SYSTEMIC LUPUS ERYTHEMATOSUS AND VIRUS C INFECTION - DIAGNOSIS, EVOLUTION AND TREATMENT PARTICULARITIES

Delia-Georgiana Tudorovici (Rotariu), Mircea Penescu

"Dr. Carol Davila" Clinical Hospital of Nephrology, Bucharest

Corresponding address:

rotariu.delia.georgiana@gmail.com

Abstract

Lupus erythematosus (SLE) is an autoimmune disease with a broad spectrum of clinical and immunologic manifestations. Hepatitis C virus (HCV) has been postulated as a potential etiologic or triggering agent among other viruses and it appears to be associated with the presence of autoimmune disorders, even mimicking SLE clinically and serologically. Data on the association between HCV infection and SLE are scarce, but an interaction between these two conditions seems possible.

As for treatment options, it is well known that the classic antiviral therapy with interferon may aggravate preexisting autoimmunity, unmask previously silent autoimmune processes, or even cause the emergence of de novo autoimmune disease, including SLE. Interferon-free treatment seems to be more efficacious, safer and more tolerable. However, it is important that clinicians be aware that DAAs (direct acting antivirals) can also trigger lupus-like immune complex-mediated glomerulonephritis.

There is scant data on the use of immunosuppressive drug therapy in HCV patients. It seems that enhanced HCV replication due to immunosuppression does not lead to clinically significant sequelae and growing evidence has been reported that supports its efficacy and safety.

Patients with SLE and virus C infection are a special category, a fact that the clinician needs to take in consideration in order to a better approach, all the more as these patients are at increased risk for developing end-stage renal disease and have a lower survival rate than general population.

Keywords: lupus erythematosus, hepatitis C virus, interferon, antivirals, immunosuppressi

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Rezumat

Lupusul eritematos sistemic este o afecțiune autoimună cu un spectru larg de manifestări clinice și imunologice. Printre posibilele cauze sau triggeri ai lupusului a fost incriminată și infecția cu virusul hepatitic C care se poate asocia cu fenomene autoimune, putând chiar mima clinic și serologic lupusul.

Opțiunile de tratament includ terapia antivirală și imunosupresia, dar terapia clasică antivirală cu interferon agravează autoimunitatea, demască fenomene autoimune silențioase sau chiar declanșează boli autoimune de novo, inclusiv lupus. Deși e mai eficace, fiind mai sigur și mai ușor de tolerat de pacienți, tratamentul cu noile antivirale cu acțiune directă poate declanșa fenomene autoimune (glomerulonefrită lupus-like). Datele despre imunosupresie în cazul pacienților cu virus C sunt puține în literatura de specialitate, dar s-a constatat că replicarea virală crescută postimunosupresie nu duce la afectare hepatică severă și tot mai multe studii susțin siguranța și eficacitatea acesteia.

Pacienții care asociază lupus și infecție cu virus C reprezintă o categorie aparte. Astfel, clinicianul trebuie să țină cont de faptul că aceștia sunt la risc crescut de a dezvolta boală cronică de rinichi în stadiu final și au, de obicei, o rată de supraviețuire mai redusă.

Cuvinte cheie: *lupus eritematos sistemic, virus hepatitic C, interferon, antivirale, imunosupresie.*

SLE (systemic lupus erythematosus) is a complex autoimmune disease with polymorphic clinical manifestations which may affect any system and which has variable evolution. The etiology of this disease is unknown, and is assumed that SLE results from the interaction of immune dysfunction with the genetic background and environmental factors. The viruses, including the C virus, has been postulated as triggering agents in SLE pathogenesis (Table 1, Table 2).

The association between SLE and HCV (hepatitis C virus)

The study conducted by Ramos-Casals on 134 patients showed a higher prevalence of HCV in patients with SLE compared with general population (11% vs. 1%), supported also by other studies on a larger number of patients⁽¹⁾ (Table 3).

Patients with C virus infection and SLE can be classified into 3 categories:

1. Patients with SLE, but false positive Anti-HCV Ab using the ELISA method

In the study conducted by Cacoub et al., it was possible to confirm Anti-HCV Ab positivity using RIBA-2 in only one patient of the seven patients with SLE and C virus infection confirmed using ELISA-2, and Kowdley et al. showed that only one out of three patients with Anti-HCV Ab detected using ELISA or Immunoblot have C virus infection confirmed by HCV RNA detection using PCR⁽⁴⁾.

2. Patients with C virus and SLE confirmed by the presence of Anti-SM Ab and of specific lupus manifestations which meet EULAR criteria

Some of the diagnostic criteria for SLE (malar rash, discoid lesions, photosensitivity, neurological manifestations, high ANA and Anti-dsDNA Ab titers, presence of Anti-SM Ab) are specific and very rarely encountered only in C virus infection.

