Triple Combination with Direct Acting Antivirals in the Treatment of Hepatitis C Does not Prolong the QT Interval

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ABSTRACT

Aims: Antiviral drugs are considered as potentially cardiotoxic, due to prolongation of QT interval which may affect incidence of severe ventricular arrhythmias. The main aim of this retrospective study was to assess the influence of treatment by three antiviral drugs on QT interval and to find patients who are at an increased risk of developing malignant ventricular arrhythmias.

Methods: The study included 23 patients (14 men, 9 women) who were treated with a combination of interferon alpha, ribavirin, and an NS3/4A protease inhibitor. The parameters from the 12 leads electrocardiograms were evaluated before treatment, and then 3 ± 1 and 6 ± 1 months after treatment.

Results: Heart rate (HR) 69 ± 12 / min and corrected QT interval (QTc) 412 ± 35 ms were obtained before the treatment and there was not observed a significant prolongation of intervals after 3 months (HR 72 ± 11 / min, QTc 412 ± 33 ms) and after 6 months (HR 64 ± 12 / min, QTc 405 ± 28 ms) respectively. In total QTc interval was prolonged from the baseline in 53% and in 43% of the patients 3 months respectively 6 months after treatment. A QTc prolongation over of 450 ms and new treatment-related repolarization change was noted in 1 (4%) patient.

Conclusion: The study demonstrates that a combination therapy of 3 antiviral drugs does not significantly prolong the QTc interval and does not cause severe pathological changes on the ECG. Patients undergoing this treatment are not at risk of developing heart disease as an undesirable side effect.

KEYWORDS

hepatitis C virus; HCV; QT interval; NS3/4A protease inhibitor; DAAs

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INTRODUCTION

The Hepatitis C virus (HCV) affects about 130–170 million people worldwide, which is approximately 3% of the population (1). About 55–85% of affected patients will develop chronic hepatitis, 30% cirrhosis and 2% hepatocarcinoma (2). Chronic HCV infection is one of the leading causes of liver-related death and it is the primary reason for having a liver transplant in many countries. The goal of HCV treatment is the eradication of the virus, which is confirmed in the laboratory as undetectable viral RNA 12 weeks after ceasing treatment. The established treatment strategy contains interferon alfa and ribavirin. There are several documented clinical cases which demonstrate dilated cardiomyopathy, conduction system disturbances and pericarditis (3–5). Otherwise, cardiotoxicity of a combination INF-alfa and ribavirin is rare and may be used safely in patients without cardiac disease (6). However, this strategy is less effective in genotypes 1 and 4. In 2011 were introduced NS3/4A protease inhibitors, also known as direct-acting antivirals (DAAs), that target different steps in the HCV life cycle – boceprevir, telaprevir and later a second-generation drug simeprevir (7–9). NS3/4A inhibitors are given in triple combination with interferon alfa and ribavirin. This strategy is more effective in sustained viral response, but also provides more interactions and side effects.

An important potential drugs side effect includes abnormalities in cardiac repolarization resulting in QT prolongation. QT interval prolongation is associated with an increased risk of life-threatening polymorphic ventricular tachycardias called Torsades de Pointes (TdP), which can lead to ventricular fibrillation and sudden cardiac death (10). The risk of developing ventricular tachycardia increases especially if the prolongation of the QT interval is simultaneously affected by other drugs or there is an inherited disease that primarily prolongs the QT interval, the risk also increases in the case of hypokalemia and bradycardia (11). Some drugs as listed at https://crediblemeds.org, especially antibiotics and antimycotics can prolong the QT interval and may contribute to the development of TdP, similar effect cannot be excluded with newly introduced antiviral drugs.

The main aim of this study was to assess the side effects of a triple antiviral combination on the QTc interval prolongation and to find patients who are at an increased risk of developing malignant ventricular tachyarrhythmias.

MATERIALS AND METHODS

TRIAL DESIGN

We conducted a single-center retrospective trial to evaluate the safety of the three antiviral drugs used in treating patients with previously diagnosed hepatitis C. Initiation of the treatment and combination of antiviral drugs were indicated by an infectious disease specialist according to established guidelines, a control group of patients treated with a placebo was not added. The study conformed to the ethical standard set out by the Declaration of Helsinki. The primary objective of our study was to look into the prolongation of the QTc interval, as a result of the triple combination of antiviral drugs, and the possible development of ventricular tachyarrhythmias. Secondary objectives included determining the PQ and QRS interval and the evaluation of new ECG changes as result of the potential cardiotoxic effects of the antivirals.

