PSYCHIATRIC ASPECTS OF HEPATITIS C TREATMENT

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SUMMARY – Hepatitis C is a public health problem worldwide. Currently recommended therapy for the treatment of hepatitis C, pegylated interferon-alpha and ribavirin, when applied in combination, are often associated with the risk of developing mood disorders, depression and anxiety. Previously, the existence of psychiatric comorbidity was the reason for therapy discontinuation, but current guidelines allow such treatment despite the presence of psychiatric illness. Close cooperation with psychiatrists is highly recommended for the treatment of patients with psychiatric comorbid disease in order to motivate the patient for treatment, stabilize his mental condition, educate him about the possible side effects, and regularly monitor the patient, so the treatment can be carried out safely and successfully. Therefore, a multidisciplinary approach is essential for successful treatment of hepatitis C virus infections.

Key words: *Hepatitis C; Interferons; Psychiatry; Comorbidity*

Introduction

Hepatitis C is a public health problem worldwide and the prevalence of hepatitis C virus (HCV) infection varies throughout the world. Infection with HCV is self-limited in a small minority of infected persons, so HCV is a major cause of acute and chronic hepatitis. Currently recommended therapy for the treatment of hepatitis C is pegylated interferon-alpha (IFN-α) and ribavirin. When applied in combination, they are often associated with the risk of developing mood disorders, depression and anxiety. Previously, the existence of psychiatric comorbidity was the reason for therapy discontinuation, but current guidelines allow such treatment despite the presence of psychiatric illness. Close cooperation with psychiatrists is highly recommended for the treatment of patients with psychiatric comorbid disease. Psychiatrist should motivate the patient for treatment, stabilize his mental condition, educate him about the possible side effects, and regularly monitor the patient, so the treatment can be carried out safely and successfully.

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Epidemiology and Symptomatology

Patients suffering from HCV infection tend to develop significant comorbidity and mortality, often at an early age. HCV is responsible for 20% of acute hepatitis, 89% of chronic hepatitis, 40% of liver cirrhosis, 70% of hepatocellular carcinomas and 30% of liver transplants[1]. In Croatia, 1.7% of the population or 75,000 people are infected with HCV. Without addressing the problem appropriately, the negative trend will continue and the number of infected individuals, as well as those who will develop severe complications of the disease can be expected to rise significantly[2]. HCV infection is transmitted through infected blood. Until the introduction of mandatory testing of volunteer blood donors (in Croatia since 1993), blood transfusion and transfusion of blood products were the main transmission path of hepatitis C, even in 85% of cases.

In Croatia, 90% of all new cases of hepatitis C are caused by intravenous drug use, the use of common syringes and needles, in which the risk of infection rises

up to 90%. HCV transmission by sexual intercourse and during birth from infected mother to newborn child (perinatal time) is less common and the risk of transmission is about 5%. After birth, if the newborn is not infected, maternal anti-HCV antibodies disappear from the blood in 6-12 months. Those children need to be re-tested at the age of 3 months, and regularly followed up to 12 months after birth. The virus can be present in the milk of a HCV-positive mother, but there is no evidence of infection during lactation. Other ways of infection are much less common (accidental thrust on needles, use of razors, toothbrushes, tattooing, etc.). In as many as 20% of infected persons, the exact transmission path cannot be determined[3].

The HCV incubation period to the onset of acute hepatitis C is 15 to 50 days, 6 weeks on an average. The presence of HCV RNA in the blood can only be confirmed by a special assay. In the initial HCV infection, only mild flu-like illness can be recorded, but usually there are no symptoms that could indicate an infection. Nonspecific symptoms occur in only 25%-30% of HCV infected patients. Therefore, acute hepatitis C is rarely diagnosed and in the majority of patients virus is detected when the disease has already widespread and is in the phase of chronic hepatitis.

Chronic hepatitis is diagnosed when liver inflammation lasts longer than six months and is accompanied by the following symptoms: loss of appetite, nausea, vomiting, abdominal pain, fever, joint pain, exhaustion and a feeling of constant fatigue. In 75%-85% of cases, acute HCV turns to the chronic form and is characterized by permanent damage to the liver. It is believed that HCV infection causes 50%-70% of all cases of malignant liver disease.

