ORIGINAL ARTICLE

AUTOIMMUNE DISORDERS DUE TO DOUBLE ANTIVIRAL THERAPY WITH PEGINTERFERON AND RIBAVIRIN IN PATIENTS WITH HEPATITIS C VIRUS INFECTION

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Manuscript received: January 2016

Abstract

During antiviral therapy with peginterferon and ribavirin in chronic hepatitis C, severe adverse events were reported in 10 - 20% of cases. Among these, autoimmune adverse events are severe even if they are rarely reported. In this study we aimed to highlight the type, incidence and biological profile of autoimmune disorders that may occur during double antiviral therapy. We investigated 320 patients with chronic hepatitis C virus infection treated with double anti-viral therapy with peginterferon plus ribavirin between February 2012 and April 2015 in the Medical Clinic II of the Emergency Regional Hospital Craiova, Romania. The incidence of autoimmune adverse events in the study group was reported in 1.87% of cases (6 patients). Thyroid disorders have been reported in 2 cases, rheumatoid arthritis in 2 cases, systemic lupus erythematosus in 1 case and in 1 case autoimmune thrombocytopenia. In all these cases, it was necessary to permanently stop the antiviral therapy and to initiate specific treatment. The determination of a broad spectrum of antibodies (anti-platelet autoantibodies, anti-double – stranded deoxyribonucleic acid (DNA) antibodies, anti-Thyroperoxidase (anti-TPO) levels, anti-mitochondrial antibodies, anti-liver-kidney microsomal antibodies type 1 (Anti-LKM-1 antibodies), anti-neutrophil cytoplasmic antibodies) is absolutely necessary and helps to diagnose of these autoimmune disorders.

Rezumat

Tratamentul hepatitei cronice virale C cu pegInterferon şi ribavirină determină apariţia reacţiilor adverse severe în 10 - 20% din cazuri. Dintre acestea reacţiile adverse autoimune, deşi au o incidenţă scăzută, au o evoluţie severă. În acest studiu a fost evaluat tipul, incidenţa şi profilul biologic al tulburărilor autoimune apărute în cursul dublei terapii antivirale. S-au luat în studiu 320 de pacienţi cu hepatită cronică virală C, în tratament cu dublă terapie antivirală cu pegInterferon şi ribavirină, internaţi în perioada februarie 2012 - aprilie 2015 în Clinica Medicală II a Spitalului Judeţean de Urgenţă Craiova, România. Incidenţa reacţiilor adverse autoimune în grupul studiat a fost de 1,87% (6 cazuri). Disfuncţiile tiroidiene au fost raportate în 2 cazuri, artrita reumatoidă în 2 cazuri, iar lupusul eritematos sistemic şi trombocitopenia autoimună, câte 1 caz. În toate aceste cazuri a fost necesară oprirea terapiei antivirale şi iniţierea tratamentului specific. Determinarea unui spectru larg de anticorpi (anticorpi anti-trombocitari, anticorpi anti-ADN (acid deoxiribonucleic) dublu catenar, anticorpii anti-tiroidperoxidaza (anti-TPO), anticorpii antimitocondriali, anticorpi anti ficat şi rinichi (LKM-1), anticorpi împotriva citoplasmei neutrofilelor) este absolut necesară şi ajută la diagnosticul complet al acestor manifestări autoimune.

Keywords: Hepatitis C, autoimmune disorders, double antiviral therapy, anti-liver-kidney microsomal antibodies type 1 (LKM-1), anti-neutrophil cytoplasmic antibodies (ANCAs)

Introduction

There are 130 - 150 million people worldwide infected with hepatitis C virus (HCV). Approximately 500,000 people die from hepatitis C-related liver diseases every year [23]. It is known the fact that most of the persons with chronic hepatitis C infection are prone to develop liver cirrhosis or liver cancer. In Romanian adult population, the prevalence rate of HCV infection is 3.23%, according to a study on adult population conducted

between 2006 - 2008 [11] and 5.4% according to the Extension at the ARSF Epidemiological Study 2008 - 2009 (A cross-sectional epidemiological study of hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV) prevalence in the SubCarpathian and South-Eastern regions of Romania) [22].

