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Sustained virologic response rate in chronic hepatitis C patients through direct-acting antivirals therapy

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ABSTRACT – **Background** – In recent years the management of hepatitis C virus infection and the possibility of its eradication have been researched due to the importance that they represent in the health of the world population. Obtaining data that help to cope with this pathology improves the quality of life of those affected by it. The present study evaluated the effectiveness of direct-acting antiviral therapies provided by the Brazilian Ministry of Health in accordance to the Clinical Protocol and Therapeutic Guidelines of 2015. **Objective** – To evaluate the epidemiological profile of patients with chronic hepatitis C and the rate of sustained virologic response using direct-acting antivirals of all individuals that attended the referral service for the treatment of chronic hepatitis C at the Hospital of the Federal University of Rio Grande. **Methods** – This was an observational, retrospective/prospective study with all patients with chronic hepatitis C who had their treatments available from December 2015 to August 2017 according to the criteria of the Clinical Protocol and Therapeutic Guidelines of 2015. In the first phase, the clinical and demographic variables of all individuals enrolled in a treatment for hepatitis C were selected and collected from the Reference Service database. In the second phase, treatment data were collected. The outcome variable, sustained virologic response, was defined as an undetectable viral load on the blood test three months after the end of treatment. The descriptive and bivariate analyzes were performed with Pearson's chi-square and Fisher's Exact test, adopting a P value ≤0.05 in the SPSS 20 software. **Results** – Of the 252 participants in the study, 228 (90.5%) had a sustained virologic response, 55.2% were male with an average age of 58.6 years (SD±9.1). Genotype 1 was the most prevalent, observed in 54.4% of the participants, and 87.4% of the patients had moderate/advanced hepatic fibrosis. After the statistical analysis, it was observed that the individuals with genotype 3 and moderate/advanced hepatic fibrosis had lower sustained virologic response rate (P=0.05 and P=0.04, respectively). **Conclusion** – It was observed that the use of direct-acting antivirals, in comparison to previous therapeutic regimens, increases the sustained virologic response, reaching all patients with mild fibrosis. This study provides information that helps in the hepatitis C treatment by showing that prescribing early treatment for patients without hepatic fibrosis and/or genotype 3 virus could increase therapeutic effectiveness.

HEADINGS – Chronic hepatitis C. Epidemiology. Sustained virologic response. Antiviral agents.

INTRODUCTION

Chronic hepatitis C has the hepatitis C virus (HCV) as its etiological agent, discovered in the late 1980's by Choo et al.[1]. This pathology may remain stable or develop into hepatic fibrosis, cirrhosis and hepatocellular carcinoma[2].

The World Health Organization estimates that about 71 million people worldwide live with chronic HCV infection. Data shows that approximately 399,000 people die every year from hepatitis C because they develop cirrhosis or hepatocellular carcinoma[3]. The study "Global Burden of Disease" (GBD) has shown that viral hepatitis remains among the top ten global killers[4].

Data from the Brazilian Epidemiological Bulletin indicate that 331,855 cases of hepatitis C were reported in 2018 with the anti-HCV or HCV-RNA markers. In 2017, the ranking of capital cities with the highest rates of hepatitis C detected Porto Alegre (RS) at the top, with 90.7 cases per 100,000 inhabitants, while the national average was of 11.9 cases per 100,000 inhabitants[5]. The constant improvement of the Clinical Protocol and Therapeutic Guidelines makes available for the year 2019 new easy-to-manage antiviral medications and dosage including the retreatment of those already tried with other direct-acting antiviral (DAA) drugs[6].

In 2015, the Brazilian government started to offer the treatment of the Clinical Protocol and Therapeutic Guidelines, with the use of DAA agents (sofosbuvir, daclatasvir and simeprevir). The objective was to eradicate the virus by providing sustained virologic response (SVR)[7,8]. The use of the previous protocols led to unsatisfactorily low SVR rates that ranged between 50% and 70%. Indices were even worse in cases with advanced fibrosis and infection by genotype 1 HCV, besides presenting adverse effects of difficult management[9-11].