A retrospective study conducted on 19 lupus patients with C virus infection and 42 lupus patients without C virus infection, has established that the prevalence of clinical manifestations of severe lupus as well as serum levels of ANA, Anti-dsDNA Ab and complement were similar. However, the prevalence of cryoglobulinemia was higher in patients who associated the 2 comorbidities, with higher ALT levels. The age of onset of SLE was higher in patients with C virus infection, possibly due to extrahepatic manifestations of C virus infection that led to delayed diagnosis of SLE⁽⁵⁾(Table 4).

Regarding the renal impairment, this may be caused by a C virus associated nephropathy, lupus nephritis or even the combination of

the two. Krajewska et al. presents the case of a 25 year old female patient with severe nephrotic syndrome, pancytopenia and retention of nitrogenous wastes syndrome, where immunological and serological tests have revealed positive ANA, elevated Anti-dsDNA Ab, no cryoglobulinemia, and active infection with genotype 1 C virus.

Renal biopsy revealed class IV lupus nephritis for which immunosuppressive therapy was initiated, with normalized the renal function and the blood cell count. Serum albumin levels and total proteins also increased slightly, with maintaining of nephrotic range proteinuria, despite low immunological activity (Anti-dsDNA Ab).

Taking into account the high levels of viral replication, antiviral therapy with ribavirin and interferon was initiated in parallel with oral maintenance corticotherapy, which led to normalization of total serum proteins and of serum albumin and the disappearance of proteinuria.

The evolution of the patient after initiation of antiviral therapy suggests that the autoimmune response to the C virus infection should also be considered⁽⁶⁾(Table 5).

3. Patients with C virus infection mimicking SLE in presence of low ANA and Anti-dsDNA Ab titer, hypocomplementemia, negative Anti-SM Ab and symptomatology (arthritis, kidney injury)

C virus infection is associated with various autoimmune manifestations mimicking SLE associated symptoms (arthralgia, myalgia, Sicca syndrome) and induces the occurrence of autoantibodies - ANA (20-40% of HCV patients), Anti-dsDNA Ab, hypocomplementemia that mislead the clinician⁽¹⁾. Seronegative patients (negative

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ANA, Anti-dsDNA Ab negative, Anti-SM Ab negative) who have as their first autoimmune disease manifestation a renal manifestation (nephrotic syndrome, nephritic syndrome, etc.) may present full-house pattern by immunofluorescence - highly suggestive of lupus nephritis. Some of them become seropositive and/or develop extrarenal manifestations of SLE while another category remains seronegative without developing clinical manifestation typical of SLE⁽⁷⁾.

Hobeika et al. describe the case of a 53 year old man, diagnosed with chronic C virus infection 3 years before the onset of kidney impairment. Increased serum creatinine, hypoalbuminemia, hypoproteinemia, proteinuria (13 g/g creatinine) and dysmorphic hematuria were detected at the admission in the clinic of the patient. The serology was negative for ANA, Anti-dsDNA Ab, AntiSSA, AntiSSB, AntiSM, cryoglobulins, and the viral load was 4.5mil IU/mL. The renal biopsy revealed cellular crescents and minimal interstitial inflammation and fibrosis, with full-house pattern by immunofluorescence (the presence of IgG, IgA, IgM, C3 and C1q in glomerular basement membrane and mesangial region). The electronic microscopy revealed subepithelial, subendothelial and mesangial immune complexes and tubuloreticular inclusions, which are highly suggestive of

lupus nephritis. The final diagnosis was "seronegative lupus" or "lupus-like glomerulonephritis"⁽⁸⁾.

Interferon and SLE

It was found that interferon is capable to exacerbate/unmask silent/pre-existing autoimmune manifestations (autoimmune hepatitis, seronegative arthropathies, rheumatoid arthritis, autoimmune thrombocytopenia) and that patients presenting with low titer of antibodies, associated with C virus infection, are at higher risk of developing an autoimmune disease, compared to those who do not have detectable antibodies⁽⁹⁾.

In patients with SLE, endogenous interferon-alpha levels are increased and correlate with disease activity and it has been hypothesized that tubuloreticular inclusion (TRI) morphogenesis in the kidney is related to endogenous (via overproduction) and exogenous (via administration) activity of interferon alpha and beta. Although the incidence of lupus-like syndrome (autoimmune disorders that do not fall within the diagnosis of SLE) is of 0.15-0.7% to 2%, only a few cases of SLE patients treated with IFN in context of hepatitis C virus occur in the literature. SLE has also been reported in patients following interferon treatment for diseases such as: chronic myeloid leukemia,

carcinoid tumors, solid tumors, with the onset between 2 weeks and 7 years after the IFN (interferon) therapy initiation⁽¹⁰⁾. The most common manifestations of interferon-induced SLE are arthralgia (most commonly the onset symptom), malar rash, mouth ulcers, photosensitivity and renal impairment (manifestation rarely encountered in drug-induced lupus). Immunological changes - hypocomplementemia, positive Anti-dsDNA Ab and Anti-SM Ab, hematologic changes - anemia, lymphopenia are associated with these. In most cases, the discontinuation of interferon alpha treatment and a short course of immunosuppression (usually corticotherapy <6 months) lead to lupus symptomatology remission and improvement of the immunological parameters⁽¹¹⁾.