PATIENTS AND TREATMENT REGIMES

Antiviral therapy was started in patients with a confirmed diagnosis of hepatitis C in the replication phase. All patients had an established genotype, and we included patients who had not yet been treated with antivirals or who had failed with previous antiviral treatment. Patients were administered with pegylated interferon alfa-2a at a dose of 180 micrograms subcutaneously once a week, and ribavirin at a dose of 1000 mg or 1200 mg daily. The third drug given in the triple combination regimen varied with three possibilities with telaprevir at a dose of 750 mg three times daily or boceprevir at a dose of 800 mg three times daily or simeprevir at a dose of 150 mg once daily. During treatment the patients underwent regular outpatient check-ups with monitoring of the HCV RNA levels in the blood, as well as mineral levels, blood count and liver tests and abdominal ultrasound exams. By default, the therapy was terminated after 24 weeks, with a good treatment effect and with an undetectable level of HCV RNA in the blood, the treatment was terminated earlier.

ECG MEASUREMENT AND ASSESSMENT

Standard 12-leads ECGs were recorded in each patient who was enrolled in our study under the standard conditions in an ECG lab during the outpatient check-ups and were submitted to the hospital database. Any newly detected pathology on the 12 lead ECG was discussed with a specialist in internal medicine. We evaluated the ECG recordings before the initiation of triple combination antiviral drugs, then at 3±1 and 6±1 months after starting treatment. After the patients ended their treatments, the ECG recordings were digitally collected and evaluated with the ImageJ program, which was recommended as a program suitable for processing graphic images by the Nature Methods journal (12). ImageJ makes it possible to evaluate the time duration of the individual ECG intervals with an accuracy of up to a tenth of a millisecond. The QTc interval was measured in three leads (lead II, V1 and V5) in three consecutive cardiac cycles. The longest QTc interval obtained from each beat was then averaged and used for the subsequent evaluation. The end of the T wave was considered as being the contact point with the isoelectric line or if the end of the T wave was unclear, we considered the end as the contact point of isoelectric line in tangent to the steepest part of the descending limb of the T wave. Concerning the RR interval, we considered the variability between the QRS complexes during the previous and current cycle. In the case of atrial fibrillation, the measurement was performed three times and the average of the measurements was chosen as the resulting RR and QT interval. The Bazett and Fridericia formulas were chosen to calculate QTc interval (Fig. 1). Other ECG parameters were also evaluated: the length of the PR

interval and the QRS complex, and any changes throughout the ECG during the treatment were searched for.

$$\mathrm{QTcB} = \frac{QT}{\sqrt{\mathrm{RR}}} \qquad \mathrm{QTcFri} = \frac{QT}{\sqrt[3]{RR}}$$

Fig. 1 Corrected QT interval according to Bazett formula – QTcB. Corrected QT interval according to Fridericia formula – QTcFri.

STATISTICAL ANALYSIS

After the creation of the patient database, the data were statistically processed. Demographic data are reported as mean and standard deviation. We compared the differences between the ECG before the initiation of treatment with the ECG taken after three and six months, respectively. Due to the negative normality test, we used the non-parametric paired Wilcoxon test. A p value < 0.05 is considered as being statistically significant.

RESULTS

DEMOGRAPHIC DATA AND FOLLOW-UP

A total of 23 patients with confirmed hepatitis C in the replication phase who underwent treatment with triple combination antiviral drugs between October 2012 and April 2016 were included in the study. The average age of the patient group was 45 ± 10 years, and 15 (65%) were predominantly male. Genotype 1b was determined in 22 patients, genotype 1a was present only in one patient. In addition, one patient was found to have hepatitis B at that time. The most administered NS3/4A protease inhibitor was telaprevir, which was used in 14 (61%) patients, boceprevir and simeprevir were administered in 3 (13%) and 6 (26%) patients, respectively. The study is consisted of a relatively healthy group of patients. Arterial hypertension was the most common comorbidity, which was present in 5 individuals; type 2 diabetes mellitus, atrial fibrillation, and bronchial asthma were each present separately among three patients in the study. Heart failure and history of myocardial infarction were not detected in any of the patients (Table 1).

Tab. 1 Characteristics of the patients at baseline.