It is estimated that half of the treated patients with double therapies - pegInterferon and ribavirin in Romania, achieved sustained virusologic response (SVR) [12]. The adherence to prescribed doses of antiviral therapy is a well-known predictor of SVR [15] and the adverse events of dual therapy could influence the adherence. During antiviral therapy with pegInterferon and ribavirin in chronic hepatitis C, severe adverse events were reported in 10 - 20% of cases. The most common adverse events were the haematological, psychiatric, dermatological and general disorders. Autoimmune disorders are rarely reported and usually cause an increased severity which is reflected by treatment discontinuation. There were reports of thyroid disorders such as autoimmune thyroiditis with hyperthyroidism and hypothyroidism, systemic lupus erythematosus, autoimmune thrombocytopenia and rheumatoid arthritis [7].

In this study we aimed to highlight the type, incidence and biological profile of autoimmune disorders that may occur during double antiviral therapy.

Materials and Methods

We investigated 320 patients with chronic hepatitis C virus infection treated with double anti-viral therapy with peginterferon plus ribavirin between February 2012 and April 2015 in Medical Clinic II of Emergency Regional Hospital Craiova, Romania. It was obtained a written informed consent from each patient included in the study and the approval of the Ethics Committee of Emergency Regional Hospital Craiova, Romania. Inclusion criteria for the treatment was based on biochemical evaluation**:** Serum Glutamic-Pyruvic Transaminase (GPT) (Hitachi 917 Automatic Analyser, Roche) normal or elevated , virusological evaluation: detectable hepatitis C virus – Ribonucleic acid (HCV – RNA) (Quantiplex HCV RNA, Bayer Diagnostics, Puteaux, France and Cobas Amplicor HCV Monitor Test Cobas v2.0, Roche Diagnostics Systems, Meylan, France), morphological evaluation: Fibromax (BioPredictive, France) with A ≥ 1, F ≥ 1 and/or S ≥ 1 or Fibroscan (Echosens, France) F > 1 or liver biopsy A ≥ 1, F ≥ 1, age ≤ 65 years and for > 65 years we evaluated the therapeutic risk based on comorbidities. The patients with neurological diseases, psychiatric diseases (dementia), autoimmune diseases, decompensated diabetes, ischemic heart disease or uncontrolled heart failure, uncontrolled severe respiratory diseases, haemoglobin < 11 g/dL, White Blood Cell Count (WBC) < 5000/mm^3, polymorphonuclear neutrophils (PMNs) < 1500/mm^3 (Hitachi 917 Automatic Analyser, Roche) are excluded from therapy with interferon.

The received treatment was peginterferon α-2b – 1.5 μg/kg bw/week plus ribavirin – 800 - 1200 mg/day based on body weight for 12 - 24 or 48 weeks and with peginterferon α-2a – 180 μg/week plus ribavirin – 800 - 1200 mg/day based on body weight for 12 - 24 or 48 weeks.