Severe interferon-induced SLE cases are very rare. Vincent Ho et al. present the case of a 43 year old man, following pegIFN and ribavirin treatment for chronic hepatitis C virus and who after the initiation of antiviral therapy developed maculopapular rash, arthritis and elevated Anti-dsDNA Ab titer. Later, after antiviral therapy discontinuation, the patient met additional criteria of SLE diagnosis: glomerulonephritis, arthritis, serositis, discoid rash, lymphopenia, mouth ulcers, ANA and Anti-dsDNA Ab in progressively increased titer. Moreover, he developed myopericarditis and leukocytoclastic vasculitis, life-threatening complications⁽¹²⁾.

DAA (direct-acting antivirals) and SLE

The interferon-free therapy acts directly on viral replication and it is considered not to be "immunomodulatory". However, Sise et al. described 3 patients who followed therapeutic regimens with sofosbuvir and simeprevir and in whom lupus-like symptomatology began at an interval of

3M/24W after the termination of antiviral treatment, respectively 2 weeks after starting the therapy, with arthralgia/rash, hematuria, leukocyturia, and progressively aggravated retention of nitrogenous wastes syndrome. It can be assumed that the elimination of viral antigen increases sensitivity to the endogenous effects of IFN in patients with predisposing background, resulting in the unmasking of autoimmunity.

As for the first 2 cases, the patients did not have any known autoimmune diseases, but the second case had an increased level of ANA prior to the diagnosis of glomerulonephritis. In the 3rd patient, DAAs therapy aggravated a previous interferon therapy-induced SLE, with the HCV clearance aggravating a pre-existing autoimmune disease. This is supported by the fact that after a period of 5 years without symptomatology, the patient presented arthralgia and increased retention of nitrogenous wastes syndrome following DAAs therapy. Also, in this case, the renal biopsy did not reveal tubuloreticular inclusions typical of lupus nephritis, and C1q deposition in the kidneys was minimal. Common changes seen on renal biopsy were: immune complex depositions (mesangial, paramesangial, subendothelial, intramembranous), tubuloreticular inclusions (case 1 and case 2) and "full house" pattern typical of lupus nephritis in IF (Ig G +, Ig M +, Ig A +, C3 +, C4+)⁽¹³⁾ (Table 6, Table 7).

Viral replication and immunosuppression

Immunosuppression reduces the inflammatory pathways that lead to liver damage, but on the other hand decreases the immune defence mechanisms against liver injury mediated directly by the virus. Discontinuation of immunosuppressive

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therapy induces a strong rebound immune response that can cause a surge of hepatitis. The incidence of viral reactivation due to immunosuppression is still unknown. There are few studies related to HCV reactivation and which therapeutic interventions are most appropriate for C virus infection or the underlying disease. There is scant data available in the literature about risk factors, prevalence and clinical outcome of reactivation⁽¹⁴⁾.

Immunosuppression inhibits the immune function of the host and increases the risk of late recurrence of viral infection, which advocates the idea of monitoring the viral load even after reaching SVR. However, viral hepatitis surges do not appear to influence the survival of SLE patients. On the other hand, patients with detectable viremia for long periods of time are at higher risk of mortality due to liver disease, so it is recommended that 2-4 months after starting the immunosuppression, the antiviral treatment to be initiated.

Although viral replication increases in about one-third of patients, cases of severe hepatitis or decompensated liver disease are rare due to a less vigorous immune response to viral antigens (which ultimately leads to a higher rate of chronicization)⁽⁵⁾.

The long term use of immunosuppressive agents may damage liver function. Older data from the literature noted an increase in

the incidence of cirrhosis and mortality due to liver disease in patients who underwent a kidney transplant, as well as a faster progression to end-stage liver disease. Moreover, the immunosuppressive therapy also has risk of hepatotoxicity (azathioprine, cyclosporin)⁽¹⁶⁾.

The antiCD20 Ab treatment is associated with a 26% incidence of hepatitis in patients with C virus infection. It appears that rituximab significantly increases the HCV RNA levels, but even in rare cases of severe hepatitis and decompensated liver disease, patient survival has not been affected.

Cyclosporine inhibits activation of helper T cells, preventing the recruitment and expansion of cytotoxic T lymphocytes. During the progressive decrease of the doses or after treatment discontinuation, a massive immune response of the host to viral antigens may occur, leading to massive liver destruction, which advocates the need for antiviral prophylaxis⁽¹⁷⁾ (Table 8).

The ALT level increases during short-term oral corticotherapy, reaching a peak in average 7 weeks after the withdrawal of treatment, indicating that the immune response to the C virus is slow. Corticosteroids seem to be safe when used in the short term (<6 months), but their discontinuation can cause the rebound of inflammatory processes (Table 9).

