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ORIGINAL ARTICLE

Long-term persistence of anti-rods and rings antibodies in patients with chronic hepatitis C after antiviral treatment

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Abstract
Anti-rods and rings (anti-RR) antibodies are related to hepatitis C virus (HCV) in patients treated with pegylated interferon (PEG-IFN) and ribavirin (RBV). Only RBV induces rods/rings structures in vitro; but in vivo, the antibody appearance is related to the combination of these drugs, because data about patients using just one of these drugs alone is missing. Some studies suggest disappearance of these antibodies over time. The aim of this study was to describe the occurrence of anti-RR in patients with chronic hepatitis C treatment-naïve or previously PEG-IFN/RBV-experienced, evaluating the persistence of anti-RR antibodies long after PEG-IFN/RBV treatment. From 2016 to 2017, 70 HCV-infected patients were screened for anti-RR using indirect immunofluorescence. Demographic and clinical data about previous treatments against HCV were assessed. Thirty-four patients (49%) had been previously treated with PEG-IFN/RBV and the average time since they had received the last antiviral treatment was 85.4 months. Anti-RR seropositivity was detected in 16 patients (23%), and all of these had used PEG-IFN/RBV (corresponding to 47% of experienced patients). Previous antiviral treatment and previous exposure time to RBV were associated with anti-RR positivity. Median time elapsed since last treatment was similar between anti-RR-positive and anti-RR-negative patients. Anti-RR seropositivity was not observed in treatment-naïve patients, but was detected in almost half of patients previously treated with PEG-IFN and RBV, even after a long period without exposure to these drugs. This antibody was related to extended prior exposure to ribavirin.

Keywords Chronic hepatitis C · Autoantibodies · IMPDH enzyme · Ribavirin · Antiviral therapy

Introduction

Hepatitis C virus (HCV) infection causes high morbimortality, leading to liver cirrhosis in 4 to 20% of those infected [1]. In addition to liver disease, this virus has been associated with autoimmune phenomena and the production of autoantibodies [2]. A positive ANA test has been reported in 7 to 65% of infected patients, the most common pattern being nuclear fine speckled [3, 4]. It is believed that HCV promotes activation and proliferation of B lymphocytes, stimulating the generation of these antibodies [5, 6].

Recently, a novel cytoplasmic ANA pattern in indirect immunofluorescence described as anti-rods and rings (anti-RR) has been reported almost exclusively in hepatitis C patients treated with pegylated interferon (PEG-IFN) plus ribavirin (RBV). RBV is known to irreversibly inhibit inosine monophosphate dehydrogenase (IMPDH), which is the main target of the anti-RR antibody [7]. However, data demonstrating that RBV alone is capable of inducing this antibody in vivo is rare. In addition, the literature available has not reported whether the immune effects induced by PEG-IFN are or are not fundamental to the emergence of these autoantibodies [7–9].

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Furthermore, previous studies investigating anti-RR after the end of hepatitis C treatment have suggested its disappearance over the course of time in most cases [9, 10]. Little is known, however, about the persistence of anti-RRs for longer periods after antiviral therapy. Despite the arrival of the new antivirals replacing PEG-IFN and RBV in the treatment of hepatitis C, a large number of patients undergoing these new treatments received the previous combination therapy with PEG-IFN/RBV in the past, and many of them may still have anti-RR seropositivity. In addition, some studies have observed a relationship between the emergence anti-RR and virus relapse, thereby raising the suspicion of a negative impact of this antibody on the treatment outcome [7, 9, 11, 12]. Therefore, this study aimed to describe the occurrence of anti-RR in patients with chronic hepatitis C treatment-naïve or previously PEG-IFN/RBV-experienced, evaluating the persistence of these antibodies long after antiviral treatment.

Materials and methods

Patient characteristics

From 2016 to 2017, 70 patients were evaluated at the Hepatology outpatient clinic in the Hospital das Clínicas of the Universidade Federal de Pernambuco (UFPE). They were all over 18 years old, with chronic hepatitis C confirmed by positive anti-HCV antibodies and circulating HCV RNA for more than 6 months. Serum samples were collected for anti-RR research and clinical and demographic data, including information about previous treatments against HCV, were collected from interviews and medical records. All procedures performed were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments. The institution's Ethics Committee approved the present study, and informed consent was obtained from all individual participants included.