Characteristic	Number	Percentage
Age (years)	45 ± 10	
Female sex	8	35%
Hepatitis C virus genotype 1a	1	4%
Hepatitis C virus genotype 1b	22	96%
Telaprevir	14	61%
Boceprevir	3	13%
Simeprevir	6	26%
Arterial hypertension	5	22%
Diabetes mellitus type 2	1	4%
Atrial fibrillation	1	4%
History of heart failure or myocardial infarction	0	0%
Bronchial asthma	1	4%
Concomitant Hepatitis B	1	4%

PRIMARY OUTCOMES

Before the initiation of treatment with the triple combination of antiviral drugs, the QTc interval according to the Bazett formula was 412 ± 35 ms and the QTc length according to the Fridericia formula was 403 ± 20 ms. During the observed period, there was no statistically significant prolongation of the QTc interval after 3 months and the corrected QT interval according to the Bazett formula (QTcB) = 412 ± 33 ms, p = 0.99; QTcFri = 401 ± 31 ms, p = 0.71. A prolongation of the QTc interval against the initial values was not observed even after 6 months of treatment, QTcB = 405 ± 28 ms, p = 0.87; QTcFri 401 ± 23 ms, p = 0.84 (Fig. 2 and Fig. 3). A treatment-related prolongation of the QTc interval above 450 ms was noted in 1 (4%) patient. No patients had had any polymorphic ventricular tachycardias or any other ventricular arrhythmias or sudden cardiac deaths during the follow-up examinations. None of the patients developed any symptoms of cardiovascular disease. During the follow-up period, 2 patients were using medications which are known to prolong the QT interval and those were indapamide and sertraline.

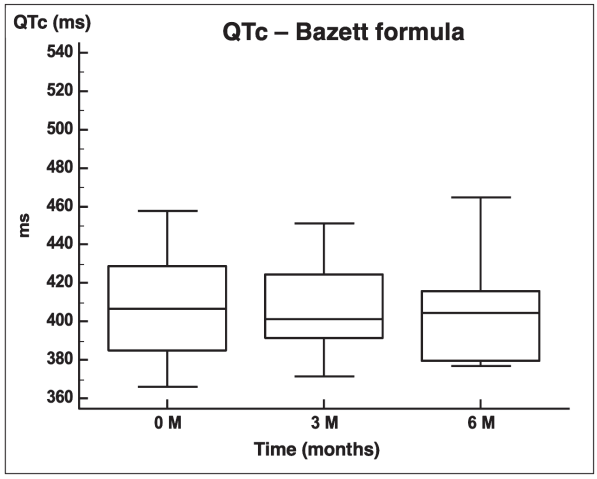

Fig. 2 Length of the QTc interval according to Bazett formula for 6 months follow-up. The middle line of the box plot indicates mean, the upper and lower line of the box plot indicate standard deviation, and the end lines indicate 10th and 90th percentiles.
QTc = corrected QT interval, ms = milliseconds.

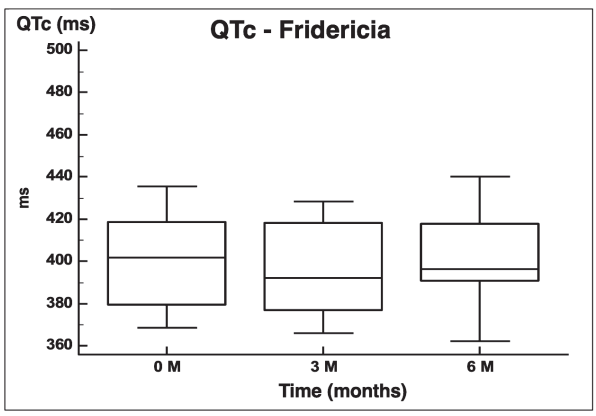

Fig. 3 Length of the QTc interval according to Fridericia formula for 6 months follow-up. The middle line of the box plot indicates mean, the upper and lower line of the box plot indicate mean standard deviation, and the end lines indicate 10th and 90th percentiles.
QTc = corrected QT interval, ms = milliseconds.

SECONDARY OUTCOMES

During the observed period, no statistically significant changes in heart rate were recorded.

Initially it was 69 ± 12 beats per minute (bmp), then after 3 months it was 72 ± 11 bpm, p = 0.29; and after 6 months it was 64 ± 12 bpm, p = 0.84. The PQ interval remained statistically unchanged throughout the follow-up period at 171 ± 21 ms, 178 ± 22 ms, p = 0.20; 174 ± 11 ms, p = 0.38; and the QRS interval did not differ significantly at 106 ± 19 ms, 102 ± 24 ms, p = 0.29; 100 ± 14 ms, p = 0.21 (Table 2). The prolongation of the PQ interval above 200 ms was detected in one patient, but it was not clinically symptomatic, and no syncope or signs of heart failure were recorded. Atrial fibrillation was present in one patient and persisted throughout the study period. An asymptomatic occurrence of left bundle branch block was noted in one patient without any progression of ventricular conduction during the follow-up examination. Even before the initiation of the treatment, incomplete right bundle branch block was detected in 3 patients, left anterior hemiblock in 1 patient, incomplete right bundle branch block and left anterior hemiblock were simultaneously present in one patient throughout treatment (Table 3). No significant changes in the ST segments and T waves were recorded during the monitored period.