DAAs are efficient and safe and increase the probability of viral eradication with few

Systemic autoimmune disease associated with C virus infection	No. of patients	Gender ratio F:M
Sjogren Syndrome	77	3:1
SLE	43	5:1
RA	14	5:2
APS	14	1:1
PAN	8	3:5
Sarcoidosis	7	4:3
Systemic sclerosis	7	6:1
Ankylosing spondylitis	3	1:2
Inflammatory myopathy	2	1:1
Wegener's granulomatosis	2	2:0
Giant cell arteritis	1	0:1
Henoch-Schönlein purpura	1	0:1
Polymyalgia rheumatica	1	1:0
Total	180	3:1

Table 1. Systemic autoimmune diseases (SAD) in 180 patients with chronic C virus infection⁽²⁾

Patients diagnosed with SAD and C virus infection, followed up in a multicenter study between 1994 and 2003. SLE - systemic lupus erythematosus; RA - rheumatoid arthritis; APS - antiphospholipid syndrome; PAN - polyarteritis nodos

Table 2. Clinical, immunological and epidemiological data of SAD-HCV positive patients compared to SAD-HCV negative patients

HCV - hepatitis C virus; CNS - central nervous system; ENA - extractable nuclear antigen antibodies

	SAD-HCV+ (n=180)	SAD-HCV (n=180)	p value
Gender (% women)	130 (72)	149 (83)	0.016
Average age at SAD diagnosis	50.46+-17.19	46.60+-18.21	0.039
Sicca symptoms	86 (48)	90 (50)	-
Joint damage	84 (47)	97 (54)	-
Raynaud's phenomenon	23 (13)	22 (12)	-
Vasculitis	38 (21)	12 (7)	<0.001
Lung injury	17 (9)	23 (13)	-
Peripheral neuropathy	17 (9)	11 (6)	-
CNS disorders	9 (5)	13 (7)	-
Renal impairment	23 (13)	17 (9)	-
Thrombotic phenomena	14 (8)	11 (6)	-
Skin damage	44 (24)	42 (23)	-
ANA	116/171 (68)	134/172 (78)	0.036
Anti-dsDNA Ab	24/159 (15)	43/153 (32)	0.005
ENA	35/160 (22)	50/155 (32)	0.038
Rheumatoid factor	90/162 (56)	57/147 (39)	0.003
Hypocomplementemia	87/154 (57)	46/146 (31)	<0.001
Cryoglobulins	92/149 (62)	10/115 (9)	<0.001
Neoplasia	27 (15)	3 (2)	<0.001
Classification criteria met	4.02+-1.2	4.61+-1.45	<0.001

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Manifestation	SLE patients (n=36)	Patients with SLE and C virus infection (n=4)	p value
Neurological ^b	6 (17)	0	>0.99
Arthritis	9 (25)	4 (100)	0.008
Myositis	3 (8)	0 (0)	>0.99
Cutaneous ^c	10 (28)	0 (0)	0.56
Mucosal ulcerations	5 (14)	0 (0)	>0.99
Serositis	2 (6)	1 (25)	0.28
Nephropathy ^d	17 (47)	4 (100)	0.11
Cytopenia	4 (11)	0 (0)	>0.99
ANA	36 (100)	4 (100)	-
Anti-dsDNA Ab	12 (33)	1 (25)	>0.99
Anti-SM Ab	9 (25)	0 (0)	>0.99
Low C3	23 (64)	3 (75)	>0.56
Low C4	10 (28)	1 (25)	0.99
SLEDAI score in the time point of testing for virus C infection	9.6	10.5	0.93

Table 3. Clinical, immunological characteristics and SLEDAI score in patients with SLE with/without Ca virus infection(3)

ANA - antinuclear antibodies; SLE - systemic lupus erythematosus ; a - the values represent the number (%) of patients; b - neurological - seizures, psychosis, headache, stroke; c - cutaneous - malar rash, discoid lesions, subacute lesions, photosensitivity; d - nephropathy: red blood cell casts, haematuria, proteinuria > 0.5 g/24 h and/or leucocyturia.

Patient	Gender	Age	SLE criteria	ANA	ENA	Anti-dsDNA Ab	aCL	Cryog	Hypocompl
1	F	62	Art, Neph, Hem	10,000	Y	Y	Y	N	Y
2	M	34	Art, Neph, Ser, Hem	320	N	Y	Y	III	Y
3	F	35	Art, Ulc, Neph, Nrl, Hem	2000	Y	N	Y	II	Y
4	F	65	Hem	10,240	N	Y	N	III	N
5	F	34	Art, Neph, NP, Ser	1000	Y	Y	NT	N	N
6	F	70	Art, Neph, Hem	100	Y	Y	Y	II	N
7	F	31	Art, Photo, Neph	5000	Y	Y	Y	III	Y
8	F	36	Art, Ulc, Malar, Hem	2500	N	N	N	N	Y
9	F	37	Art, Subac, Malar, Hem	160	Y	N	Y	N	N
10	M	45	Art, Ulc, Malar, Ser, Hem	320	N	Y	Y	N	N
11	F	53	Art, Ser, Ulc, Subac, NP	1000	N	Y	N	III	N
12	M	52	Art, Ser, Hem	5000	Y	Y	Y	III	N
13	F	33	Art, Neph	640	N	Y	Y	N	N
14	F	36	Hem	1280	N	N	N	II	N
15	F	46	Art, Subac, Neph, Hem	1000	Y	Y	N	III	Y
16	F	20	Art, Photo, Neph, Hem	1280	N	Y	Y	N	Y
17	F	46	Art, Subac	1280	Y	Y	Y	N	N
18	F	25	Art, Subac	1280	N	Y	Y	III	Y
19	F	30	Art, NP, Photo, Hem, Neph	1280	N	Y	Y	N	N