The present study was motivated by the limited availability of Brazilian research documenting and recording real-life data regarding the success rates of DAAs[12-14]. Here we evaluated the

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epidemiological profile of patients with chronic hepatitis C and the rate of SVR of all individuals treated in accordance to the Clinical Protocol and Therapeutic Guidelines of 2015 that attended the Reference Center for the treatment of chronic hepatitis C of the Federal University of Rio Grande, termed Center for the Application and Monitoring of Injectable Medicines (CAMMI).

METHODS

This was an observational, retrospective/prospective study that evaluated the epidemiological profile and determined the SVR rate of all chronic hepatitis C patients who had their treatments available in the period from December 2015 to August 2017 and attended CAMMI, in the Hospital of the Federal University of Rio Grande. The eligibility criteria was defined by the inclusion of all individuals treated in the service according to the 2015 Protocol.

The first phase of the study consisted in the selection of the participants using the CAMMI database. This study included all patients registered for treatment following the Clinical Protocol and Therapeutic Guidelines of 2015 in accordance to clinical setting and previous diagnosis, resulting in 357 eligible individuals. Demographic variables (sex and age) were also collected in this phase.

During the second phase, medical records were used to collect data on the treatment of hepatitis C (genotype, fibrosis, therapeutic regimen, duration, previous use of protease inhibitor, coinfection, extrahepatic criteria and previous treatment). SVR and HCV genotype data was obtained by the undetectable viral load test, which consisted of a HCV-RNA measurement test performed by Real Time PCR at least 12 weeks after the end of treatment. Both the viral load test and the HCV genotyping are molecular biology tests performed from blood samples sent from the central laboratory of the University Hospital. Samples were analyzed in the Viral Load laboratory situated in the academic area of the Health Campus.

Fibrosis was considered in the evaluation tests to characterize liver damage. Tests included hepatic biopsy (METAVIR), hepatic elastography (KPa ≤7.1 = F1, KPa ≥7.2 = F2, KPa ≥9.5= F3), abdominal ultrasound, endoscopy or scores calculations that take into account laboratory findings (transaminases and prothrombin time) and clinical evaluation, which are called APRI and FIB4 (APRI ≥0.5 or FIB4 ≥1.45 = F2 and APRI >1.5 or FIB4 >3.25 = F3). The results obtained followed the METAVIR classification, which is the most commonly used method to stage hepatic fibrosis[15,16]. METAVIR score was based on Rockey et al.[17] F1 and F2 were characterized as mild fibrosis, F3 as moderate to advanced fibrosis, and F4 as cirrhosis and esophageal varices. In the extrahepatic criteria are included the situations that did not include the evaluation of the hepatic damage, patients with kidney or liver transplantation and also cases where prescriptions were based on clinical manifestations of the virus such as problems in articulations (arthralgias) and in the skin (porphyria cutanea tarde).

The database was organized in Microsoft Excel spreadsheets with the following variables: SVR, sex, age, genotype, fibrosis, coinfection, extrahepatic criteria, treatment regimen and duration (weeks), previous use of first-generation protease inhibitors (PI) and treatment-naïve. The descriptive and bivariate analyzes were performed with Pearson's chi- square and Fisher's Exact tests, adopting a *P* value ≤0.05 in SPSS 20 software.

The present study followed the ethical precepts recommended by the Resolution CNS 466/12 of the Ministry of Health, and was approved by the Research Ethics Committee of the Federal University of Rio Grande – FURG under the number 203/2018 CEPAS 96/2018.

RESULTS

Of the 357 eligible individuals, 27 were excluded for not initiating treatment within the pre-established period, discontinuing treatment or dying. There were 78 participants that were excluded because the record of the viral load test performed three months after finishing the treatment were not found. Therefore, 252 (76.4%) patients were included in the statistical analysis. No statistical difference was found between the study group and the losses (TABLE 1) when considering sex, age, genotype, fibrosis and treatment-naïve.

TABLE 1. Comparison of sociodemographic factors, C virus genotype and host characteristics among participants and losses of the sustained viral response rate study in patients with chronic hepatitis C treated with direct-acting antivirals (n=330).