DISCUSSION

In this population of patients, treatment with a triple combination of antiviral drugs – pegylated interferon alfa, ribavirin and an NS3/4A protease inhibitor – was not found to significantly prolong the QTc interval and did not cause any significant pathological changes on the ECG. A QTc interval prolongation over 450 ms was detected in one patient, which can increase the risk of developing TdP. However, during the observed period, malignant ventricular tachyarrhythmias were not documented in any patient, nor were their clinical symptoms detected such as syncope, palpitations, or sudden cardiac death.

None of the patients developed any signs of heart failure and there were no statistically significant prolongations of the PQ and QRS intervals, yet one patient had a PQ interval longer than 200 ms at the end of the study period, which was asymptomatic. According to the results of our study, we consider treatment with a triple combination of antiviral drugs to be safe and patients undergoing this treatment are not at risk of developing heart disease as an undesirable side effect.

Tab. 2 Secondary ECG parameters during treatment. bpm = beats per minute, ms = milliseconds.

ECG parameter	Before treatment	3 months after treatment	P value	6 months after treatment	P value
Heart rate (bpm)	69 ± 12	72 ± 11	0.29	64 ± 12	0.84
PQ interval (ms)	171 ± 21	178 ± 22	0.20	174 ± 11	0.38
QRS complex (ms)	106 ± 19	102 ± 24	0.29	100 ± 14	0.21
QT interval (ms)	386 ± 32	381 ± 38	0.31	393 ± 30	0.33

Tab. 3 Persisted ECG findings during follow-up. LBBB = left bundle branch block, iRBBB = incomplete right bundle branch block, LAH = left anterior hemiblock.

ECG findings	Number of patients	Percentage
Atrial fibrillation	1	4%
LBBB	1	4%
iRBBB	3	13%
LAH	1	4%
iRBBB + LAH	1	4%

TREATMENT SUCCESS

The HCV RNA was detected in all patients before starting treatment. Ten patients underwent previously unsuccessful antiviral treatment with a double combination of antivirals (interferon alfa and ribavirin). Treatment with a triple combination of antivirals was successful in 16 patients who did not have detectable viral RNA in their blood at the end of the monitored period. Eight patients had elevated aminotransferase levels before treatment and 4 of them regained normal aminotransferase levels during treatment.

SIDE EFFECTS OF THE TRIPLE THERAPY REGIMES

Successful treatment of HCV infection has undeniable long-term benefits with respect to reducing morbidity and mortality, and the virological response have been recently increased by the introduction of DAAs to the antiviral treatment regimens. The most common side effects with boceprevir are anemia, neutropenia and dysgeusia (altered taste sensation). The most common side effects of telaprevir include anemia, rash, pruritus, and anorectal discomfort (13). Other common side effects of telaprevir treatment include skin toxicity, most often manifesting as eczematous lesions or nonscaling macular lesions. Most toxoallergic exanthems after telaprevir treatment resolve with corticosteroids, but some are refractory to this treatment and the discontinuation of antiviral treatment is therefore something to be considered (14). Another study in patients with an advanced stage of hepatitis C infection and simultaneously diagnosed liver cirrhosis, showed relatively frequent side effects in up to 50% of patients, which led to the worsening of liver function, severe infections, and 2% of the patients died during the study period (15). The first generation DAAs boceprevir and telaprevir, are being replaced by second generation DAAs, such as simeprevir, which lead to higher rates of virologic response, are better tolerated and have lower pill burden,

but are very costly (16). In simeprevir, a second generation AAD, the side effects were generally mild, with mainly headaches, fatigue, and nausea. Only 2% of the patients presented with serious adverse events (2). It is known from the literature that the most common side effects of DAAs are hematological, skin exanthemas and problems with the gastrointestinal tract. So far, only a few clinical cases have been documented with dilated cardiomyopathy, cardiac conduction system disturbances and pericarditis with the combination of pegylated interferon alpha and ribavirin (3–5). There have not been any published cases of significant damage to the cardiovascular system following the addition of DAAs to the standard dual combination antivirals. In addition, no major cardiac events, electrocardiographic or echocardiographic changes were recorded among patients treated with DAAs during regular follow-up (17). In our study, we were not able to confirm any cardiotoxic effects of the triple combination antivirals, and we can consider them safe for the cardiovascular system. However, the drug–drug interactions constitute another concern.