Table 4. Clinical manifestations of patients with C virus and SLE(5)

ANA - antinuclear antibodies; ENA - extractable nuclear antigen antibodies; aCL - anticardiolipin antibodies; cryog - cryoglobulin type; hypocompl - hypocomplementemia; art - arthritis; neph - nephropathy; hem - hemocytopenia; Ser - serositis; ulc - mouth ulcers; NP - neuropsychiatric manifestations; Photo - photosensitivity; malar - malar rash; subac - subacute cutaneous lesions; NT- not taken; Y - yes; N - no. Start IFN and RBV

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adverse effects in context of combination with immunosuppressive agents. The study conducted by Colombo et al. reported a SVR (sustained virologic response) in 98% of patients who underwent a kidney transplant without acute renal rejection⁽¹⁷⁾(Table 10). The DAAs' success in achieving SVR demonstrates that inhibition of viral replication without further inducing an immune response is enough to eradicate HCV. However, it is still unclear how intact the immune system should be for an effective viral eradication using DAAs.

SLE is a disease requiring immunosuppressive therapy, but it is still unclear whether SLE patients are at higher risk of HCV reactivation or if the immunological profile influences the reactivation.

The study conducted by Chen et al. followed 26 patients with C virus and SLE over an average time of 8.4 years, of whom 10 met the criteria of viral infection reactivation and 16 patients did not meet these criteria (reactivation of viral infection - recurrence of HCV RNA if it was previously undetectable or an elevation of $>1 \log_{10}$ IU/mL compared to baseline) and 16 did not meet these criteria. It has been noted that the immunosuppression period was similar in both groups (5.2 years vs. 5.4 years) and that there was no statistically significant difference regarding age, gender, liver function, SLE immunological profile. Moreover, lupus activity was

exacerbated by hepatitis surges and neither by interferon and ribavirin therapy. Of the total patients, 20% of those with genotype 1b and 66.7% of those with genotype 2a obtained RVR (rapid virologic response - undetectable HCV RNA in the 4th week of antiviral treatment), similar to the general population with C virus.

However, none of the patients treated with glucocorticoids reached RVR, probably because glucocorticoids attenuate the host immune function and increase viral replication, leading to a poor initial response to antiviral therapy, which increases the risk of late relapse (recurrence of HCV RNA after obtaining SVR - 24 W after antiviral therapy)⁽¹⁸⁾(Table 11).

Long term prognosis

Patients with C virus present a faster progression to chronic end-stage kidney disease, with 10 year renal survival being statistically significantly lower, which is consistent with the study conducted by Tsui et al., demonstrating that C virus infection is associated with a 3 times higher risk of progression to chronic end-stage kidney disease. C virus infection is also associated with a higher incidence of cardiovascular diseases (increased risk of atherosclerosis) and diabetes (insulin resistance - it reduces the insulin receptor expression)⁽¹⁹⁾.

Month	Hgb (g/L)	WBC (10 ³ /μL)	PLT (x10 ³ /μL)	ALT (U/L)	GGT (U/L)	Serum creatinine (mmol/L)	Serum total protein (g/L)	Serum albumin (g/L)	Proteinuria (g/24h)	RNA HCV (copies/mL)	ANA	Anti-dsDNA Ab (IU/mL)
0	10.2	2.4	93	10	15	129.6	46	14	7.5	Positive	1L1280	774.82
5	12.9	4.8	208	36	61	83.9	48	24	5.1	-	1:640	Negative
12	14.6	6.6	239	39	53	91.5	49	-	4.6	1.02 x10 ⁴	1:320	Negative
17	14.5	4.8	189	37	38	100.7	49	26	4.5	1.12x10 ⁶	1:320	104.67
21	14.3	6.76	232	44	78	88.5	55	30	4.0	2.21 x10 ⁶	1:320	162.83
29	10.4	4.2	162	19	44	72.4	51	27	No data	Not detectable	1:100	52.14
37	12.9	2.3	140	22	75	70.9	59	36	2.0	Not detectable	1:320	80.16
54	13.7	4.77	296	34	97	70.9	60	35	Absent	Not detectable	1:100	63.77
Normal	12-16	4-10	140-440	0-35	0-38	62-99	66-83	35-52	Absent	Not detectable	negative	<100

Table 5. Laboratory test results after initiation of antiviral treatment⁽⁶⁾

Hgb - haemoglobin; WBC - white blood cell; PLT - platelets; IFN - interferon; RBV - ribavirin.

