World Journal of Medical Sciences 8 (3): 238-246, 2013
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2013.8.3.73213

Effectiveness of Antiviral Therapy for Post Transplantation Recurrence of Hepatitis C Virus Genotype 4: A Retrospective Study

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Abstract: Recurrent hepatitis C after liver transplantation is universal. Treating HCV recurrence after successful liver transplantation has a number of major challenges. This study was carried out to assess the effectiveness of antiviral therapy for post transplantation recurrence of HCV genotype 4 infected Egyptian patients. Retrospective cohort study included 20 patients showing significant HCV recurrence post living donor liver transplantation and they completed their antiviral therapy course where 15 patients showed end virological response (EVR). Patients were categorized according to their response to therapy into group I (n=14) non-responders to interferon therapy where 5 patients of them had discontinued Interferon prematurely due to intolerability, Group II (n=6) sustained virological response (SVR) where all the patients had completed their full course of therapy, with no statistically significant difference between both groups regarding acute rejection episodes either before or after therapy (p-value > 0.05), moreover there was no statistically significant difference between treated and untreated group of patients regarding acute rejection episodes. Most of the studied parameters didn't significantly influence the viral response to Interferon regimen used. In conclusion: HCV recurrence following liver transplantation is considerable. Virological response is suboptimal and a premature cessation of therapy due to intolerability of treatment goes with poor response. No significant association detected between both antiviral therapy and graft rejection.

Key words: HCV recurrence · Graft rejection · Side effects · SVR · EVR

INTRODUCTION

Interventions to prevent, improve, or halt HCV recurrence have been evaluated by multiple studies worldwide, however, their results are largely incomparable due to differences in definition of recurrent hepatitis, timing of anti-viral therapy relative to transplantation, type and dose of drugs used and study endpoints [1].

Re-transplantation for recurrent HCV-induced graft failure is a challenging and controversial matter plagued with issues ranging from survival to utilization of a scarce resource and the cost of re-transplantation that carries significant mortality and morbidity risks [2, 3]. In Terrault and Berenguer [4] it was reported that Combination therapy of ribavirin (RBV) and interferon (INF) is superior to monotherapy with INF, but overall SVR rates remain suboptimal. (Higher SVR rates may be achievable with peg-INF plus RBV).

Recently 66.6% sustained virological response (SVR) was reported in patients previously treated with peg-interferon monotherapy and to 69.9% SVR in relapsers previously treated with peginterferon plus ribavirin [5].

Also, it was reported that response of HCV transplant patients to peg- INF RBV can closely mirror the response obtained in the non-transplant population. Tolerance though is unsatisfactory and rejection remains a matter of concern in these patients. [6] Despite almost universal recurrence of HCV after LTx, results of transplantation are relatively good. Modification of immunosuppression, younger organ selection and avoiding steroid pulses for rejection improve the results. Inclusion of combination therapy with interferon and Ribavirin allows for more than 40% SVR [7].

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This study was carried out to evaluate the recurrence of HCV after LDLT in Egyptian patients infected with HCV genotype 4 and to assess the efficacy of combined peg IFN & RBV therapy in them.

MATERIALS AND METHODS

After proper selection of adult patients with end stage liver disease who met the UNOS [8] allocation system status 2B and 3, 128 patients were admitted for living donor liver transplantation unit in Dar Alfouad Hospital, Egypt. During the period between August 2001 and January 2007, liver transplantation was performed followed by immunosuppressive therapy but all the patients showed HCV recuurence. Patients with significant recurrent post transplantation HCV-related liver disease were defined by the elevated transaminases levels, HCV PCR test showing viral replication and confirmatory histology showing the fibrosis stage ≥ 7/18 according to Ishak's modification of Kondell's classification [9] and ≥ A2F2 according to Metavir scoring system. Of the 128 patients studied 113 were proved to be HCV infected patients while the other 15 patients were HBV & HCV infected patients. The patients were followed up on daily basis during hospital stay by clinical, laboratory and imaging techniques where complete blood picture, coagulation profile, C-reactive protein, liver function tests, kidney function tests, Alpha-fetoprotein, HCV RNA PCR, conventional abdominal ultrasonography and color doppler ultrasonographic imaging, HAI index and Stage of fibrosis, was performed. Then the patients were followed up on weekly basis after hospital discharge during the first three months then on monthly basis till the end of the first six months and then every two month by clinical and laboratory assessment. Histological evaluation and grading of rejection was done by calculating rejection activity index according to Banff Schema [10]. Twenty five HCV infected patients died within 3 months after LDLT, 29 patients of those who had survived had shown significant HCV recurrence, only 20 patients of them fulfilled the inclusion criteria for antiviral therapy. Patients were treated with weekly pegylated interferon alfa-2a 180 mcg/wk and weight based ribavirin.