All the patients were clinically, ultrasound and haematologically monitored monthly. HCV - RNA was determined at the beginning of the therapy, at 4 weeks of therapy, at 12 weeks of therapy, if the HCV - RNA was detectable at 4 weeks, at 24 weeks of therapy. An indicator of the favourable response is obtained three months after initiation of antiviral therapy an early virologic response - undetectable HCV-RNA or decreased by 2 $\log_{10}$ (e.g. From 2 million to 20,000 IU) of viral load base. When clinical and haematological (anaemia and thrombocytopenia) conditions imposed it, the patients were immunologically evaluated. For autoimmune thrombocytopenia, we determined specific anti- platelet glycoprotein antibodies GP IIb/IIIa, GP Ib/IX and GP Ia/IIa using qualitative enzyme-linked immunosorbent assay (ELISA) method, reference value: negative. For systemic lupus erythematosus we determined the presence of specific antibodies in particular anti-double - stranded DNA antibodies (anti-dsDNA) using ELISA (Stat Fax-3300, CPC Diagnostics) method (reference values: < 100 UI/mL – negative; ≥ 100 UI/mL – positive), for rheumatoid arthritis we determined the presence of rheumatoid factors (RF) using a immunoturbidimetric assay (reference values < 14 UI/mL) (Cobas analyser, Roche Diagnostics) and the specific radiological changes and for thyroid disorders we determined the specific thyroid antibody titres - anti-TPO levels using electrochemiluminescence immunoassay method (ECLIA) (Cobas analyser, Roche Diagnostics) (reference values: < 34UI/mL) and hormonal changes: serum thyroid-stimulating hormone (TSH) using electrochemiluminescence immunoassay method (ECLIA) (Cobas analyser, Roche Diagnostics) (reference values: > 20 years old: 0.27 - 4.20 μUI/mL); serum free triiodothyronine (FT3) using electrochemiluminescence immunoassay method (ECLIA) (Cobas analyser, Roche Diagnostics) (reference values: > 20 years old: 2.21 - 4.43 pg/mL); serum free thyroxine (FT4) using electrochemiluminescence immunoassay method (ECLIA) (Cobas analyser, Roche Diagnostics), (reference values: > 20 years old: 0.82 - 1.77 ng/dL). Other immunoassays performed were anti-mitochondrial antibodies (AMA) using ELISA method (reference values: ≤ 20 AU/mL – negative; 20.1 - 24.9 AU/mL – inconclusive; ≥ 25 AU/mL – positive) (Stat Fax-3300, CPC Diagnostics);

anti-liver-kidney microsomal antibodies type 1 (LKM-1 antibodies) using ELISA method (reference values: < 4U/mL – negative; 4 - 5 U/mL – inconclusive; > 5 U/mL – positive) (Stat Fax-3300, CPC Diagnostics); anti-neutrophil cytoplasmic antibodies (ANCAs) using indirect immunofluorescence assay method (reference values <1/10 - negative, for positive values we determined also c-ANCA, p-ANCA and x-ANCA) (LumiStat, Awareness Technology, INC.); IgG using an immunoturbidimetric assay (reference values: adults 700 - 1600 mg/dL); IgA using an immunoturbidimetric assay (reference values: adults: 70 - 400 mg/dL; IgM using an immunoturbidimetric assay (reference values: adults: 40 - 230 mg/dL) (Cobas analyzer, Roche Diagnostics) [2].

Sustained virusologic response (SVR) is defined as an undetectable HCV-RNA level 24 weeks after treatment discontinuation. Early virusologic response (EVR) is defined as an undetectable serum HCV-RNA or a 2 $\log_{10}$ or greater decrease in HCV-RNA at week 12 of therapy. End-of-treatment response is defined as an undetectable serum HCV-RNA when therapy is completed. Responders refer to patients who achieved a sustained virusologic response (SVR) at 6 months after completion of antiviral therapy. Non-responders mean the patients who didn't achieve an undetectable HCV-RNA during the first 24 weeks of antiviral treatment. The breakthrough response represents the temporary virological response occurring during therapy followed by reappearance of HCV RNA before the end of treatment. Relapsers (patients with transient response) refer to patients who had an end-of-treatment response and HCV RNA reappears at 24 weeks after the end of treatment.

Results and Discussion

In our study group we had 57.8% females and 42.2% males. Distribution by age showed an increased incidence in the age group 50 - 60 years and 60 - 70 years with a median age of 58.4 ± 3 years. Distribution by type of interferon used showed that 56.25% of the patients were treated with peginterferon α-2b plus ribavirin and 43.75% of the patients were treated with peginterferon α-2a plus ribavirin.

The patients that obtained a sustained virusologic response (SVR) at 6 months after completion of antiviral therapy are considered as responders to antiviral therapy and basically healed. A number of 186 patients (58.12%) had a SVR at 6 months after completion of antiviral therapy. This percentage is close to, even a bit higher than the percentage presented in the literature [3], which was gratifying for our group because more than half of patients under this therapy were healing (Figure 1).