Anti-RR detection

All serum samples were stored at − 20 °C and processed for an indirect immunofluorescence (IIF) assay with HEp-2 slides from Euroimmun (Lubeck, Germany), at a screening dilution of 1/40. Following initial dilution with a phosphate-buffered saline (PBS), the samples were incubated with HEp-2 cells for 30 min at room temperature. Next, after washing with PBS for 10 min, the cells were incubated with fluorescein-labeled anti-human IgG for another 30 min in the dark. After further washing, the slides were assembled with 10 μL of glycerol. Analyses were made using an Olympus BX 41 immunofluorescence microscope under × 100 magnification. These were undertaken by an experienced observer who did not know the patient's clinical status.

All patients considered to have the anti-RR antibody presented the ANA rods and rings pattern, designated AC-23 by the International Consensus of ANA Patterns [13] with a titer greater than or equal to 1/40. Positive samples were then titrated and analyzed again.

Statistical analysis

The data were analyzed using STATA/ SE 12.0 and Excel 2010. All tests were applied with 95% confidence. Chi-square test and Fisher's exact test were used in the descriptive analysis and to check if there was an association between the categorical variables. The Kolmogorov-Smirnov normality test was used for quantitative variables ($n \geq 30$). Comparisons between groups were performed using Student's t test and Mann-Whitney test depending on data distribution.

Results

Study population

During the study period, 70 patients were evaluated. Their mean age was 60.9 ± 10.9 years. Genotype 1 was the most prevalent, present in 50 patients (71.4%). Five patients (7.1%) were HIV co-infected and one patient had diagnosed systemic lupus erythematosus. One patient was using azathioprine and another one mycophenolate mofetil.

Concerning previous treatments against HCV, 36 (51.4%) were treatment-naïve, and 34 of the 70 patients (48.6%) had already used a therapeutic regimen, six of them having undergone two attempts and four of them three attempts. The combination of PEG-IFN/RBV was the most used regimen, having been received by 31 of the 34 experienced patients. Four of the 70 patients (5.8%) received a regimen with telaprevir. Relapse after a previous treatment was observed in 13 (38%) patients and 21 (62%) of the 34 patients do not respond to previous antiviral therapy. Demographic, clinical, virological, and previous treatment data of the 70 patients are described in Table 1.

The mean time since the last treatment was 85.4 ± 57.5 months, ranging from 10 to 225 months. The mean total length of time that each patient had used antiviral medications was 16.3 ± 19 months, ranging from 1 to 107 months, with the mean time of ribavirin use being 15.7 ± 18.9 months, ranging from 1 to 107 months. Previous treatment data of the 70 patients are described in Table 2.

Table 1 Demographic, clinical, and virological data of the 70 patients with chronic hepatitis C

Characteristics	$n = 70$ (%)
Demographic	
Age (mean ± SD)	60.9 ± 10.9
Males	37 (52.9)
Clinical	
Cirrhosis	22 (31.4)
Diabetes mellitus 2	19 (27.1)
Hepatosplenic schistosomiasis	14 (20.0)
Co-infection HIV-HCV	5 (7.1)
Tenofovir or lamivudine use	5 (7.1)
HCV characteristics	
Genotype 1	50 (71.4)
Genotypes 2 and 3	20 (28.6)
HCV RNA > 400.000 UI/ml	46 (65.7)

Values presented as *n* (%) unless otherwise indicated. *HCV* hepatitis C virus, *HIV* human immunodeficiency virus

Anti-rods and rings seropositivity

Anti-RR reactivity was detected in the sera of 16 of the 70 patients studied (22.8%), and all of them (47% of the 34 experienced patients) had been previously treated.

The mean age among the individuals with a positive antibody was higher than among those with a negative antibody (65.4 years vs 59.6 years; $p = 0.064$). There was no significant relationship between sex, genotype, viral load, diagnosis of cirrhosis, HIV co-infection, schistosomiasis or diabetes with the seropositivity of the antibody. None of the HIV co-infected patients were positive. Patient with systemic lupus erythematosus and patients in use of azathioprine and mycophenolate mofetil did not show antibody positivity. Table 3 presents clinical characteristics of the 70 patients according to anti-RR positivity.