Patient Selection and Data Collection: Patients of our study were selected to meet the UNOS (United Network for Organ Sharing) allocation system status 2B and 3 for listing for liver transplantation. After patient's informed consent form was approved by local Ethics Committees and Health Authorities, Patients were evaluated preoperatively using the Child- Turcotte- Pugh score and Model for End-Stage Liver Disease (MELD) Score [11]. The data was collected from the patients including demographic features of the patients including age and sex, detailed medical history, pre-operative laboratory investigations including During liver transplantation the following data was collected including cold ischemia time, Warm ischemia time, duration of ICU stay in days and duration of hospital stay in days. Post-operative the following data was collected including time till HCV recurrence in days, time till the start of interferon therapy in days, duration of Interferon therapy in weeks, ALT values pretreatment, at the twelfth week of therapy and after two months of EOT. HCV RNA PCR values pre-treatment and at the twelfth week of therapy. The side effects encountered during antiviral therapy also reported.

Immunosuppressant Used:

Steroids:

Solumedrol (*Methylprednisoone IV*): Intraoperative 10mg/kg single dose.

D1-D3--------Solumedrol, 1MG/KG single dose
D4-D6-------- Solumedrol, ½ MG/KG single dose
D7 ---------- Solumedrol, 1/3 MG/KG single dose

Oral Prednisolone:

D8--- Till end of 1ST month------ Oral Hostacortin 0.3 MG/KG
2ND month --------- Oral Hostacortin 0.2 MG/KG
3RD Month ---------- Oral Hostacortin 0.1 MG/KG

Calcneurin inhibitors

FK (tacrolimus), Neoral (cyclosporine):

FK: Starts at night of D1, accepted level 2-3 weeks 10-15 ng/ml, 2 month 10-12 ng/ml, Later 8-10 ng/ml.

Neoral (Cyclosporine): Used when FK cannot be used due to severe side effects (especially neurological). Trough level 250-350 ng/ml decreased 50 ng/ml every 2w until 100-250 ng/ml. Usually the patient requires additional immunosuppression with Calcineurin inhibitors as:

Celecept (Mycophenolate Mofitel): Dose up to 3 gm/day In cases of side effects of Calcineurin inhibitors (neurotoxicity or nephrotoxicity) we add either: Rapamune - Rapamycin - Syrolimus or Evrolimus/ Certican (Antineoplastic better in HCC) together with Cellcept.

In case of renal impairment preoperative
Simulect (Basaliximab) we give doses at D0, D4, then start the Calcineurin inhibitor after the second dose.

Statistical Methods: Data were statistically described in terms of range; mean ± standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

