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PREPARATION OF HCV INFECTED PATIENTS TO THE TRIPLE THERAPY WITH FIRST GENERATION PROTEASE INHIBITORS

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ABSTRACT

In 2011 the European Medicines Agency approved two new drugs (boceprevir and telaprevir) to treat patients with chronic hepatitis C or compensated liver cirrhosis infected with genotype 1 HCV. Their usage together with a standard therapy, ie. pegylated interferon alfa and ribavirin significantly increased the chance of sustained virologic response among both previously unsuccessfully treated and naïve patients. However, this involves a greater number of side effects that poorly monitored can be life threatening. To the known side effects of standard therapy joined new, such as dysguasia, anorectal symptoms. Both drugs can compromise cardiac complications, especially in predisposed patients. Furthermore there is also a greater risk of rash and serious skin reactions. New problem is the interaction between drugs and first generation protease inhibitors resulting from the inhibition of cytochrome p450, common to many drugs pathway.

Key words*: protease inhibitors, triple therapy, long QT syndrome, drug – drug interaction*

INTRODUCTION

In 2011 the European Medicines Agency approved two new peptidomimetic NS3-4A protease inhibitor drugs (boceprevir and telaprevir) for the treatment of genotype 1 hepatitis C virus infections. This April, they were included in the Medicine Program of the National Health Fund (NFZ) with a recommendation for patients with chronic infections (fibrosis ≥2) and compensated cirrhosis (1). In conjunction with standard therapy, i.e. pegylated interferon alfa and ribavirin, these drugs considerably increase the chance for achieving sustained virological response (SVR) among both treatment-naïve patients and those who undergo repeated therapy. However, the increased effectiveness of the therapy carries with it a greater number of adverse events, which, if inappropriately monitored and approached, can be danger for the patient's life. Additional risks are caused by concomitant medication administered to the patient to treat comorbidities. It is why physicians are expected to carefully examine the patient's history and familiarise themselves with the characteristics of these new drugs (2-6).

The authors want to draw attention to the peculiarities and difficulties of triple first-generation protease inhibitor therapy for patients infected with genotype 1 HCV.

GENERAL GUIDELINES

The basic rule of treatment with first-generation protease inhibitors (PI) is combining them with standard therapy. Monotherapy with these products is prohibited, due to a high risk of developing drug resistance. Boceprevir and telaprevir must not be dose reduced, the occurrence of adverse events can only be countered by ending treatment. After the effects have passed, the PIs should never be restarted.

Protease inhibitors should always be taken with food. The meal can be light in the case of boceprevir, but should contain at least 21g of fat in the case of telaprevir. The physician should present examples of such meals to the patient, e.g. a baguette with dry cottage cheese for breakfast, or a sandwich with a slice of regular cheese. The patient should also be advised that some herbs (St John's wort) and grapefruit juice are

discouraged because they contain cytochrome p450 (CYP 3A4) inducers and inhibitors which disturb the metabolism of the drugs in question.

Dosage. The patient must be made aware of the necessity of adhering to the therapeutic regimen. Telaprevir is administered in doses of three capsules taken twice daily (2x1125mg) from the beginning of therapy for 12 weeks. This new regimen, recently approved by the EMA, is bound to increase patient compliance. The previous regimen (3x750mg) remains an alternative (7-9). Boceprevir is administered in doses 4 capsules three times a day (3x800mg) for 24-44 weeks after a 4-week lead-in phase. If the patient misses a dose of boceprevir and the next one is scheduled to be taken in less than two hours, the patient should not take it at all (10). In the case of telaprevir a forgotten dose can be taken within 4 (in a 3 times per day regimen) or 6 (in a twice per day regimen) hours of when it was originally planned (9).

Chances of shortening treatment. The 2011 recommendations of the Polish HCV Expert Group (PGE 2011) contain detailed guidelines for triple therapy with protease inhibitors. It should be noted that one of its advantages is the possibility of reducing treatment duration by half in comparison to standard therapy for patients without cirrhosis. This criterion should be considered when selecting candidates for treatment. 24-week therapy is possible for treatment-naïve patients or relapsers, when HCV RNA remains undetectable in their system in the 4th and 12th weeks of treatment. These conditions apply to patients who are undergoing triple therapy with telaprevir, in which three drugs are used for the first 12 weeks, and are subsequently reduced to only pegylated interferon alfa and ribavirin in weeks 13-24. The possibility of shortening boceprevir therapy applies only to treatment-naïve patients, when HCV RNA is undetectable in the blood serum during the 8th and 24th weeks of treatment. In such a case, therapy lasts for 28 weeks, with pegylated interferon alfa and ribavirin being administered for the first 4 weeks, adding boceprevir in week 5.