Case no.	Serological baseline values	Serological changes after DAAs administration
1	Cryoglobulins: negative Other serology: unavailable	ANA: 1:320 Anti-DNA Ab : negative Anti-histone Ab : NT Anti-SM Ab: negative Complement C3: 74 (low), C4: 14 Cryoglobulins: negative RF: negative Anti-SM Ab :1:80 ANCA: negative
	ANA: 1:640 in 2007 Cryoglobulins: negative RF: positive in 2007 Other serology: unavailable	ANA: >1:5120 Positive Anti-DNA Ab :1:80 Anti-histone Ab: >7.0 Anti Ro/La: negative Anti-SM: negative C3: 54 C4: 9 (low) Cryoglobulins: negative RF: negative
3	ANA: 1:160. Anti-dsDNA Ab : negative Anti Ro/La Ab: negative Anti-SM Ab: negative Cryoglobulins: 5% RF: negative Complement: C3: 87 C4 : 20 (normal) Other serology: unavailable	ANA: 1:160 Anti-dsDNA Ab: negative Anti-histone Ab: 1.5U Anti Ro/La: positive Anti-SM Ab: negative Cryoglobulins: 1% C3: 42 (low) C4: 7 (low) RF: negative

Table 6. Comparison of serological changes before and after DAAs treatment⁽¹³⁾

Ab - antibody; NT - not taken; complement normal values: c3 81-157 mg/dL; c4=12-39 mg/dL; Anti-histone Ab N<1.0 U (Presence of Antihistone Ab has raised the likelihood of drug-induced lupus, but this is rarely associated with glomerulonephritis)

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Case	Patient characteristics	Clinical presentation	Immunosuppression	Outcome
1	Asian female, 51 years old	Morbilloform rash	MP 500 mg iv x 3 days, followed by prednisone 60 mg/day	Rapid improvement of kidney function
	Genotype 3a, viral load 3.6×10^5	Elevated transaminases		SVR12
	Previous treatment: Peg-IFN/RBV	Increasing creatinine		Death due to sepsis, fungal pneumonia and empyema
	Cirrhosis diagnosed on biopsy	Proteinuria and hematuria		
2	Caucasian female, 56 years old	Joint pain	MP 250 mg iv x 3 days, followed by prednisone 60 mg/day	Rapid improvement of kidney function
	Genotype 1b, viral load 2.8×10^6	Increasing creatinine	Prednisone was decreased rapidly to 20 mg/day due to the occurrence of delirium, then discontinued until W4	HCV relapse, treated with Sofosbuvir and Ledipasvir
	Previous treatment: Peg-IFN/RBV	Hematuria and leucocyturia	MMF maintenance therapy, 250 mg x 2/day, 5 months	Recurrence of joint pain under DAAs; resuming steroids and MMF with improving symptoms
	Cirrhosis diagnosed on allograft biopsy			SVR12
3	Hispanic female, 47 years old	Rash (face, chest, hands)	MP 250 mg iv x 3/day, followed by prednisone 60 mg/day	Improvement of kidney function
	Genotype 1, viral load 8.4×10^4	Low back pain, physical fatigue	Rituximab 1000 mg iv/week x 3	SVR 12
	Previous treatment: IFN α	Increasing creatinine		Death due to bacteraemia, bacterial pneumonia
	Clinically diagnosed cirrhosis	Proteinuria and hematuria		

Table 7. Patient outcome with lupus-like syndrome after administration of DAAs (direct-acting antivirals)⁽⁴³⁾

MP - methylprednisolone; MMF - mycophenolat mofetil; IFN - interferon; HCV - hepatitis C virus; SVR - sustained virologic response

Study	Type	N	Age	Males %	Immunosuppression	AT (antiviral therapy)	Outcome	Adverse effects	SVR %	Clinical response
Sise, 2016	Case series	5	N/A	N/A	Rituximab x 4 patients Rituximab x 1 patient	Sofosbuvir + RBV; Or Sofosbuvir + Simeprevir x 12W	SVR12 in 3/4 patients on Rituximab and 0/1 patients on Ustekinumab (reactivation)	Not reported	60%	-
Saadoun, 2014	Cohort, prospective study	4	N/A	N/A	Rituximab administered one month before AT	Peg IFN α + RBV x 48W + Telaprevir x 12W or Boceprevir 44 W	PR in 2/4 CR in 2/4	Not reported	-	100%
Humphrie 2014	Case report	1	59	100%	MP 500 mg x 2 days and 5 days plasmapheresis	Telaprevir, IFN, RBV x 24W	PR. Progression to st.5 CKD and HD at W7 after the end of the treatment. SVR.	Anemia with transfusion requirements, EPO, interruption of IFN and RBV	100%	0%
Zaidan, 2012	Case report	2	44	50%	Cyclophosphamide and pulse steroid, afterwards prednisone 50 mg/day; case 4: prednisone 1 mg/kg bw/day x 5 days, plasmapheresis, rituximab iv	Peg IFN α + RB	Case 3: SVR. Purpura remitted. Kidney function PR. Case 4: Cutaneous lesions remitted. Recovered kidney function.	Not reported	-	100%
Rodrigo, 2012	Case report	1	34	100%	Prednisone 10 mg x 2/day + Cyclophosphamide	Peg IFN 2 α + RBV	Healed cutaneous lesions. Improved muscle weakness. No relapse at 6 months.	Not reported	-	100%
Kiremitci, 2012	Case report	1	34	0%	MP 0.5mg/kg bw/day starting with the AT	PegIFN 2 α	Remitted nodules. Normalised kidney function, but viral reactivation	Not reported	-	0%