A retrospective study conducted on 20 patients showed significant recurrence of an active HCV related liver disease after LDLT, where nine patients of them were found to be not indicated for Interferon therapy. The other twenty patients fulfilled the criteria of Interferon therapy and completed their antiviral therapy and their data is represented in (Table 1). Side effects from antiviral therapy in our studied group were documented. As regards virological response; 3 patients (15%) were primary non responders, 2 patients (10%) showed acute rejection and the other 15 patients (75%) were early responders then on following up the 15 early responder patients during their antiviral therapy course six patients (40%) achieved SVR, representing a SVR rate of 30% of the whole treated group (Figure 1) and the rest nine patients (60%) turned to be non-responders to antiviral therapy. According to their response to therapy they were categorized into two groups (Table 2), group I (n=14) patients non-responders to antiviral therapy, where 10 (71.4%) patients had discontinued their antiviral therapy, 5 (35.7%) patients prematurely discontinued treatment and 5 patients (35.7%) showed no EVR, while 4 patients (28.5%) completed their scheduled treatment and revealed to be non-responders to Interferon therapy and group (II) (n=6) patients sustained virological responders to antiviral therapy, all patients of group (II) had complete their scheduled treatment course, where there is no statistically significant relationship between the virological response and premature discontinuation of antiviral therapy with a p-value=0.13, with no statistically significant difference between both groups regarding age and sex distribution or therapy duration. Clinical, laboratory and graft parameters were revised and compared between both groups. Pre-therapy acute rejection episodes were reported in 7 cases, 4 cases (33.3%) revealed to be NR to Interferon therapy while 3 cases (50%) revealed to be of the SVR group with no statistically significant difference between both groups with a p-value=0.62. Pre-antiviral therapy rejection episodes were all managed with Pulse steroid. After start of Interferon therapy acute rejection was reported in 6 cases (33.3%), (4 during treatment and 2 after end of treatment). The majority of acute rejection cases were non responders but there is no statistically significant difference with a p-value=0.6 between both groups regarding episodes of acute rejection after Interferon therapy where five cases (35.7%) of the non-responders group had experienced acute rejection while only one case (16.7%) of the SVR group had acute rejection. Available data for the 8 cases with recurrent HCV, who were not candidates for antiviral therapy were revised and showed that there is no statistically significant difference between treated and untreated group of patients regarding the incidence of acute rejection with a p-value of 0.75.

It was also reported that the viral load measured by PCR is greater in non-responders group than that of SVR group but this difference is not statistically significant with a p-value=0.45. A total of 15 patients of the whole 20 patients who had received antiviral therapy had achieved EVR (75%) where EVR was detected in 9 patients of the non-responders group while the EVR was reported in all patients of the SVR group with no statistically significant difference between both groups where the p-value=0.73, which indicates that SVR was not influenced by the pattern of EVR whether rapid or slow response. Therapy was discontinued in 5 patients (35.7%) of the non-responders group at a median of 16 weeks due to side effects experienced by the patients. While another 5 patients showed lack of primary response.

Table 1: Descriptive parameters of patients whom comleted the treatment

Group completed antiviral therapy (n=18)					
Sex: M/F: 19/1					
Age: mean: 48.5±4.64					
Parameter	Mean	SD±	Parameter	Mean	SD±
Pre-operative					
Alphafetoprotein ng/ml	26.2	43.9	PCR IU/ml	706000	976000
Post-operative					
Time till recurrence (days)	410	348	Time till INF therapy (days)	598	409
Pre-treatment ALT (IU/L)	130.5	40.9	Pre-treatment PCR (IU/ml)	2567000	4567000
ALT at week 12 of therapy (IU/L)	97.6	54.5	Duration of therapy (weeks)	34.9	17.7
ALT after 2 months of EOT (IU/L)	48	19.6	PCR at week 12 weeks (IU/ml)	340000	630000

Table 2: Comparison between responders and non responders

		Virological response				
		Non responder (n=14) Males= 11		SVR (n=6) Males=6		
		Mean	SD	Mean	SD	P-value
Age		48.3	3.8	49.5	4.9	0.86
Parameters	Variables	Number/mean	% -SD	Number /mean	%- SD	p-value
Child score	B	3	25	0	0	0.529
	C	9	75	6	100	
Hepatic focal lesions	Yes	3	25	1	16.7	0.99
	No	9	75	5	83.3	
ALT level	Pre-therapy	126	± 35	147	± 54	0.437
	At week 12	116	± 63	76	± 31	0.149
Viral load	Pre-therapy	2919000	± 1112000	890000	± 543000	0.456
Liver Biopsy% at diagnosis	Stage	2.08	± 1.56	1.33	± 1.03	0.131
	HAI	7.9	± 2.43	8.1	± 2.83	0.843
Hospital stay (days)	ICU	9	± 3.4	6.1	± 2.3	0.067
	Non-ICU	47.2	± 32.2	25.1	± 6.1	0.180
Graft characters	Cold ischemia	110.8	±12.4	106.7	± 12.1	0.589
	Warm ischemia	31.7	±6.2	29.2	± 5.8	0.325
	GRWR	0.86	±0.08	0.81	± 0.12	0.239
Onset of therapy	Months from surgery	13.5	± 12.5	13.7	± 11	0.867
Dose reduction*	No	4	28.6	5	83.3	0.13
	Yes	10	71.4	1	16.7	
Immunosuppressant	Cyclosporine	5	41.7%	2	33.3	0.57
	FK 506	7	58.3	4	66.7	
Pre therapy rejection episodes**	No	8	66.7%	3	50	0.62
	Yes	4	33.3	3	50	
Biochemical response	No	6	50	0	0	0.13
	Yes	6	50	6	100	