Table 2 Previous treatment data of the 70 patients with chronic hepatitis C

Characteristics of previous HCV treatments	$n = 70$ (%)
Treatment-naïve	36 (51.4)
Previously treated	34 (48.6)
Treated with PEG-IFN + RBV	31 (44.2)
Previous relapse	13 (18.6)
Treated more than once	10 (14.3)
Use of telaprevir	4 (5.8)
Number of months since the last treatment (mean + SD)	85.4 ± 57.5
Period (in months) of previous treatments (mean + SD)	16.3 ± 19
Period (in months) of RBV use (mean + SD)	15.7 ± 18.9
Period (in months) of IFN use (mean + SD)	11.6 ± 7.9

Values presented as *n* (%) unless otherwise indicated. *HCV* hepatitis C virus, *RBV* ribavirin, *IFN* alpha-interferon, *PEG-IFN* pegylated interferon

Table 3 Clinical characteristics of the 70 patients with chronic hepatitis C according to the positivity of the anti-rods and rings

Characteristic	Anti-RR		*p*
N	Positive 16	Negative 54	
Male	8 (50)	29 (53.7)	0.794[1]
Age (mean ± SD)	65.4 ± 10.5	59.6 ± 10.8	0.064[3]
Genotype 1	12 (75)	38 (70.4)	1.000[2]
HCVRNA > 400.000 UI	10 (62.5)	36 (66.6)	1.000[1]
Cirrhosis	6 (37.5)	16 (29.6)	0.615[1]
DM2	5 (31.2)	14 (25.9)	0.757[2]
HSS	3 (18.7)	11 (20.3)	1.000[2]
HIV	0	5 (9.2)	0.582[2]

Values presented as *n* (%) unless otherwise indicated. 1: Chi-square test; 2: Fisher's exact test; 3: Student's *t* test; *Anti-RR* anti-rods and rings, *HIV* human immunodeficiency virus, *DM2* diabetes mellitus type 2, *HSS* hepatosplenic schistosomiasis

Previous treatment against HCV infection showed a strong association with the presence of the anti-RR antibody. Among the 16 anti-RR-positive patients, all had received at least one previous therapeutic regimen against HCV ($p = 0.000$), four of them (25%) having received it twice and two of them (12.5%) three times. But even though six of the 10 patients (60%) who received more than one regimen presented positive anti-RR, comparing patients with single treatment versus multiple treatments did not show differences in the presence of the antibody (62.5% vs 37.5%, $p = 0{,}329$). Eight anti-RR carriers (50%) had relapsed in one of these treatments ($p = 0.213$) and the other eight were non-responders.

Three of the 16 anti-RR-positive patients (18.8%) had received telaprevir previously, whereas only one of the 54 negative ones (1.9%) received it ($p = 0.035$), but when comparing the appearance of the antibody between patients with PEG-IFN/RBV and PEG-IFN/RBV and telaprevir, no relationship was found between telaprevir use and anti-RR positivity. There was no relationship between mean duration of previous treatment (22.2 months vs 10.9 months; $p = 0.100$) or mean duration of IFN use (12.4 months vs 10.9 months; $p = 0.603$) according to the occurrence of anti-RR. The median time of previous use of ribavirin was 14.5 months between the positive ones and 9 months among the negatives ($p = 0.04$). The mean time elapsed since the last treatment was long but similar in both anti-RR-positive and -negative patients (82 months vs 88.3 months; $p = 0.756$). Table 4 presents the characteristics of previous treatments of the 70 patients, according to anti-RR positivity.

Table 4 Characteristics of the previous treatments of 70 chronic hepatitis C patients according to the positivity of anti-rods and rings

Characteristics	Anti-RR		*p*
	Positive	Negative	
N	16	54	
Previous treatment	16 (100)	18 (33.3)	0.000[1]
Relapse	8 (50)	5 (9.4)	0.213[1]
Telaprevir used	3 (18.7)	1 (1.9)	0.035[2]
Number of months since the last treatment (mean + SD)	82	88.3	0.756[3]
Period (in months) of previous treatments (mean + SD)	22.2	10.9	0.100[3]
Period (in months) of IFN use (mean + SD)	12.47	10.9	0.603[3]
Period (in months) of RBV use (median)	14.5	9.00	0.04[4]

Values presented as *n* (%) unless otherwise indicated. 1: Chi-square test; 2: Fisher's exact test; 3: Student's *t* test; 4: Mann-Whitney test; *IFN-α* alpha-interferon, *RBV* ribavirin

Anti-RR titers

The titers of anti-RR reactivity for all anti-RR-positive patients varied from 1/80 to 1/2.560. Seven of the 16 patients (43.7%) had an antibody titer of 1/320. The highest titer was 1/2.560 in only one patient.