Treatment should be discontinued prematurely if it remains ineffective. For triple therapy with telaprevir this means a value of more than 1000IU/mL of HCV RNA in week 4 or 12, while for boceprevir it implies over 100IU/L in week 12 or over 25IU/L in week 24. Stopping treatment in accordance with these rules decreases costs and reduces the risk of adverse effects (9-11).

DRUG – DRUG INTERACTIONS

During standard therapy no adverse drug interactions were noted, because neither pegylated interferon alfa nor ribavirine interact with other medications. By contrast, first-generation protease inhibitors increase the risk of such interactions by inhibiting a metabolic pathway common to other drugs, namely the cytochrome p450 (CYP3A4/5 and CYP3A4) (9,10). In order to avoid risks, it is necessary to know all the types of rescue and chronic medication that the patient takes. The patient should also be advised against using any non-prescription drugs, whether on their own or after being told to do so by another physician, without first consulting the expert supervising the antiviral therapy. Drug interactions influence both the treatment of HCV infection and comorbidities. They may result in decreasing the amount of PI in the organism, which renders antiviral therapy ineffective. This situation occurs when boceprevir is administered with other drugs that are strong CYP3A4 inducers, e.g. antiepileptic drugs (carbamazepine, phenobarbital, phenytoin) (10). On the other hand, protease inhibitors may lead to an increase (toxicity) or decrease (reduced therapeutic efficacy) in the levels of a drug used for treating a comorbidity. Used alongside midazolam, they increase its amount in the blood plasma several-fold, thus raising the risk of adverse effects, mainly hypoventilation. Likewise, using protease inhibitors in conjunction with lovastatin or simvastatin is strictly prohibited due to the danger of producing miopathy, including rhabdomiolysis. The reason for increased adverse effects of HMG Co-A reductase inhibitors is the rise of their amount in the blood plasma due to CYP3A inhibition caused by boceprevir or telaprevir. Protease inhibitors have a different effect on the levels of another statin – atorvastatin; while boceprevir increases its amount in the plasma only slightly, telprevir multiplies it 8-fold. Hence, in practice atorvastatin should not be taken with telaprevir, but may be used with boceprevir on the condition of reducing its dosage and carefully monitoring the patient for miopathy. Protease inhibitors reduce the levels of ethynylestradiol, the main component of many contraceptives, which means that fertile women must switch to non-hormonal contraceptives (barrier methods, female condoms) during therapy and up to two months after it (9,10). Another group of drugs commonly used by HCV-infected patients are antidepressants, including selective serotonin reuptake inhibitors. Concentration of escitalopram in the plasma can drop by up to 30% when used in combination with telaprevir. If major depressive/anxiety disorder conditions become more severe at the beginning of triple therapy with telaprevir, increasing the dosage of escitalopram, which previously kept the disorder in check, is necessary. Similarly, reducing the symptoms of a major depressive disorder caused by antiviral treatment requires using an increased dose of escitalopram (9).

Only selected drug – drug interactions were discussed, since describing all of them would go beyond the limits of this article. In certain scenarios, it is admissible to stop taking a drug for the duration of protease

inhibitor treatment. Such a solution seems possible in the case of statins or sedatives. Modifying the treatment of comorbidities may also be allowed, e.g. exchanging calcium channel blockers, used in hypertension therapy, for other antihypertensive drugs. In order to make the right decision, it is always helpful to read the information contained in the characteristics of both products and at the website http://www.hep-druginteractions.org. One must remember, however, that this data is incomplete, as it only contains the interactions that were already discovered. If it becomes necessary to use a drug which was not tested for interactions with PIs (not present on the list), then the safest route is checking the metabolic pathway of that drug and eliminating substances that metabolise using CYP3A4. Table I lists selected drugs and their interactions with protease inhibitors (*tab. I*).

ADVERSE EVENTS

Triple therapy with protease inhibitors together with both pegylated interferon alfa and ribavirine results in new adverse events being discovered, and the intensification of adverse effects that were already known. In standard therapy, hematological and mental disorders, as well as rashes were observed in addition to general symptoms which can be very acute (fatigue, weakness, headaches, fever). In the case of boceprevir disorders of taste were also reported, and some telaprevir patients suffered from anorectal symptoms. In addition, cutaneous adverse reactions may occur, leading to stopping the therapy in severe cases. Both drugs carry the risk of cardiac disorders, especially for predisposed patients.