According to recent data, 46% of intravenous drug users are hepatitis C positive, while 10% are hepatitis B positive[2]. These data point to the importance of testing drug users for the infection and referring them to treatment in the early stages of infection in order to prevent severe complications.

In Croatia, available pharmacotherapy for the treatment of hepatitis C are pegylated IFN-α, IFN-α (conventional interferon) and ribavirin[3,4]. The predominant genotypes are genotype 1 and 3, while other genotypes occur by far less frequently. Determination of HCV genotype is important in determining the length of treatment.

Etiology

There are various theories of the biological mechanisms of mood disorders induced by IFN therapy. HCV changes brain metabolism and replicates in the brain tissue[5,6].

The etiology of depression caused by IFN therapy rests on especially reduced values of 5 HT (serotonin) receptors. The disorder involves changes in the hypothalamic-pituitary-adrenocortical (HPA) axis, activation of inflammatory cytokines, reduced levels of peptidases, increased intercellular adhesion of molecule 1 (ICAM-1) and increased levels of nitric oxide. Storage levels of serotonin and monoamine oxidase B activity (MAO-B) are significantly lower in chronic HCV patients. Genetic differences in the 5-HTTLPR (serotonin 'reuptake' transporters) are associated with major depression during IFN therapy[7]. IFN-α therapy changes other monoamines such as dopamine and norepinephrine, which can also cause depression. IFN-α directly stimulates the release of corticotropin hormone, which increases the production of adrenocorticotropic hormone, resulting in increased cortisol, and these stress hormones are directly responsible for anxiety and depressive symptoms[8].

The treatment of choice for chronic hepatitis C is six- or twelve-month therapy with IFN-α and ribavirin, which is effective in a substantial proportion of patients (40%-88%)[9,10]. IFN-α significantly modulates the function of cytokine system and enhances antiviral immune response[11]. Ribavirin does not induce neuropsychiatric side effects directly, although it may disturb thyroid function and indirectly affect brain function[12]. Low-doses of IFN-α therapy are often associated with neuropsychiatric side effects, most frequently depression, mild cognitive impairment and fatigue, which disappear upon cessation of IFN-α in almost all patients[13,14]. Psychotic disturbances as adverse neuropsychiatric side effects of IFN therapy have been observed infrequently[15-17].

Although depression is the most widely reported neuropsychiatric side effect of IFN therapy, clinicians should be aware that other symptoms, such as simple fatigue, anxiety, insomnia, irritability, cognitive impairment, and mania, may occur. Suicide is a real threat for patients on treatment for HCV. Suicidal thoughts are a common complication of IFN therapy and stem from a combination of depressive symptoms

along with anxiety, agitation, and irritability. Dieperink *et al*. report on the rates of suicidal ideation as high as 27% in HCV patients who were not on IFN and 43% of patients with IFN endorsed suicide ideation at some point during therapy[18]. Screening for suicide ideation must occur at regular, closely spaced intervals.

Treatment of Psychiatry Symptoms during IFN Therapy

All patients scheduled for IFN therapy initiation should undergo psychosocial screening, which at a minimum should include past psychiatric history and current assessment for mood or anxiety symptoms, substance use, and suicidality. It is useful to employ depression screening tools such as the Beck Depression Inventory (BDI), Zung Self-Rating Depression Scale, Hamilton Depression Rating Scale, Hamilton Anxiety Scale or Neurotoxicity Rating Scale.

The primary treatment for IFN-induced depression is traditional antidepressant therapy. Nevertheless, a number of adjuvant medications have been utilized to assist with symptomatic relief[19].

Depressive disorder starts usually after 1-3 months of IFN therapy introduction and the rate of depression is higher among patients on intravenous IFN compared to subcutaneous administration. Co-administration of ribavirin contributes to a higher rate of depression. In addition to psychological complications, there is a number of somatic side effects that are encountered such as fever, chills, muscle pain and

Table 1. Common medications used for treatment of psychiatric complications of interferon therapy[21]