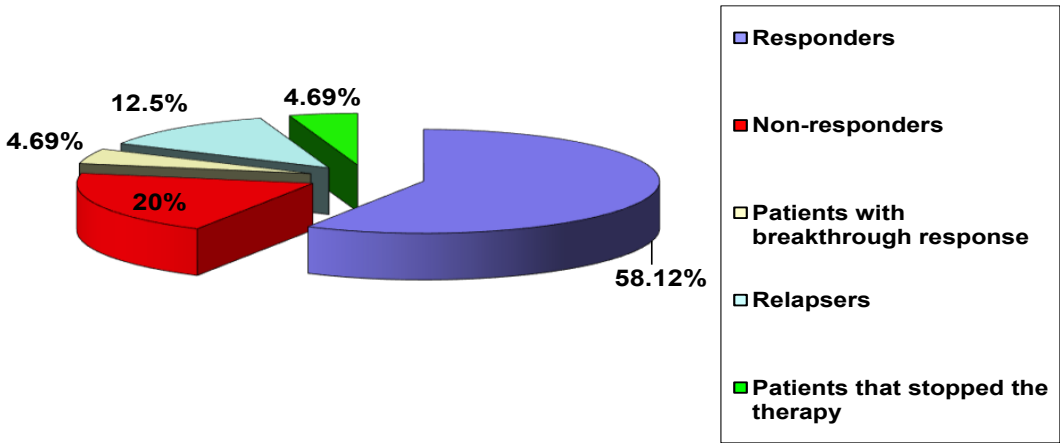

Figure 1.
Types of therapeutically response to double anti-viral therapy with peginterferon plus ribavirin

64 patients (20%) were non-responders of antiviral therapy because they didn't achieve an early virusologic response (EVR) at 3 and 6 months of therapy. 55 patients (17.18%) were developing virusologic relapse after antiviral therapy. In 15 patients (4.69%), the virusologic relapse occurs at the end of the therapy (breakthrough response) and in 40 patients (12.5%) this occurred at 6 months after the therapy was finished (relapsers). 15 patients (4.69%) stopped the antiviral therapy due to severe adverse effects of which 6 with autoimmune adverse events.

Autoimmune adverse events are among the most severe adverse events encountered during double antiviral therapy. The incidence of autoimmune adverse events in the study group was reported in 1.87% of cases (6 patients).

0.31% of cases (58 years-old male patient) were diagnosed with autoimmune thrombocytopenia (AITP) after 4 months of starting the antiviral

therapy with ribavirin 1000 mg per day plus peginterferon α-2b 120 µg/week. Positive diagnosis of this disease has been put by determining the platelet antibodies. Anti-dsDNA, LKM-1 antibodies, IgG and IgM showed elevated levels. It is known that mild thrombocytopenia is a common adverse effect of pegylated interferon treatment, but the cases of autoimmune thrombocytopenic purpura are rarely reported. This autoimmune adverse effect is in general associated with interferon therapy. In the literature there were also reported some cases of severe thrombocytopenia with probable autoimmune mechanism related to patients during the course of therapy with pegylated interferon α plus ribavirin for hepatitis C virus infection [8, 16]. There are no correlations between the type of pegylated α interferon used and the incidence of autoimmune thrombocytopenia, this autoimmune side effect could occur both following therapy with pegylated interferon α 2a [10] and following therapy with pegylated interferon α 2b [16]. In the literature we found reports of severe autoimmune thrombocytopenia in a 54 years-old female patient with chronic hepatitis C caused by a single administration of pegylated interferon α 2a subsequent to 48 weeks of pegylated interferon α 2b plus ribavirin therapy [6]. Even if autoimmune thrombocytopenia is rare during antiviral therapy with pegylated interferon plus ribavirin for hepatitis C virus infection, it leads immediately to treatment discontinuation and establishment of specific therapy usually with cyclosporin a and intravenous gamma-globulin. Evolution was reversible within 6 weeks after discontinuation of antiviral therapy and specific treatment: cyclosporine a 3 mg/kg bw/day for 8 weeks and gamma-globulin 0.4g/kg bw/day for 5 days (Table I).