Variable	Participants n (%)	Losses n (%)	
Sex			0.320
Male	139 (55.2)	48 (61.5)	
Female	113 (44.8)	30 (38.5)	
Genotype			0.175
1	137 (54.4)	47 (60.3)	
2	24 (9.5)	11 (14.1)	
3	91 (36.1)	20 (25.6)	
Age			0.678
≤59 years	136 (54.0)	40 (51.3)	
≥60 years	116 (46.0)	38 (48.7)	
Fibrosis			0.792
Mild	29 (12.6)	10 (14.5)	
Moderate	83 (36.1)	22 (31.9)	
Advanced	118 (51.3)	37 (53.6)	
Naïve			0.182
Yes	140 (55.6)	50 (64.1)	
No	112 (44.4)	28 (35.9)	

SVR was obtained from 228 (90.5%) of the sample. Among the 252 participants, 55.2% were males, with a mean age of 58.6 years (SD±9.1). In relation to chronic hepatitis C, the genotype 1 was the most prevalent for HCV (54.4%), and 87.4 % of participants presented a moderate to advanced degree of hepatic fibrosis. HIV coinfection was observed in 19 (7.5%) of the participants, and 12 (4.8%) individuals had extrahepatic complications. In the aspects related to the therapeutic regimen, the combination sofosbuvir-daclatasvir was used by 44.4% of the patients, followed by sofosbuvir-daclatasvir-ribavirin, used by 29% of the sample. Concerning the duration of the treatments, 90.5% were carried out for 12 weeks. In addition, it was observed that 16 (6.3%) patients received triple therapy with IP, and 140 (55.6 %) of the subjects were naïve (TABLE 2).

TABLE 2. Descriptive and bivariate analysis of the sustained viral response rate in patients with chronic hepatitis C treated with direct-acting antivirals (n=252).

Variable	Sample description n (%)	SVR n (%)	*P*-value
Sex			0.105
Male	139 (55.2)	122 (87.8)	
Female	113 (44.8)	106 (93.8)	
Age			0.984
≤59 years	136 (54.0)	123 (90.4)	
≥60 years	116 (46.0)	105 (90.5)	
Genotype			0.055
1	137 (54.4)	128 (93.4)	
2	24 (9.5)	23 (95.8)	
3	91 (36.1)	77 (84.6)	
Fibrosis			0.044
Mild	29 (12.6)	29 (100.0)	
Moderate/advanced	201 (87.4)	179 (89.1)	
Genotype/Fibrosis			0.021
G1 G2 / Mild	20 (8.7)	20 (100.0)	
G1 G2/Mod. Advan	128 (51.7)	119 (93.0)	
G3/Mild	9 (3.9)	9 (100.0)	
G3/Mod. Advan	73 (26.1)	60 (82.2)	
Coinfection (HIV)			0.877
Yes	19 (7.5)	17 (89.5)	
No	233 (92.5)	211 (90.6)	
Extra-hepatic criteria			0.681
Yes	12 (4.8)	11 (91.7)	
No	240 (95.2)	217 (90.4)	
Therapeutic Regimen			0.006
Sofo[a]/Dacla[b]	112 (44.4)	108 (96.4)	
Sofo[a]/Dacla[b]/Riba[c]	73 (29.0)	61 (83.6)	
Sofo[a]/Sime[d]	41 (16.3)	34 (82.9)	
Sofo[a]/Sime[d]/Riba[c]; Sofo[a]/Riba[c]; Sofo[a]/Peg[e]/Riba[c]	26 (10.3)	25 (96.2)	
Therapeutic Regimen [#]			0.002
Sofo[a]/Dacla[b]	112 (44.4)	88 (96.7)	
Sofo[a]/Dacla[b]/Riba[c]	73 (29.0)	42 (79.2)	
Sofo[a]/Sime[d]	41 (16.3)	27 (79.4)	
Sofo[a]/Sime[d]/Riba[c]; Sofo[a]/Riba[c]; Sofo[a]/Peg[e]/Riba[c]	26 (10.3)	22 (95.7)	
Duration (weeks)			0.347
12	228 (90.5)	205 (89.9)	
24	24 (9.5)	23 (95.8)	
Previous use of PI[f]			0.536
Yes	16 (6.3)	15 (93.8)	
No	236 (93.7)	213 (90.3)	
Naïve			0.886
Yes	140(55.6)	127 (90.7)	
No	112(44.4)	101 (90.2)	

[a]sofosbuvir; [b]daclatasvir; [c]ribavirina; [d]simeprevir; [e]peginterferon; [f]protease inhibitor. [#]Terapeutic Regimen with moderate/advanced fibrosis.