Anti-RR titers were lower in those who had been treated a long time before, suggesting the reduction of titers in accordance with time progression after therapy ($r = -0.49$). Figure 1 shows an inverse correlation between time elapsed since last treatment and anti-RR titers. Moreover, the mean titer of the eight patients who had been treated the longest time before was 1/450 ± 368 and the mean titer of those eight treated more recently was 1/880 ± 741 ($p = 0.163$).

Discussion

In the current study, 16 of the 70 patients (22.8%) evaluated presented anti-RR reactivity even after a long period without receiving antiviral therapy. We did not found anti-RR occurrence in the 36 treatment-naïve patients with chronic hepatitis C.

The presence of anti-RR seropositivity was related to previous therapy since this antibody was detected in almost half of patients previously treated. According to the literature, among the HCV-infected population who receive IFN/RBV, anti-RR is found in approximately 25% of cases [9, 10, 12, 14]. A study from Keppeke et al. suggests that anti-RR reactivity appears in approximately 40% of patients treated once with IFN/RBV, and in 70% of those treated two or three times [15]. The data from our study showed 41.6% of anti-RR seropositivity in those treated once, and 60% in those treated more than one time.

However, a population-based study found the presence of anti-RR reactivity in 39 of the 4.738 subjects analyzed (0.74%), of whom only one presented hepatitis C, indicating that this antibody can occur in healthy individuals [16].

In our study, the mean time since the patients received their last treatment against HCV was long, 85.4 months. Nevertheless, despite this long period, previously treated patients had a high occurrence of anti-RR reactivity. On the other hand, some authors have suggested the disappearance of this antibody over a few months. In fact, Keppeke et al. revealed anti-RR disappearance in half of their patients after 6 months of the end of treatment [10]. Novembrino et al. also reported the loss of this antibody in

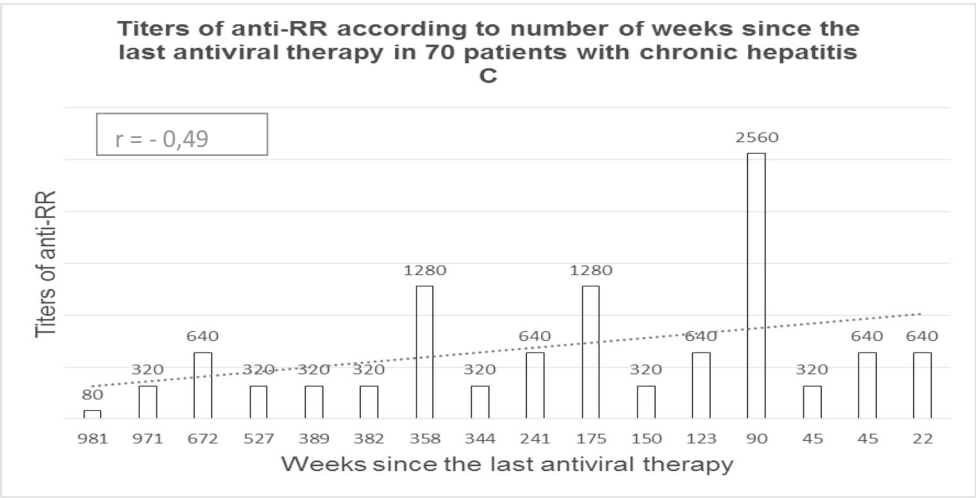

Fig. 1 Titers of anti-RR according to number of weeks since the last antiviral treatment in 70 patients with chronic hepatitis C

80% of their patients after 1 year [9]. However, in the literature reviewed, no published study was found that evaluated the presence of this antibody in patients such a long time after previous treatment as we did in our study.

It is known that the immune response that leads to the emergence of anti-RR is similar to that occurring after an infection, but slower, starting months after the antigenic stimulation [17]. In cases of immune response to infection or other external antigens, after the end of the antigenic stimulus, long-lived plasma cells maintain low IgG plasma levels specific for that antigen, causing continuous antibody production. However, in the case of autoimmune diseases, it has already been shown that there may be fluctuations in the levels of autoantibodies detected by IIF or other methods, independent of treatment or disease activity [18, 19]. It has not been established whether this occurs because it is part of the natural history of these autoimmune diseases or because of limitations in those methods of antibody detection.