Medication	Specific medications to consider	Target disorder or symptom	Comments
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, paroxetine, escitalopram, sertraline	Depression Anxiety Irritability	SSRIs are a good first-line treatment.
Serotonin-norepinephrine reuptake inhibitors (SNRIs), dopaminergic or other antidepressants	Bupropion, Venlafaxine, Duloxetine, mirtazapine	Depression Irritability (SNRIs)	Bupropion has a potential for seizure in combination with IFN. Duloxetine may be problematic in patients with chronic liver disease. Mirtazapine may assist with insomnia and poor appetite.
Stimulants	Modafinil, methylphenidate	Adjuvant Depression Fatigue	May cause heightened anxiety or insomnia in some patients. Traditional stimulants such as methylphenidate may exacerbate psychotic symptoms.
Anxiolytics	Lorazepam		Use short half-life medications (glucuronidated) because of liver disease: use caution with addictive medications in this population.
Dopamine agonists	Amantadine	Depression	Still experimental and with limited evidence.
Hypnotics	Zolpidem trazodone Mirtazapine	Insomnia	Zolpidem has a potential for abuse, but lower than benzodiazepines.
Mood stabilizers	Quetiapine, Olanzapine	Hypomania Mania	First-line treatment would be atypical antipsychotics, pending further psychiatric evaluation.

sweating, which is particularly risky in this population because addicts can evoke memories of the withdrawal symptoms and this may lead to relapse as a way of removing the somatic side effects[20].

An overview of the possible options of medications is shown in Table 1[21], and is by no means inclusive of all possible therapies. Guidelines for screening and ongoing monitoring and specific treatment recommendations for IFN-induced depression are reviewed in Table 2[21].

Selective serotonin reuptake inhibitors (SSRIs) clearly appear to be optimal first-line therapy for IFN-induced depressive disorders. Case reports and limited studies can be found for many of the SSRIs, including sertraline, citalopram, and paroxetine. There is some evidence for excellent results with sertraline, potentially because of the serotonergic and dopaminergic effects of this medication. Sertraline can be somewhat activating for some patients and may induce additional anxiety, which is less common with citalopram or escitalopram.

Antidepressants with serotonergic activity and benzodiazepines also have value in the treatment of irritability associated with IFN therapy[22].

Depression Treatment during IFN Therapy

Some studies advocate the use of prophylactic antidepressants for patients who have a family history of depression or had an episode of depression in the past, but there is still a lack of evidence to support such use of antidepressants[23].

For the patients suffering from depression, it is suggested that IFN treatment be delayed until improvement of the mental state[24]. Depression during IFN treatment is treated with antidepressants combined with psychotherapeutic support. Antidepressants, particularly SSRIs, should be introduced 2-3 weeks

Table 2. Suggested guidelines for treatment of interferon (IFN)-induced depressive disorders[21]

1. All candidates cleared for IFN medically should receive psychiatric screening: past psychiatric history; current screening for mood or anxiety symptoms – useful to employ screening tools such as Beck Depression Inventory (BDI), Zung Self-Rating Depression Scale; inquire about substance use; educate patients about the risk of interferon-induced neuropsychiatric disorders and how to recognize symptoms; explain that treatment options are available if these problems emerge.
2. Patients require psychiatric management in the following circumstances: complex psychiatric history (severe depression, suicide ideation, bipolar disorder, schizophrenia, anxiety disorders, etc.); history of alcohol or substance use disorder; patient in ongoing psychiatric treatment; history of significant psychiatric hospitalizations.
3. In patients with current depression or anxiety of moderate or severe intensity or patients with a history of severe depression or IFN-induced depression who are currently asymptomatic: offer pre-treatment with antidepressant at least 4 weeks before interferon; delay interferon therapy for patients whose symptoms remain significant after 4 weeks; monitor at a minimum every two weeks during first three months of treatment (frequency may decrease after that time to every two to four weeks).
4. For patients who do not require pre-treatment: initiate interferon; monitor at a minimum every 2 weeks during the first three months, then every 2 to 4 weeks thereafter – perform psychiatric screens and ask about suicidal thoughts at every visit; if depressive symptoms occur, initiate antidepressant therapy immediately; be aware that some patients may minimize symptoms because of concern regarding discontinuation of treatment; during interferon therapy, physical symptoms may be secondary to interferon and not frank depression. Focus especially on more psychological symptoms such as depressed mood, anhedonia, ruminatory thoughts, helpless and hopeless feelings, crying spells, irritability, social withdrawal, and guilt.
5. If depression or anxiety symptoms worsen during treatment, increase antidepressant dosage and consider augmentation with second antidepressant from a different class. Refer immediately for emergent psychiatric assessment/hospitalization and discontinue interferon for the following circumstances: suicide or homicide ideation; hypomania, mania; severe depression, anxiety, or other psychiatric symptoms; psychosis.
6. Throughout treatment, closely monitor patients with concurrent or previous substance use disorders for relapse.

