–420
34. Eremina V, Jefferson JA, Kowalewska J *et al*. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008; 358: 1129–1136
35. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; 120: c179–c184
36. Levey AS, Eckardt KU, Tsukamoto Y *et al*. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67: 2089–2100
37. Goodship THJ, Cook HT, Fakhouri F *et al*. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) controversies conference. *Kidney Int* 2017; 91: 539–551
38. D'Agati VD, Fogo AB, Bruijn JA *et al*. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis Dis* 2004; 43: 368–382
39. Assurance Maladie. *Médic'AM: Données Mensuelles et Annuelles Sur les Médicaments Remboursés Par l'Assurance Maladie*. . https://assurance-maladie.ameli.fr/etudes-et-donnees/medicaments-type-prescripteur-medicam-2008-2013
40. Kundra A, Wang JC. Interferon induced thrombotic microangiopathy (TMA): analysis and concise review. *Crit Rev Oncol Hematol* 2017; 112: 103–112
41. Buob D, Decambron M, Gnemmi V *et al*. Collapsing glomerulopathy is common in the setting of thrombotic microangiopathy of the native kidney. *Kidney Int* 2016; 90: 1321–1331
42. Giovannoni G, Barbarash O, Casset-Semanaz F *et al*. Immunogenicity and tolerability of an investigational formulation of interferon-β1a: 24- and 48-week interim analyses of a 2-year, single-arm, historically controlled, phase IIIb study in adults with multiple sclerosis. *Clin Ther* 2007; 29: 1128–1145
43. Crow MK. Type I interferon in the pathogenesis of lupus. *J Immunol Baltim* 2014; 192: 5459–5468
44. Kimmel PL. HIV-associated nephropathy: virologic issues related to renal sclerosis. *Nephrol Dial Transplant* 2003; 18(Suppl 6): vi59–vi63
45. Anders HJ, Lichtnekert J, Allam R. Interferon-alpha and -beta in kidney inflammation. *Kidney Int* 2010; 77: 848–854
46. Genovese G, Friedman DJ, Ross MD *et al*. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; 329: 841–845