We believe that the detection of this high frequency of anti-RR reactivity after so many years without its stimulus (PEG-IFN/RBV) occurred possibly due to the persistence of antibody production by long-lived plasma cells. It is important to highlight that in our study 37.5% of the subjects received more than one treatment, whereas the patients studied by Keppeke and Novembrino had been treated only once. However, we could not demonstrate that the presence of multiple treatments was significant for the presence of anti-RRs.

Although we found the presence of anti-RR seropositivity a long time after treatment, the patients who received antiviral treatment a long time ago had lower titers than those who receive it in the recent past. The median titer of the eight patients who undergone treatment for a longer period was half of the median titer of those treated more recently. In addition, there was a trend to an inverse correlation between the time elapsed since last treatment and anti-RR titers.

Despite the absence of statistical significance, the mean duration of previous treatment in those with positive anti-RR was twice as long as the duration for those with a negative antibody. The highest frequency of the antibody in the patients whose treatments lasted longer has been described in previous studies [9, 10].

Regarding the duration of previous RBV use, there was a positive association between longer exposure to this drug (and consequently higher cumulative dose) and the presence of anti-RR. Indeed, Novembrino et al. had already described a positive relationship between the RBV dosing and the occurrence of anti-RR reactivity (1000 mg in the positive vs 800 mg in the negative cases, $p = 0.04$), but this effect was excluded by multivariate logistic regression [9]. Information about the relationship between the emergence of anti-RR and the duration of RBV use is limited. No relationship was observed between the previous duration of alpha-interferon (PEG-IFN or conventional) use and the occurrence of antibodies.

Interestingly, we observed a higher frequency of anti-RR positivity in patients who previously received telaprevir. However, the three patients receiving telaprevir had a mean duration of previous treatment and RBV use of 17.3 months, both superior to the negative patients, and this may be the factor associated with antibody positivity. Calise et al. evaluated 52 patients treated with PEG-IFN/RBV plus telaprevir and found an anti-RR occurrence of 19%. Dammermann et al. evaluated 37 patients receiving PEG-IFN/RBV plus boceprevir and 67 patients receiving PEG-IFN/RBV plus telaprevir, with an anti-RR positivity of 46% and 32%, respectively. Both studies concluded that boceprevir and telaprevir had no influence on the emergence of anti-RRs [12, 14].

In our study, no association was observed between the presence of anti-RR reactivity and demographic parameters such as gender, viral load or genotype, as already mentioned in published studies [9–11]. The data of the present study revealed no relationship between anti-RR and the presence of hepatosplenic schistosomiasis, HIV co-infection, or the presence of diabetes mellitus. Although some of these factors are capable of inducing immunosuppression, there was apparently no greater induction of the antibody in these cases.

Contrary to previous studies, in which no difference in age was observed, we found a trend towards older age in patients positive for anti-RR. This finding is attributable to the older age of the population in our study in comparison with subjects in other anti-RR studies, given a greater tendency for autoantibodies in the elderly [20].

Considering the titers of anti-RR, this study found lower titers than most previous studies, despite the heterogeneity of the data [9, 17]. Carcamo et al. in 2013 found titers between 1/50 and 1/819.200, which are values far above those found in other studies [11]. In effect, the anti-RR titers in our patients were lower probably because they arose a long time ago, during a previous treatment, and had decreased over time, as was shown in Fig. 1.

In our study, there was no association between relapse in previous treatment and the frequency of anti-RR reactivity, although almost 50% of the patients had relapsed in at least one of their prior antiviral schemes. In some studies with IFN/RBV use, the anti-RR has been more related to relapsers than to non-responders and responders [7, 9, 11, 12]. Non-responders usually interrupt the therapeutic regimen as soon as the lack of response is verified, not taking their medication for the total length of time recommended. However, sustained responders and relapsers received the medication for the same

period, which does not explain why the antibody would be more present in relapsers, except for some possible immunological effect on treatment outcomes.

The present study has limitations, mainly due to its design. Because it was a retrospective analysis, the number of patients was limited and we do not know the initial titers and the exact time of anti-RR appearance.

Further and prospective studies will be necessary to evaluate the impact of the anti-RR emergence in virological responses during HCV therapy using the new direct-acting antivirals associated with RBV.

In conclusion, in the present study, anti-RR was not observed in treatment-naïve patients but was detected in almost half of patients who had been previously treated with PEG-IFN/RBV, even after a long period without antiviral using. Time of RBV use in this previous therapy was related to the occurrence of this antibody, and the anti-RR persisted after periods as long as 225 months without contact with antiviral agents against hepatitis C.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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