before the start of IFN therapy. Following the latest guidance, if depression occurs during the treatment of hepatitis C, it should be treated without interrupting IFN therapy. Among the SSRIs, the least potent in interactions with certain liver cytochrome oxidase enzyme systems, such as escitalopram, citalopram, sertraline or paroxetine, should be used in treatment[25].

In severe hepatic impairment, the dose of these drugs should be reduced, and in patients on methadone maintenance therapy, paroxetine (which is safe for the liver) should be used cautiously because it increases the concentration of methadone. It is possible to prescribe an antidepressant that bypasses the cytochrome oxidase enzyme, e.g., tianeptine. Other antidepressants are still secondary options (fluoxetine, fluvoxamine, mirtazapine, venlafaxine, duloxetine, moclobemide, maprotiline, clomipramine), and a higher degree of caution is required when prescribing them because of their stronger impact on the hepatic enzyme systems (they are toxic for the liver).

Those patients who had other psychiatric comorbidities prior to the commencement of the treatment for hepatitis C are advised to stabilize on appropriate pharmacotherapy before starting IFN therapy, in order to reduce its destabilizing effect. When prescribing antipsychotics to patients with hepatic impairment, drugs with a low degree of risk for progression of liver damage such as zuklopentixol, flupentixol, haloperidol, sulpiride, amisulpride and aripiprazole, should be opted. Promazine, clozapine, quetiapine, olanzapine and risperidone have a moderately high risk for liver damage.

Benzodiazepines and hypnotics may help with irritability, anxiety and insomnia, but they present a potential risk of addiction. If they are prescribed, then it should be those that are metabolized by glucuronidation, like lorazepam, oxazepam and temazepam. Hypnotics (non-benzodiazepines) that could be prescribed, such as zolpidem and zopiclona, are by far less addictive. Sedating antidepressants, such as mirtazapine and trazodone, could also be effective.

For the treatment of opiate addicts, it is essential to stabilize them on substitution therapy (methadone, buprenorphine) to reduce the risk of relapse and therefore interruption of the treatment of hepatitis C[26]. For all comorbid psychiatric disorders during the treatment of hepatitis C, frequent psychiatric support is needed along with psychopharmacy, so that patients could successfully endure treatment till the end[27].

Conclusion

It may be suggested that early identification of psychiatry disorders and appropriate psychopharmacological treatment might prevent subsequent development of serious debilitating symptoms. Considering all specifics of the treatment of hepatitis C, it is necessary to provide regular psychiatric consultations not only for patients who have risk factors to develop neuropsychiatric side effects, but for all patients undergoing long-term treatment with IFN. Therefore, a multidisciplinary approach (psychiatrists, hepatologists, nurses, etc.) is essential for successful treatment of HCV infections.

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Sažetak

PSIHIJATRIJSKI ASPEKTI LIJEČENJA HEPATITISA C

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Hepatitis C je javnozdravstveni problem u svijetu. Trenutno se u liječenju hepatitisa C preporučuje terapija pegiliranim interferonom-alfa i ribavirinom, a ta kombinacija se povezuje s rizikom razvoja poremećaja raspoloženja, depresije i anksioznosti. Ranije je postojanje psihijatrijskog komorbiditeta bio razlog za ukidanje liječenja, ali današnje smjernice dozvoljavaju takvo liječenje unatoč postojanju psihijatrijskih bolesti. Preporučuje se bliska suradnja s psihijatrima kod liječenja bolesnika s psihijatrijskim komorbiditetom kako bi se bolesnika motiviralo za liječenje, stabiliziralo njegovo mentalno stanje i upoznalo ga s mogućim nuspojavama. Uz ovakvo kontinuirano praćenje bolesnika liječenje se može provoditi sigurno i uspješno. Stoga je multidisciplinarni pristup neophodan za uspješno liječenje infekcije virusom hepatitisa C.

Ključne riječi: *Hepatitis C; Interferoni; Psihijatrija; Komorbiditet*