Table I

Composition and codification of metronidazole gel formulations

	At onset	**After 2 weeks**	**After 4 weeks**	**After 6 weeks**	**After 8 weeks**
Anti-platelet autoantibodies	positive	positive	positive	negative	negative
Anti-dsDNA (IU/mL)	150	132	110	80	20
RF (IU/mL)	6	6	4	2	2
Anti-TPO (IU/mL)	18	16	17	15	12
TSH (µIU/mL)	1.8	1.9	2.1	1.8	1.6
FT3 (pg/mL)	3.2	2.8	2.6	2.2	2.4
FT4 (ng/dL)	1.13	1.23	1.16	1.14	1.12
AMA (AU/mL)	9	8	6	7	10
LKM-1 antibodies (U/mL)	6	5	3.5	3	2
ANCAs	negative	negative	negative	negative	negative
IgG (mg/dL)	2100	2000	1800	1550	1300
IgA (mg/dL)	250	280	300	260	220
IgM (mg/dL)	290	260	220	210	200

Anti-dsDNA = anti-double - stranded DNA antibodies; RF = rheumatoid factors; Anti-TPO = anti- Thyroperoxidase; TSH = serum thyroid-stimulating hormone; FT3 = free triiodothyronine; FT4 = serum free thyroxine; AMA = anti-mitochondrial antibodies; LKM-1 antibodies = anti-liver-kidney microsomal antibodies type 1; ANCAs = anti-neutrophil cytoplasmic antibodies

0.31% of cases (44 years-old female patient) after 5 months of starting the antiviral therapy with ribavirin 1000 mg per day plus peginterferon α-2a 180 µg/week have presented clinical manifestations of systemic lupus erythematosus (SLE) confirmed by the presence of specific antibodies in particular anti-dsDNA, RF, anti-TPO, AMA antibodies, LKM-1 antibodies, IgG, IgA and IgM showed elevated levels. ANCA are positive with xANCA positive. The incidence of systemic lupus erythematosus during the antiviral therapy with pegylated interferon plus ribavirin for hepatitis C virus infection is very low and in the literature we found isolated cases occasionally reported [4, 17]. The appearance of this autoimmune adverse event leads immediately to treatment discontinuation and establishment of specific therapy with hydroxyl-chloroquine 400 mg/day associated with methyl-prednisolone 16-32 mg/day for 2 months and then only hydroxychloroquine 200 mg/day as maintenance treatment. In literature this immune side effect is associated with female sex [19]. Clinical remission appeared after 5 weeks and biological parameters were improved after 8 weeks after discontinuation of antiviral therapy and were reversible within 16 weeks after discontinuation of antiviral therapy (Table II).

0.62% of cases (2 patients – one male and one female) were confirmed with rheumatoid arthritis (RA). 0.31% of cases (a 61 years-old male patient) were confirmed after 7 months of antiviral treatment with ribavirin 1000 mg/day plus peginterferon α-2b 120 µg/week and 0.31% of cases (a 63 years-old female patient) were confirmed after 8 months of antiviral therapy with ribavirin 1200 mg/day plus peginterferon α-2a 180 µg/week. They presented positive RF and specific radiological changes for the disease. The 61 years-old male patient showed elevated levels of anti-TPO, LKM-1 antibodies, IgG, IgM. ANCA are positive with xANCA

positive. The 63 years-old female patient showed elevated levels of IgG, IgM, IgA. Rheumatoid arthritis is rarely induced by antiviral therapy with pegylated interferon plus ribavirin for hepatitis C virus infection, but it leads to discontinuation of treatment and in severe cases it is required specific therapy such as anti-inflammatory, immuno-suppressive and antimalarial drugs [1]. For the cases that appeared in our study the treatment was made with diclofenac 150 mg/day and azathioprine 100 mg/day for 6 months. Evolution of the first case (1) was favourable, clinical remission appeared within 16 weeks after stopping antiviral therapy. In the second situation (2) the evolution was unfavourable and after 24 weeks after stopping antiviral therapy biological therapy with infliximab was initiated (Table III).