Table representing virological response in relation to different clinical and laboratory parameters

*Dose reduction means receiving less than 80% of the totally specified doses

** Rejection episodes pre antiviral therapy were all managed with pulse steroids

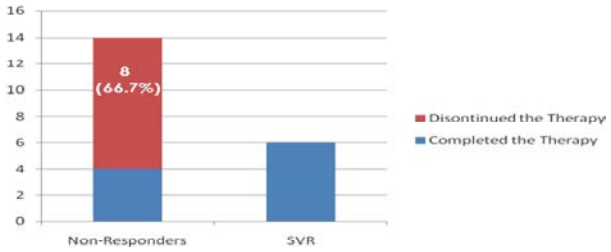

Fig. 1: Virological response in relation to premature discontinuation of antiviral therapy

Mortality was reported in 3 cases, one patient due to severe fibrosing cholestatic hepatitis, the other due to recurrent HCV infection with graft failure and the third patient was due to biliary complications. Post operative time till death was 155, 755 and 1812 days, respectively.

DISCUSSION

Recurrence of HCV infection in the transplanted organ is universal and the consequences are still being unraveled [12-15]. The natural history of recurrent HCV is quite variable and ranges from rapidly progressive liver failure within months of transplantation to a more benign hepatitis, which can slowly progress over years [12].

Patients were defined to be with significant recurrent post transplantation HCV-related liver disease by the elevated transaminases levels, HCV PCR test showing viral replication and confirmatory histology showing the fibrosis stage ≥ 7/18 according to Ishak's modification of Kondell's classification [13] and ≥ A2F2 according to Metavir scoring system. In our studied group of transplanted patients (n=128) only 29 (33%) patients showed significant recurrence of an active HCV related liver disease.

Hepatic regeneration may promote viral replication and accelerate recurrent hepatitis C with the risk of eventual graft failure. Viral replication is dependent upon translation of a large polyprotien mediated by the internal ribosomal entry site, the latter is hyperactive in growing cells during mitotic phases [14, 15]. Antivirals have been used in an attempt to modify the course of HCV-disease and it is believed that sustained viral eradication leads in most cases to histologic improvement thus preventing cirrhosis and loss of the graft [16, 17].

It is generally believed that changes in the circulating HCV quasispecies and in the gene expression profiles of the graft might influence response to treatment after liver trasnplantation [18]. This imposed a growing interest to investigate the pattern of viral response in these cases.

In our studied group of patients 20 patients with HAI index of 7.85±2.46 and with a fibrosis stage of 1.6±1.3 had completed a course of antiviral therapy,15 patients (75%) showed early virological response which goes with what was reported by Feliu *et al.* [18], where they reported a values of 73%, while five patients were primary non-responders. On continuing the antiviral therapy course six patients (30%) showed sustained virological responce which goes with the percent reported in other studies 28% [19] and 26.7% [20] while other studies showed a higher percent of SVR 56% this may be attributed to difference in the studied population [21]. While the rest of the patients turned to be non-responders. The antiviral therapy was discontinued prematurely for five patients who had experienced intolerable side effects. There was no statistically significant difference between the mean HAI index value of the non-responders group (7.9 ±2.43) and that of the SVR group (8.1±2.83). The same goes to the fibrosis stage where there is no statistically significant difference between the mean fibrosis stage of the non-responders group (2.08 ± 1.56) and that of the SVR group (1.33± 1.03).