The bivariate analysis (TABLE 2) showed that SVR was observed in 95.8% of the individuals infected with HCV genotype 2, while it was of 93.4% and 84.6% for infections of HCV 1 and 3, respectively (*P*=0.055). Concerning the cases of liver fibrosis, SVR was found in 100% of participants with mild fibrosis and in 89.1% of those with moderate to advanced fibrosis (*P*=0.044). When we analyzed SVR in relation to HCV genotype and the degree of hepatic fibrosis, SVR was observed in 100% of the patients with mild fibrosis infected by HCV genotypes 1 and 2, while it was of 93% in patients with moderate to advanced fibrosis. SVR rate was of 100% in patients infected by HCV genotype 3 with mild fibrosis, while it was significantly less prevalent in patients with moderate to advanced fibrosis, being observed in of 82.2% of the cases (*P*=0.021). The therapeutic regimen that achieved better SVR results was sofosbuvir-daclatasvir (96.4% recovery), closely followed by sofosbuvir-simeprevir-ribavirin, sofosbuvir-ribavirin, and sofobuvir-peginterferon-ribavirin, with a success rate of 96.2% (*P*=0.006). The association of the therapeutic regimen with the degree of hepatic fibrosis, showed that 100% of SVR rate for the mild fibrosis was observed regardless of the therapeutic regimen. However, SVR rates varied in cases of moderate to advanced fibrosis, with sofosbuvir-daclatasvir scheme reaching a rate of 96.7% and with sofosbuvir-simeprevir-ribavirin, sofosbuvir-ribavirin, sofosbuvir-peginterferon-ribavirin schemes achieving a rate of 95.7% (*P*=0.002).

DISCUSSION

The demographic profile of the population with chronic hepatitis C showed that this pathology is more diagnosed among men with a mean age of 58.6 years (SD±9.1). According to the epidemiological bulletin, since 1999 in Brazil there is a predominance of males aging about 60 years among the confirmed cases of hepatitis C[5]. Chronic hepatitis C discovery is recent, dating back to 1989, and epidemiological findings in relation to the age group shows that the majority of the individuals were suffering the consequences of the disease prior to this date, when the virus was unknown and therefore there was no testing in the blood banks.

In this study, with the use DAAs indicated by the Clinical Protocol and Therapeutic Guidelines of 2015, the SVR rate was of 90.5% in a total of 252 individuals. In previous studies conducted in Europe, SVR rates with the use of DAAs ranged from 58% to 97%[18-24]. In the first report of a real world experience in southern Brazil the authors describe in your results a total of 219 patients a SVR rate of 95% (n=208) in patients with cirrhosis (n=89) the SVR was 92.7% and for genotype 3 with cirrhosis (n=21) the SVR was 87.5%[12]. In addition, this study observed that the rate of SVR was higher among women (93.8%) than among men (87.8%). Although not significant, this dissimilarity may conceivably be due to the different adherence and discipline to the therapeutic regimen between women and men. Among the factors studied, the ones that showed a significant association with SVR were related to the characteristics of the virus, liver damage and therapeutic scheme.

In relation to patients with HCV genotype 3, the treatment success rate was of 84.6%, which is low when compared to SVR between 93% and 95% for HCV genotypes 1 and 3, respectively. European surveys have observed an SVR rate of 79-97% for genotypes 1 and 2 and of 58-97% for genotype 3[18-24]. Also in research carried out in Brazil, we find in Ferreira et al. (2008), results the SVR rates between 88-96% for various schemes interferon-free and the genotype 3 as the hardest to be treated[25]. Studies conducted in