Boceprevir and telaprevir are metabolized by Cyp3A pathway and both molecules are inhibitors of Cyp3A4. Therefore, DAAs are involved in the metabolism of many drugs and, when used simultaneously, the levels of boceprevir and telaprevir may be increased, or their use may elevate the serum levels of other drugs. Interactions should therefore be checked when prescribing DAAs, and increased attention is required especially with drugs such as statins, antidepressants, anticonvulsants, analgesics, and sedatives (13). However, the patients included in the study did not receive the mentioned medication. Their chronic medication was checked, if it was affected by the antiviral treatment, but no interactions were found. Therefore, the levels of administered drugs were not routinely determined.

QTC INTERVAL PROLONGATION AND MEASUREMENT

The QT interval approximates the time interval between the start of depolarization and the end of repolarization of the ventricular myocardium. Drug induced prolongation of the QT interval is associated with an increased risk for ventricular arrhythmias such as TdP and may lead to sudden cardiac death. The association between treatment related QT interval prolongation and proarrhythmic cardiac toxicity has been repeatedly reported and therefore the assessment of QT interval prolongation, has become an integral part of preclinical and clinical drug studies (18). However, a standardized assessment of QT prolongation is still problematic. First, there is a major problem with measuring due to the morphological abnormalities of the T wave. The QT interval could be measured from the beginning of the Q wave until the T wave returns to the baseline or by a tangent inserted to the steepest slope of the downward part of the T wave and the baseline, which provides less inter-reader variability (19). Second, lead II is preferred for measurement because it has the longest QT interval among all leads, but unfortunately, it is present only in approximately 60% of the normal ECGs. Therefore, it is recommended to measure the QT interval in at least 6 leads (3 limb leads and 3 chest leads) and to take the median duration in case of a healthy heart and a similar approach should be applied for patients with heart disease – heart failure, cardiomyopathy, ischemic heart disease, etc. Nevertheless, in other individuals and especially in cardiac patients, it might be safer to replace the median duration by the maximum QT interval (20, 21). In addition, the duration of the QT interval can vary from beat to beat. For this reason, multiple beats (from 3 to 5) should be measured in each ECG lead and averaged, then a median from six or more leads should be taken. Third, the length of the QT interval varies depending on the heart rate; therefore, the corrected QT interval is calculated according to a formula that takes the heart rate into account. The Bazett formula is the most used in clinical practice; however, it unfortunately leads to overcorrection at high rates and under correction at lower rates (11). The relationship between QT and heart rate has been shown to be stable across individuals, but interindividual variation occurs throughout the population. Therefore, individual heart rate correction seems to be the most advantageous, but this requires a previous series of ECGs with different heart rates, which are not usually available in clinical practice (22).

When comparing available formulae, Fridericia and Framingham showed the best heart rate corrections and a significantly improved prediction of the 30-day and 1-year mortalities and thus have the potential to replace the Bazett formula in the standard clinical evaluation of the QTc interval (11). Fourth, an accurate reference interval should include all healthy individuals and identify individuals who are at increased risk of malignant ventricular tachycardias. As an upper limit of normal was set for the QTc interval at 450 ms for men and 470 ms for women (20). However, the Bazett formula leads to an overestimation of patients with a prolonged QTc interval and a reported upper limit of normal should be longer in this formula; 470 ms for men and 480 ms for women respectively, so as to avoid an unnecessary withholding of first line treatment due to a false interpretation of the QTc interval. The lower limit of normal is determined as 350 ms for both men and women and is set for all QTc formulae (11).

CONCLUSION

The study demonstrates that treatment with a triple combination of antiviral drugs: pegylated interferon alfa, ribavirin and an NS3/4A protease inhibitor can be considered as being safe regarding cardiotoxicity and the patients are not at risk of developing any polymorphic ventricular arrhythmias and heart failure as potential side effects of the treatment.

ABBREVIATIONS

bmp = beats per minute, DAAs = direct acting antivirals, HCV = Hepatitis C virus, QTc interval = corrected QT interval, QTcB interval = corrected QT interval according to the Bazett formula, TdP = Torsades de Pointes

AUTHOR CONTRIBUTIONS

JS: manuscript writing, ECG evaluations; RP: manuscript revision, ECG evaluations; MF, FV: manuscript preparation; SP: patients follow-up and management of the treatment; PP: manuscript revision.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in relation to this article.

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BRIEF SUMMARY

This study focuses on the evaluation of ECG changes in patients undergoing hepatitis C treatment with a triple combination of antiviral drugs – interferon alpha, ribavirin, and an NS3/4A protease inhibitor. During the 6-month follow-up, treatment was not found to prolong the QTc interval and not cause any severe pathological changes on the ECG's. The principles of measuring the QTc interval are further described in the study.

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