There is no statistically significant difference between both responders and non responders groups regarding the patients demographics, laboratory results, Child score, ALT level, liver biopsy results, radiological investigations results and graft characters, hospital stay and graft characteristics. Even the mean time of onset of therapy had no significant impact on virological response, this goes with what was reported in Fernandez *et al*. [22]. Regarding the fibrosis stage of the 20 patients pretherapy was 1.6±1.3 to become 2.08 ± 1.56 in non-responders and 1.33 ± 1.03 in sustained virological responders after therapy with no statistically significant difference between both groups with a p-value=0.13, denoting an insignificant effect of pre-treatment fibrosis stage on the virological response, this goes with the results of other studies Firpi *et al*. [23] and Menon *et al*. [24]. Several attempts have been made to create a prediction model for risk assessment in HCV transplanted patients. These models have not been able to identify a cohort of HCV patients at highest risk for poor outcomes in terms of severe recurrent disease, progression to cirrhosis and mortality.

Berenguer *et al.* [7], reported that pre therapy viral load doesn't have a significant impact on viral response, this goes with what was reported in our study, although the mean viral load in the non responder group was higher than sustained responders (2919x1000 and 890x1000 IU/ml respectively) yet the difference was not statistically significant.

In our study 15 patients had an EVR & SVR was achieved in 6 of them 40% of cases, while the other 60% of cases failed to achieve a concomitant SVR which doesn't go with what was reported by other studies by Berenguer *et al*. [7] and Dumortier *et al*. [25]. This difference in reports may be due to the genotypic difference of the virus or different host immune status.

In our study 10 of the 20 patients (50%) were withdrawn from treatment at a median of 16 weeks leading to significant derangement of SVR which goes with results of Marroni CA. [26] where it was reported that dose reduction and interruption of therapy occurs in 30 to

60% by side effects. SVR was achieved in none of the patients who prematurely discontinued therapy compared to 60% (n = 6/10) of those who finished 48 weeks of treatment (P value 0.013). Picciotto *et al.* [19], reported that premature discontinuation of antiviral therapy had a significant impact on SVR with P value <0.01. While in another study done on 67 patients, SVR was achieved in 29.5% of the patients who discontinued therapy at a median of 26 weeks from initiation compared to 35% of those who finished the established 48 weeks of treatment. The difference in results may be due to the different timing when therapy was discontinued.

55% of our patients needed dose reductions (< 80% of both their total PEG-INF and ribavirin doses) (n = 11). Of that group only one patient (9 %) achieved SVR compared to 55.5% (5 patients) achieving SVR in those who received full dose regimens (p-value=0.131). In a larger study Picciotto *et al*. [19], 61.8% of the patients needed dose reductions and 23.5% compared to 42.9% of the patients who didn't need dose reductions achieved SVR (P-value= 0.15). Marroni CA. [26] reported that More efficacious and better tolerable antiviral therapies are needed although Combination therapy with PEG INF and ribavirin showed the better results.

Our results goes with what was reported by Berenguer [27] where it was reported that inferior to the substantial improvements made in HCV treatment in the non-immune compromised host, peg-interferon/ribavirin results in the liver transplant setting have been less impressive. With standard interferon ribavirin combination SVR is as low as 22% of treated transplant recipients [27], which is significantly lower to that reported in the immune competent population. With pegylated interferon combination therapy SVR may reach up to 33-47% [28, 29]. Low SVR rates may be due to high viral load, prevalence of genotype 1, low tolerability with difficulties in achieving full-dose treatment, high prevalence of prior non responders and impaired immune function [30]. In several studies, a beneficial effect of SVR on liver histology has been reported [31-33] while a positive impact on patient survival has never been demonstrated. In almost all previous studies a high rate of side effects was observed and dose reduction or interruption of treatment was necessary in up to 92% of patients [31].

In our studied group most of the patients experienced many side effects of antiviral therapy and the mortality was reported in 3 cases. Post operative time till death was 155,755 and 1812 days respectively. This goes with what was reported by Sharma *et al.* [32], In our study 7 patients had developed neutropenia during their antiviral therapy, disabling only one patient from completing his antiviral therapy course. Our studied group of patients had additional risk factors for depression which is attributed to direct effects of HCV and immunosuppressive agents and indirect effects of liver transplantation. Interferon therapy may additionally precipitate depression in such patients [33]. In fact none of our patients exhibited depression to the extent of discontinuation of therapy.