the last decade have shown that HCV genotype 3 progresses faster to cirrhosis and its complications in comparison to HCV genotypes 1 and 2, and it is theoretically associated with a lower survival free of hepatocellular carcinoma. Thus, HCV genotype 3 is considered to be more steatogenic, more frequently leading to metabolic syndrome (viral steatosis)[26,27]. In addition to the worst response to treatment, HCV genotype 3 was also the second most prevalent, with 36.1% of cases, while HCV genotypes 1 and 2 accounted for 54.4% and 9.5% of the cases, respectively. The most prevalent HCV genotypes in Brazil are 1 (65%), 3 (30%) and 2 (5%). Concerning the Brazilian regions, the highest prevalence of HCV genotype 3 is in the South (43.2%), while of HCV genotype 2 in the Central West (11.4%)[28]. The Clinical Protocol and therapeutic guidelines, in force in Brazil in 2019, changed the treatment management to genotype 3, including the antiviral velpatasvir and increasing the treatment duration to 24 weeks in individuals with cirrhosis[6]. Knowing that HCV genotype 3 induces more liver fibrosis and for this reason leads to a lower rate of SVR, it was assumed that this genotype is the most difficult to be treated. The inclusion of new DAAs in the Brazilian therapeutic schemes is urgent, as well as the revision of the antiviral combinations for future treatments in patients did not or will not respond to the current scheme. However, besides the HCV genotype, the degree of hepatic fibrosis was another relevant and significant characteristic for the SVR rate.

We found moderate to advanced hepatic fibrosis in 87.4% of the patients studied. SVR in this group was of 89.1%, while in the group without hepatic injury or mild fibrosis this rate was of 100% (P=0.044). When analyzing the SVR associating the genotype with the degree of hepatic fibrosis, we observed that the degree of mild fibrosis remained at 100% for every HCV genotype, but for infections with genotypes 1 and 2 with moderate to advanced fibrosis it was of 93%, although this difference was not significant. However, for patients with HCV genotype 3 with moderate to advanced fibrosis, SVR rate was 82.2%, and this decrease was significant (P=0.021). Studies show that independently of the HCV genotype, the association of the virus with hepatic fibrosis decreases the effectiveness of the therapy[8]. Also in relation to the European studies, the rate of SVR for patients with hepatic fibrosis was of 58% for HCV genotype 3 and 79% for genotypes 1 and 2, being lower than the success rate for patients without hepatic injury[22,24]. Finding that liver damage directly influences SVR highlights the need to extend the therapeutic access to all patients, regardless of the degree of the hepatic injury. Unfortunately, this hypothesis was not considered as relevant at the time of this study, and the Clinical Protocol and Therapeutic Guidelines of 2015 never considered treating patients without advanced fibrosis. Nevertheless, other studies[29] developed over the years have also shown the efficacy of treating patients that did not present hepatic disease, leading to the revision and release of new Clinical Protocol and Therapeutic Guidelines in 2017 and 2018, enhancing treatment for all infected with HCV[30].

When evaluating the SVR rates in relation to the antiviral combinations used to treat patients with moderate to advanced fibrosis, it was observed that the most commonly used therapeutic regimen was sofosbuvir-daclatasvir, with a success rate of 96.7%, followed by the combinations sofosbuvir-simeprevir-ribavirin, sofosbuvir-ribavirin and sofosbuvir-peginterferon-ribavirin, with a success rate of 95.7%. All other therapeutic regimens achieved SVR rates under 80% (P=0.002). The effectiveness of the therapeutic regimens persisted even when we associate the variable of moderate to advanced fibrosis, considered by previous studies as a criterion of negative influence for therapeutic success[7]. Thus, effectiveness of these schemes was demonstrated even in patients with more serious clinical profiles, fitting to emphasize SVR rates were of 100% for patients with a mild degree of hepatic fibrosis, regardless of the scheme used.

The assessment of the success rate achieved by people with chronic hepatitis C treated in accordance to the Clinical Protocol and Therapeutic Guidelines of 2015 allowed us to provide information on the current status of the treatment strategies, on the detection of HCV carriers and also on strategies for the prevention of the progress of liver disease, enabling improvements in the quality of life of the infected individuals and facilitating the global strategies for the eradication of viral hepatitis as a public health problem until 2030. We believe that even though DAAs act on the virus, they do not eliminate the great influence that host characteristics have on the outcome. In addition, although SVR is used to measure the effectiveness of the treatment, the evolution of liver disease may persist even after the eradication of the virus, not eliminating the risk of clinical decompensation and hepatocellular carcinoma. For this reason, it is wise to take into consideration that HCV genotype 3 infections, with or without mild fibrosis, after liver fibrosis aggravation will have a significantly lower SVR in comparison to carriers of other genotypes regardless of the degree of the fibrosis. Thus, the best perspective of SVR for HCV genotype 3 infections is to receive treatment before the development of cirrhosis, as the natural evolution of this disease is usually slow for those who are only chronic carriers of hepatitis C.