Table 8. Cryoglobulinemia and vasculitis - immunosuppression and antiviral therapy⁽¹⁷⁾

MP - methylprednisolone; PR - partial remission; CR - complete remission; IFN - interferon; RBV - ribavirin; CKD - chronic kidney disease; HD - hemodialysis; EPO - erythropoietin; SVR - sustained virologic response

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Study	Type	N	Age	Males %	Disease	Immuno - suppression	AT (antiviral therapy)	Out - come	Adverse effects	SVR %
Basu, 2016	Randomized controlled trial	35	50	74%	Inflammatory bowel disease	Antagonist TNF alpha Maintained during AT	LDV+SOV+ RBV 1000mg x 8W or LDV+SOF 12W	RVS12 in 34/35	Hb<8.5 in 2 pt; The severity of other adverse effects is unclear	97%
Sise, 2016	Case series	5	N/A	N/A	Cryoglobulinemia Mixt	Rituximab x 4pt Ustekinumab x 1 pt	Sofosbuvir+ RBV or Sofosbuvir+ simeprevir x 12 W	RVS12 in 3/4 pt on Rituximab and 0/1 pt on Ustekinumab (reactivation)	Not reported individually	60%
Hahn, 2015	Case series	1	50	100%	RA	HQ, MP 8mg x 4/day, Sulfasalazine	Sofosbuvir/ ledipasvir/GS-9451 x 6W	SVR24	Surge of arthritis at 1W after finishing AT	100 %

Table 9. Immunosuppression and DAAs⁽¹⁷⁾

RA - rheumatoid arthritis; HQ - hydroxychloroquine; MP - methylprednisolone; LDV - ledipasvir; SOV/SOF - sofosbuvir; RBV - ribavirin; Hb - hemoglobin; pt - patients; W - week

Study	Type	N	Age	Males (%)	IS reason	Immuno-suppression (IS)	AT (antiviral therapy)	Outcome	Adverse reactions	SVR	Clinical response
Wu, 2013	Case report	1	57	0%	MPGN cryoglobulinemic	MP 40mg/day	Peg IFN α 2b+RBV	Remitted thrombocytopenia, improvement of kidney function. Persistently elevated cryoglobulins	Not reported	-	100%
Kiremitci 2012	Case report	1	34	0%	MPGN cryoglobulinemic, purpura, pneumonitis	MP 0.5mg/kg/day	PegIFN-2 α	Remitted nodules. Normalised kidney function, afterwards relapse	Not reported	-	0%
Ahmed 2008	Case report	1	35	100%	MPGN type 1 negative cryoglobulin	MP before AT Prednisone 40 mg/day starting with AT	PegIFN α , RBV added after 3 months	Improved kidney function. SVR. Elevated albumin (38g/L)	No major adverse effect	100%	100%
Oeda, 2012	Case report	2	50	0%	Auto-immune hepatitis + HCV	Prednisolone 30-40 mg/day before AT and reduced to 20 mg/day when starting AT	Peg IFN α 2b+RBV x 24-48 W	SVR in both cases. Normalised ALT and Ig G.	Not reported	100%	100%
Scherze 2008	Case report	3	47	67%	Crohn's disease	Azathioprine	PEG-IFN α 2a + RBV x 24W	SVR, NR, relapse	Surge of Crohn's disease in 2/3 of patients	33%	-
Azhar, 2010	Case report	1	40	0%	Auto-immune hepatitis +HCV	MMF	IFN+RBV	SVR. No surge of hepatitis.	Cytopenia requiring Filgrastim and erythropoietin	100%	-
Scherze, 2008	Case series	1	56	100%	Crohn's disease	MMF	PEG-IFN α 2a+RBV 48 W	SVR	Surge of Crohn's disease - stenosis	100%	-

Table 10. Immunosuppression and antiviral treatment in C virus infection⁽¹⁷⁾

MP - methylprednisolone; MPGN - membranoproliferative glomerulonephritis; IFN - interferon; RBV - ribavirin; SVR - sustained virologic response; MMF - mycophenolat mofetil; NR - no response; HCV - hepatitis C virus

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Figure 1. Kidney function in patients with lupus nephritis with and without virus C infection at the last follow-up⁽²¹⁾ Statistically significant difference between the group with C virus infection and the one without C virus infection in patients with serum creatinine >350 mmol/L ($p<0.02$)

Figure 2. Creatinine clearance in patients with lupus nephritis with/without virus C infection at the enrolment in the study and at the end of the study Statistically significant difference between the patients with C virus and those without C virus at the last follow-up ($p<0.043$).