Virological response, especially SVR, translates into markedly improved long-term patient outcomes in patients transplanted for hepatitis C [34]. Our study showed that 6 patients (30 %) experienced acute rejection (ACR) after starting antiviral therapy. Three uncontrolled trials of pegylated IFN and ribavirin have yielded conflicting results with no cases of ACR in two studies [35, 36] and a rate of 25% of ACR in Dumortier *et al*. [25]. Agreeing with our results, Berenguer M [27] reported that acute rejection had no significant effect on SVR. It has been suggested that IFN therapy may increase risk of organ rejection, relatively lower rates of rejection occur during combination therapy. In uncontrolled trials of IFN and RBV combination therapy, the rate of acute rejection varies from 0 to 35% and the rate of chronic rejection varies from 0 to 4% [37, 38]. This may be attributed to different regimens of antivirals and immunosuppressant used, different viral genotypes, small number of the study groups, different tolerability in the studied groups and different protocols for the use of liver biopsy. Histological difficulty in distinguishing rejection from ongoing hepatitis [39] and the lack of biopsies performed during and at the end of therapy limit the interpretation of these data. In our study 30 % acute rejection were encountered after starting treatment (20 % on treatment, 10% following treatment) in addition to 10% chronic rejection. On the other hand, 7 cases (35%) developed acute rejection episodes before starting therapy (4 non responders and 3 sustained responders), of these, 3 achieved SVR while 3 of those who didn't experience any rejection episodes, turned to be non responders with no statistically significant difference between both groups.

Cyclosporin has been reported to inhibit HCV replication *in vitro* [40]. In a retrospective study Firpi *et al*. [23] suggested that cyclosporin compared to tacrolimus-based immunosuppression increases the chance of achieving SVR with anti-viral therapy. This intriguing finding needs to be confirmed in a prospective randomized trial [41]. Cyclosporine appears to have antiviral effects against many other viral agents *in vitro*. For the immunosuppression activity, tacrolimus binds to FK-binding protein and cyclosporine binds cyclophilins; the latter have been shown to mediate HCV replication by

activating NS5B. Accordingly, Nakagawa *et al*. [40] reported that cyclosporine alone has been shown to inhibit HCV replication in vitro. These effects have been difficult to demonstrate *in vivo* manifested by little effect on HCV RNA levels [42]. However, it was interesting to note that HCV RNA levels did not rise with immunosuppression. The results of several recent studies comparing the effects of cyclosporine versus tacrolimus in transplanted patients with HCV infection have not provided any significant data, likely due to the short duration of follow-up because graft and patient survival rates tend to fall off [43]. More studies are required to delineate advantages to immunosuppressive regimens. Our study shows that there is no significant impact of the calcineurin inhibitor used whether cyclosporine or tacrolimus on the virological response.55% (n=11) of our studied group received tacrolimus while, 35 % (n = 7) received cyclosporin. Regarding SVR, 4 patients of those receiving tacrolimus achieved SVR (36.4%) while 2 patients of those receiving cyclosporine achieved SVR (28.6%) with no statistically significant difference (p-value= 0.57). Similarly, results published by Berenguer *et al*. [27] showed that SVR was achieved in 28.2% of the tacrolimus group and 39% of the cyclosporine group While in Picciotto *et al*. [19] it was reported that Inclusion of combination therapy with interferon and Ribavirin after liver transplantation allows for more than 40% SVR.

CONCLUSION

Our study showed that HCV recurrence following liver transplantation is considerable. Virological response is suboptimal and a premature cessation of therapy goes with such a poor response. Therapy does not induce more rejection episodes in our patients and even pre-therapy rejection does not influence the pattern of virological response. Most of the studied parameters did not significantly influence viral response. Alternatively, a better definition of factors linked to a favourable outcome and strategies directed to ameliorate treatment toxicity may improve current results of the antiviral therapy for HCV infection in the post transplantation setting.

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