Table II

Evolution of biological and immunological parameters in patients with systemic lupus erythematosus in the first 16 weeks from onset

	At onset	**After 4 weeks**	**After 8 weeks**	**After 12 weeks**	**After 16 weeks**
Anti-platelet autoantibodies	negative	negative	negative	negative	negative
Anti-dsDNA (IU/mL)	450	380	180	140	90
RF (IU/mL)	96	84	63	21	12
Anti-TPO (IU/mL)	112	94	106	42	28
TSH (μIU/mL)	2.2	2.4	1.8	1.9	2.1
FT3 (pg/mL)	2.9	2.7	3.1	2.8	2.9
FT4 (ng/dL)	1.32	1.41	1.38	1.46	1.39
AMA (AU/mL)	51	41	38	26	22
LKM-1 antibodies (U/mL)	9	7	4.2	4.6	3.8
ANCAs	positive; xANCA-positive	positive; xANCA-positive	positive; xANCA-positive	positive; xANCA-positive	negative
IgG (mg/dL)	1800	1700	1400	1450	1500
IgA (mg/dL)	600	550	460	360	320
IgM (mg/dL)	320	280	260	220	210

Anti-dsDNA = anti-double - stranded DNA antibodies; RF = rheumatoid factors; Anti-TPO = anti- Thyroperoxidase; TSH = serum thyroid-stimulating hormone; FT3 = free triiodothyronine; FT4 = serum free thyroxine; AMA = anti-mitochondrial antibodies; LKM-1 antibodies = anti-liver-kidney microsomal antibodies type 1; ANCAs = anti-neutrophil cytoplasmic antibodies

Table III

Evolution of biological and immunological parameters in patients with rheumatoid arthritis in the first 24 weeks from onset

	1 at onset	**1 after 8 weeks**	**1 after 16 weeks**	**1 after 24 weeks**	**2 at onset**	**2 after 8 weeks**	**2 after 16 weeks**	**2 after 24 weeks**
Anti-platelet autoantibodies	negative	negative	negative	negative	negative	negative	negative	negative
Anti-dsDNA (IU/mL)	20	24	18	16	10	14	8	6
RF (IU/mL)	230	160	12	10	110	160	180	220
Anti-TPO (IU/mL)	76	22	24	18	21	24	16	18
TSH (μIU/mL)	1.9	1.7	1.8	2.1	2.4	2.2	2.3	2.4
FT3 (pg/mL)	3.5	3.2	3.4	3.6	2.7	2.4	2.5	2.6
FT4 (ng/dL)	1.21	1.24	1.18	1.16	1.41	1.38	1.45	1.16
AMA (AU/mL)	8	16	14	12	24	18	26	27
LKM-1 antibodies (U/mL)	6	4	3	4	2	4	6	7
ANCAs	positive; xANCA- positive	negative	negative	negative	negative	negative	negative	negative
IgG (mg/dL)	2200	1800	1400	800	1950	1770	2100	2300
IgA (mg/dL)	100	120	200	280	650	500	720	680
IgM (mg/dL)	310	320	210	200	280	240	290	310

Anti-dsDNA = anti-double - stranded DNA antibodies; RF = rheumatoid factors; Anti-TPO = anti- Thyroperoxidase; TSH = serum thyroid-stimulating hormone; FT3 = free triiodothyronine; FT4 = serum free thyroxine; AMA = anti-mitochondrial antibodies; LKM-1 antibodies = anti-liver-kidney microsomal antibodies type 1; ANCAs = anti-neutrophil cytoplasmic antibodies

Autoimmune thyroiditis with hyperthyroidism was reported in 0.31% of cases (39 years-old female patient) after 4 months of antiviral treatment with ribavirin 1000 mg per day plus peginterferon α-2a 180 μg/week and with hypothyroidism in 0.31% of cases (51 years-old female patient) after 7 months of antiviral treatment with ribavirin 1000 mg per day plus peginterferon α-2a 180 μg/week. The