Cutaneous adverse reactions. Rashes and itching were the most common reported adverse events during telaprevir therapy. The frequency of their occurrence increased by almost 100% in comparison to standard therapy (9,12). A similar tendency has been observed among patients treated with boceprevir (5). Nevertheless, for the majority of patients (more than 90%) the skin changes were mild or moderate, did not progress and did not require modification of the therapy. In less than 1% of patients treated with protease inhibitors very rare and life-threatening severe cutaneous adverse reactions (SCAR) were noted. The most common were Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) (6, 9, 12).

Table I. Interactions between boceprevir or telaprevir and other drugs (9, 10).

DRUGS	BOCEPREVIR/TELAPREVIR		
	☺	☻	!
Antiepileptic	– gabapentin – valproic acid	– clonazepam (**T**)	– carbamazepine – phenobarbital – phenytoin
Hypolipidemic		– atorvastatin (**B**) – pravastatin, – bezafibrate – fenofibrate – ezetimibe	– simvastatin – lovastatin – atorvastatin (**T**)
Hypotensive	– atenolol – propranolol – enalapril – ramipril	– bisoprolol – carvedilol – nebivolol – amlodipine – diltiazem – verapamil – lisinopril (**B**) – valsartan (**B**)	– sotalol (**T**)
Antibiotics	– aminoglycosides iv – amoxicilin – azithromycin – ciprofloxacin – III generation cephalosporins	– claritromycin – clindamycin – ofloxacin	
Antiarrhythmic		– amiodarone (**B**) – propafenone – digoxin	– bepridil – amiodarone (**T**)
Antihistamine	– desloratidine – levocetirizine	– hydroxyzine	
Herbs		– Grapefruit juice	– St. John's Wort
Others	– omeprazole – pantoprazole	– lansoprazole – loperamide – metoclopramide	

☺ - permitted drugs, can be safely used; ☻ - drugs which may cause interaction, monitoring of treatment or change of dosage required; ! – not to be coadministered; (**B**) – boceprevir; (**T**) – telaprevir; no parenthesis next to drug name – valid for both protease inhibitors

Table II. Recommendations for skin care (12).

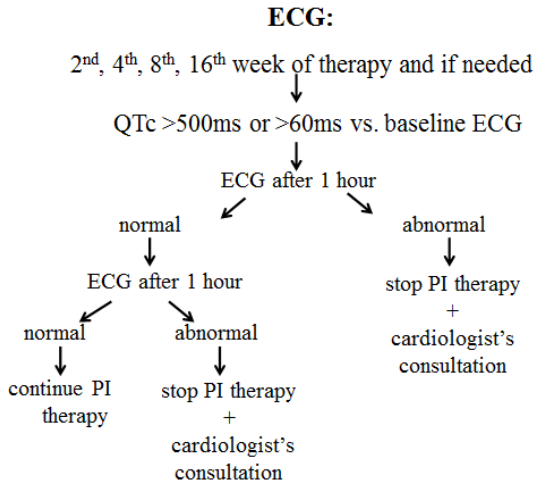
Skin care – Use moisturisers and emolients – Use hypoallergenic cosmetics – Avoid alcohol-based cosmetics – Avoid perfumes – Drink plenty of water – Wear loose-fitting clothes made of natural materials – Use air moisturisers in enclosed areas and maintain moderate air temperature – Dedicate at least 15 minutes daily to skin care	**Bathing** – Avoid hot showers and baths – Add unscented oils and oats to bathwater – Directly after bathing use moisturisers, vaseline **Exposure to sunlight** – Avoid direct sunlight – Stay in the shade and wear protective clothing – Use high sun protection factor sun cream **Laundry** – Use mild, unscented detergents – Avoid dryer sheets

Before treatment begins, it is necessary to inform patients about the risk of skin changes occurring and to offer recommendations for proper skin care (*tab. II*). Adhering to these recommendations may reduce or delay cutaneous adverse reactions. In addition, patients must be instructed to immediately consult the physician in charge of the antiviral therapy in case of experiencing any form of rash, its intensification, or any other symptoms, including: fever, fatigue, facial swelling or enlarging of lymph nodes.