Among the limitations of the study is the comprehensiveness of the CAMMI reference center, as the center receives patients both from the public system and from private health insurance services. This posed an obstacle to verify the SVR outcome, resulting in losses that were withdrawn from the study. We are aware that sample size may influence results, making important differences unnoticed. For this reason, we analyzed the 78 individuals of the losses and the characteristics found were similar to those of the studied sample. However, we reached a number of subjects inferior to what was estimated, because our commitment was to analyze all the individuals treated in accordance to the Clinical Protocol and Therapeutic Guidelines of 2015.

CONCLUSION

It was observed that, in comparison to previous therapeutic regimens, the use of DAAs led to an increased SVR, reaching the totality among patients with mild fibrosis. This study provided information that helps in the treatment, showing that indicating early treatment in patients without hepatic fibrosis and infected HCV genotype 3 can enhance therapeutic effectiveness.

Authors' contribution

Torres AD: elaboration and execution of the research, collection of data, writing of the text and statistical analysis. Sparvoli JMH: data collection and research execution. Sparvoli AC: data collection and research execution. Gonçalves CV: statistical analysis and writing of the text.

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RESUMO – **Contexto** – O manejo e a possibilidade de erradicação da infecção pelo vírus da hepatite C têm sido muito pesquisados nos últimos anos pela importância que representam na saúde pública para a população mundial. A obtenção de dados que auxiliem o enfrentamento dessa patologia resulta na melhor qualidade de vida dos seus portadores. O presente estudo avaliou a efetividade da terapêutica com os antivirais de ação direta, fornecida pelo Ministério da Saúde, através do Protocolo Clínico e Diretrizes Terapêuticas de 2015. **Objetivo** – Avaliar o perfil epidemiológico dos portadores de hepatite C crônica e a taxa de resposta viral sustentada com o uso dos antivirais de ação direta em todos os indivíduos atendidos no Centro de Referência no tratamento da hepatite C crônica do Hospital Universitário da Universidade Federal do Rio Grande. **Métodos** – Estudo observacional retrospectivo/prospectivo com todos os portadores de hepatite C crônica que tiveram seus tratamentos disponibilizados no período de dezembro de 2015 a agosto de 2017 segundo os critérios do Protocolo Clínico e Diretrizes Terapêuticas de 2015. Na primeira fase foram selecionadas e coletadas as variáveis demográficas e clínicas, no banco de dados do centro de referência de todos os indivíduos cadastrados para tratamento para hepatite C e na segunda fase foram coletados dados referentes ao tratamento. A variável desfecho, resposta viral sustentada, foi definida pela carga viral indetectável no exame sanguíneo três meses após o término do tratamento. Foram realizadas as análises descritivas e bivariadas com cálculo do qui quadrado de Pearson e Exato de Fisher, adotando um valor $P \leq 0,05$, no programa SPSS 20. **Resultados** – Dos 252 participantes do estudo 228 (90,5%) obtiveram resposta viral sustentada, sendo 55,2% do sexo masculino com média de idade de 58,6 anos (DP±9,1). O genótipo 1 foi o mais prevalente, presente em 54,4% dos participantes, 87,4% dos estudados apresentavam grau de fibrose hepática moderada/avançada. Após a análise estatística observou-se que os indivíduos com genótipo 3 e fibrose hepática moderada/avançada, tiveram menor taxa de resposta viral sustentada ($P=0,05$ e $P=0,04$ respectivamente). **Conclusão** – Observou-se que com o uso dos antivirais de ação direta as taxas de resposta viral sustentada foram altas, em relação aos esquemas terapêuticos anteriores, podendo chegar à totalidade nos pacientes com fibrose leve. Este estudo mostra que a realização do tratamento precoce, ou seja, de forma antecipada em pacientes sem fibrose hepática e genótipo 3 pode aumentar a taxa de sucesso.

DESCRITORES – Hepatite C crônica. Epidemiologia. Resposta viral sustentada. Antivirais.

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