positive diagnosis was certified through the presence of specific thyroid antibody titres (anti-TPO levels) and hormonal changes (serum TSH, FT3 and FT4). The case with autoimmune thyroiditis with hyperthyroidism presented elevated levels of FT3, FT4, anti-TPO, RF, AMA, LKM-1 antibodies, IgG. The TSH level was low. The case with auto-immune thyroiditis, with hypothyroidism presented low levels of FT3 and FT4. TSH, anti-TPO, IgG and IgM showed elevated levels. Autoimmune thyroiditis is usually correlated with antiviral therapy with interferon α for the treatment of hepatitis C virus infection, but no significant difference was found in relation to the type of interferon α used (pegylated interferon or simple interferon) [9, 21]. The incidence of interferon-induced autoimmune thyroiditis has been reported in the literature from 2.5% to 42% depending of dose and duration of therapy and also to patient characteristics. Interferon α can initiate auto-immune thyroiditis [18]. In our study group autoimmune thyroiditis was correlated with female gender in accordance with other studies that also demonstrated that the development of antithyroid antibodies was significantly higher in women compared to men (14.8% *versus* 1%) [14]. Huang Y.X. *et al.* also showed that the female sex is a risk factor for developing thyroid dysfunction during peginterferon plus ribavirin (peg-INF-α-2a/RBV) therapy in patients with hepatitis C virus infection [5]. In all cases the antiviral therapy was stopped and specific treatment was initiated by endocrinologist. Autoimmune thyroiditis with hyperthyroidism was treated with carbimazole and autoimmune thyroiditis with hypothyroidism was treated with levothyroxine. Evolution of the cases was favourable, clinical remission appeared within 8 weeks after stopping antiviral therapy (Table IV).

Table IV

Evolution of biological and immunological parameters in patients with autoimmune thyroiditis with hyperthyroidism (AT hyper) and with autoimmune thyroiditis with hypothyroidism (AT hypo) in the first 12 weeks from onset

	AT hyper at onset	**AT hyper after 4 weeks**	**AT hyper after 8 weeks**	**AT hyper after 12 weeks**	**AT hypo at onset**	**AT hypo after 4 weeks**	**AT hypo after 8 weeks**	**AT hypo after 12 weeks**
Anti-platelet autoantibodies	negative	negative	negative	negative	negative	negative	negative	negative
Anti-dsDNA (IU/mL)	25	28	16	24	18	23	26	18
RF (IU/mL)	46	18	12	10	4	8	6	9
Anti-TPO (IU/mL)	350	280	32	28	280	140	28	18
TSH (μIU/mL)	0.12	0.25	0.32	0.9	26	8	4.1	3.8
FT3 (pg/mL)	6.2	5.4	3.8	3.6	1.4	1.8	2.3	2.4
FT4 (ng/dL)	4.25	4.16	3.8	2.6	0.42	1.2	2.6	3.2
AMA (AU/mL)	38	36	19	14	14	16	8	12
LKM-1 antibodies (U/mL)	7	5	3	2	2.2	3.2	1.8	2
ANCAs	negative	negative	negative	negative	negative	negative	negative	negative
IgG (mg/dL)	2050	1800	1200	900	2080	1820	1400	1200
IgA (mg/dL)	230	260	280	160	270	240	210	48
IgM (mg/dL)	190	160	180	210	265	243	186	190

Anti-dsDNA = anti-double - stranded DNA antibodies; RF = rheumatoid factors; Anti-TPO = anti- Thyroperoxidase; TSH = serum thyroid-stimulating hormone; FT3 = free triiodothyronine; FT4 = serum free thyroxine; AMA = anti-mitochondrial antibodies; LKM-1 antibodies = anti-liver-kidney microsomal antibodies type 1; ANCAs = anti-neutrophil cytoplasmic antibodies

Conclusions

During antiviral therapy with peginterferon plus ribavirin in chronic hepatitis C autoimmune adverse events are rare, but severe. Autoimmune adverse events often cause discontinuation of antiviral therapy and initiation of specific treatment for these conditions. No correlations were found between the autoimmune adverse events and the type of interferon used. All the patients with autoimmune adverse events at double anti-viral therapy with peginterferon plus ribavirin had elevated levels of IgG and IgM. ANCA were positive with xANCA positive in the patient with systemic lupus erythematosus and in one patient with rheumatoid arthritis. LKM-1 antibodies showed elevated levels in the patients with autoimmune thrombocytopenia, systemic lupus erythematosus and autoimmune thyroiditis with hyperthyroidism and in one patient with rheumatoid arthritis. AMA were elevated in the patients with systemic lupus erythematosus and with autoimmune thyroiditis with hyperthyroidism. RF presented elevated levels in the patients with rheumatoid arthritis but also at the patients with systemic lupus erythematosus and with auto-immune thyroiditis with hyperthyroidism.

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