Cardiac disorders. Heart-related conditions appeared rarely among patients undergoing standard therapy. Arterial hypertension, supraventricular arrhythmia, heart failure and cardiac arrest were noted (13). The risk of cardiac disorders increased moderately after adding protease inhibitors, since they have arrhythmogenic properties, causing QT elongation. This may lead to a sudden heart failure due to Torsades de Pointes polymorphic ventricular tachycardia. Hence, these drugs require cautious application in patients with an acquired elongated QT interval, bradycardia and heart failure (9,10). The most common causes of acquired QT interval elongation are drugs (clarithromycin, salmeterol, ketoconazole) or electrolyte disorders (hypomagnesemia, hypocalcemia, hypocalemia) (14). In addition, telaprevir should be avoided by patients with inhereted long QT syndrome (LQTS), episodes of this syndrome, or cases of sudden cardiac death in the family. It should be noted that LQTS is sometimes misdiagnosed as epilepsy. The risk of not diagnosing the disease in young adults qualified for triple therapy also exists, although the first symptoms usually occur at a young age (5-15 years) (14).

Hence, before taking the decision to qualify a patient for triple therapy a physician should run an electrocardiography test (ECG), calculate the corrected QT interval (QTc) according to Bazett's or Friedric's formula (the norm is < 440ms) and specify the amount of potassium, magnesium and calcium in the blood serum. If doubts arise, a cardiologist's consultation is recommended. PI treatment can continue if the QTc does not elongate beyond 60ms above the initial value, or does not exceed 500ms. In order to maintain the correct level of electrolytes in the blood serum it may be necessary to use supplements. The rules for monitoring QTc during therapy are presented in figure 1 (fig. 1).

Figure 1. Monitoring the length of the corrected QT interval during protease inhibitors therapy



ECG – electrocardiogram; QTc – corrected QT interval; PI – protease inhibitor

TREATMENT STANDARDS AND THE NFZ DRUG PROGRAM

The PGE 2011 standards, as well as the recommendations of other scientific societies create the possibility of applying the triple treatment to treatment-naïve patients, regardless of gene rs 12979860 Il 28B polymorphism (11, 15). In contrast to these standards, the NFZ drug program requires marking IL 28B polymorphism and offers a chance for treatment only to TT homozygous patients (1). Studies have shown a higher efficacy of the triple therapy in this group in comparison to standard treatment, however the biggest beneficiaries were patients with the CC Il28B genotype; 90% and 80% of patients treated with telaprevir and boceprevir, respectively, achieved sustained virological response in comparison with 69% of patients receiving standard therapy. For patients with the TT Il28B gene these

values were 73%, 59% and 27%, respectively (16-18). Another criterion that limits access to financing the triple treatment by the NFZ which is not mentioned in the PGE 2011 standards is the score of liver fibrosis. Candidates for treatment must score at least 2nd degree liver fibrosis on the Scheuer scale. This applies both to treatment-naïve patients and those were unsuccessfully treated before (1). Therefore, the selection of patients for triple therapy in the drug program is based on unfavourable prognostic factors, which decreases the patients' chance of achieving SVR.

The high costs of triple therapy and the above limiting criteria will cause specialists conducting antiviral treatment to face the dilemma of whom to treat: the patient with less severe fibrosis, or the one with chronic cirrhosis who had been unsuccessfully treated, and for whom this may be the last chance of eliminating infection? In patients with cirrhosis, achieving therapeutic success may be accompanied by a large number of adverse events, including severe ones, such as general infections, decompensated liver function and death. The frequency of their occurrence in a CUPIC study was rated as 40% and 6,4% respectively. Almost 30% of patients suffered from anaemia (Hb ≤ 9g/dl) which required using erythropoietin for 50,7%, reducing the dose or removing ribavirin from the therapy for 16,1% and blood transfusion for 12,1% of the patients. Independent predictive factors related to anaemia were female gender, age above 65 years, low baseline haemoglobin level: ≤ 13g/dl for men and ≤ 12g/dl for women. Deaths and severe adverse events occurred among patients with a baseline platelet count below 100k/mm^3 and an albumin level below 35g/dl (6). These facts must be taken into account when qualifying patients for triple treatment.

SUMMARY

Preparing a patient for triple therapy requires giving him or her more time than in the case of standard treatment. A properly educated patient is quicker to react to all disturbing symptoms which offers the physician a chance to counteract sooner. A careful qualification process for triple therapy which takes all contraindications into account helps to minimise the risk of severe adverse events. The patient's compliance to the therapeutic regiment and a proper understanding of risks resulting from adverse drug reaction are important elements of therapeutic success. To sum up, we are receiving a new weapon for fighting against HCV, which is more effective but carries a greater risk of side effects.

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