Figure 3. Long term survival for patients with SLE⁽²⁸⁾ Patients with positive Hbs Ag had lower survival compared to patients negative for HB and also negative for Anti HCV Ab

	HCV activation Yes (n=10)	No (n=16)	p value
Age at diagnosis	42.5+-17.1	35.0+-13.2	0.201
Females (n)	8 (80%)	15 (93.8%)	0.538
ALT (U/L)	40.6+-23.1	29.4+-13.4	0.436
AST (U/L)	37.6+-12.6	27.8+-10.2	0.156
ANA >1:160	6/10 (60%)	15/16 (93.8%)	0.055
Anti SSA/Ro positive	6/9 (66.7%)	6/9 (66.7%)	1.000
Anti SSB/La positive	2/8 (25%)	1/6 (16.7%)	1.000
Anti-SM positive	1/9 (11.1%)	2/8 (25%)	0.576
Anti-RNP positive	1/9 (11.1%)	3/8 (37.5%)	0.294
Anti dsDNA positive	9/10 (90%)	10/16 (62.5%)	0.190
Treatment before IS	7 (70%)	11 (68.8%)	1.000
Duration of IS treatment	5.4+-6.8	5.2+-5.0	0.93
Previous treatment with >2 IS	4 (40%)	7 (43.8%)	1.000
Corticosteroids	7 (70%)	10 (62.5%)	1.000
Hydroxychloroquine	1 (10%)	5 (31.3%)	0.352
Azathioprine	2 (20%)	2 (12.5%)	0.652
Mycophenolate	1 (10%)	1 (6.3%)	1.000
Corticosteroids with other immunosuppressive agents	4 (40%)	7 (43.8%)	1.000
Mortality	2 (20%)	1 (6.3%)	0.538
Haematological disease	7 (70%)	10 (62.5%)	1.000
Renal impairment	3 (30%)	8 (50%)	0.425
CNS disorders	3 (30%)	3 (18.5%)	0.644
Psychosis	1 (10%)	0 (0%)	NA
Serositis	0(0%)	1 (6.3%)	NA
Mesenteric vasculitis	1 (10%)	2 (12.5%)	1.000
Livedo reticularis	3 (30%)	3 (18.8%)	0.644
Joint damage	7 (70%)	15 (93.8%)	0.264
Skin damage	9 (90%)	13 (81.3%)	1.000
Lung injury	1 (10%)	0 (0%)	NA
PH	1 (10%)	1 (6.3%)	1.000

Table 11. Characteristics of patients with SLE and HCV with/without post IS (immunosuppression) HCV reactivation⁽¹⁸⁾

CNS - central nervous system; PH - pulmonary hypertension.

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Taking into consideration that they are recently introduced in the antiviral treatment regimen, the safety of DAAs in patients with chronic kidney disease is under continuous evaluation.

Studies conducted on patients with lupus showed that although discontinuation of immunosuppression during DAAs treatment due to fear of possible interactions between the 2 treatment categories, proteinuria and inflammatory markers decreased significantly from week 4 of antiviral therapy, especially in patients who previously have had a response to immunosuppression. Moreover, patients are able to reach SVR⁽²⁰⁾.

In case of lupus nephritis, patients are at high risk of developing chronic end-stage kidney disease, with an estimated incidence of 15%, and the association with C virus infection increases the progression rate to this type of pathology, decreases the survival rate of patients.

Mitwalli et al. included 134 patients with class IV lupus nephritis with/without C virus infection in the study, followed up between 1995-2008 over a period of 6.7 ± 3.3 (1-14.4) years.

Patients received the same immunosuppression regimen (corticotherapy and cyclophosphamide), without antiviral treatment. Higher proteinuria was found in patients with C virus infection, but similar immunological profile and liver function.

Furthermore, patients with lupus nephritis and C virus infection presented a faster deterioration of kidney function towards stage 5 CKD, with an interval of 95% and 80% until the initiation of dialysis, for the group without C virus infection and of 90% and 65% for the group with C virus infection at 5 and 10 years of follow-up, respectively⁽²¹⁾ (Figure 1, Figure 2, Figure 3).

Conclusions

The increased prevalence of C virus infection in SLE patients advocates the hypothesis that C virus is a potential triggering agent of SLE. However, for diagnosis the clinician should take into consideration the 3 situations: False positive SLE and Anti-HCV Ab, confirmed SLE and positive Anti-HCV Ab, C virus infection mimicking SLE via the presence of specific antibodies and symptomatology. In terms of treatment, on the one hand immunosuppression influences viral replication, on the other hand antiviral therapy itself may trigger lupus-like diseases or even SLE.

Obviously, the prognosis of patients is poor, having a faster evolution towards chronic end-stage kidney disease and a higher mortality than the general population. This category of patients therefore need a personalized diagnosis, treatment and follow-up, taking into account also the particularities of each patient.

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