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NEW APPROACHES IN THE THERAPY OF HEPATITIS C IN DIALYSIS PATIENTS

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A b s t r a c t: Patients with renal disease are at increased risk of acquiring hepatitis C virus (HCV) infection because of their frequent exposure to blood from transfusions or exposure to HCV-contaminated medical equipment during hemodialysis. The prevalence of anti-HCV antibodies among hemodialysis patients varies between 5–10% in the developed world, and 10–70% in developing countries. Acute hepatitis C is often mild and associated with few, if any symptoms. The major complication of acute HCV infection is chronic hepatitis, which occurs in up to 80% of the cases, the long-term outcome being cirrhosis, portal hypertension, hepatic failure, and hepatocellular carcinoma. Interferon alpha (IFN-α) has shown activity against HCV. Twenty four to 48 week course of therapy with interferon could lead to a sustained loss of HCV RNA, normalization of alanine aminotrasferase (ALT) levels, and resolution of the liver disease. Sustained viral response was achieved in approximately half of the treated patients. Therapy with interferon was associated with a number of adverse events such as: "flu-like" symptoms, neurological, gastrointestinal symptoms, anemia, fatigue, thrombocytopenia, leucopenia. A major advance in therapy came with the addition of ribavirin to interferon therapy. Peginterferon-alpha-2a (40KD) is a new 'pegylated' subcutaneous formulation of interferon-alpha-2a, that was developed to improve the pharmacokinetic profile and therapeutic efficacy of interferon-alpha-2a. In our study, fourteen hemodialysis patients with chronic hepatitis C received 135 μg PEG-IFN alpha-2a subcutaneously, once a week, after dialysis session for a period of 48 weeks. In the intention-to-treat analysis, sustained viral response was present in 36% of the patients (five out of fourteen patients) at the end of the follow up period. The biochemical response with normalization of serum ALT levels during the treatment was observed in all treated patients (83 ± 20.1 U/L at base line *vs.* 23.4 ± 4.6 U/L after the 48 weeks; $p < 0.01$). At

present, therapy for hepatitis C should be considered in hemodialysis patients with significant liver disease, minimal other co morbidities, and a reasonable likelihood of prolonged survival or if renal transplantation is planned.

Key words: chronic kidney disease, hepatitis C, hemodialysis, interferon, ribavirin.

Background

Both hepatitis C and chronic renal disease are common and potentially serious medical problems. They could be interrelated in several important ways. Some forms of renal disease are precipitated by hepatitis C virus (HCV). Extra hepatic complication of HCV infection may lead to renal failure in the native as well as in the transplanted kidneys, resulting in so-called "de novo" glomerulonephritis, which may lead to non-functioning renal allograft [1]. In addition, patients with renal disease are at increased risk of acquiring HCV because of their frequent exposure to blood from transfusions or exposure to HCV-contaminated medical equipment during hemodialysis. Despite these known associations, the role of hepatitis C in the course, morbidity, and mortality of renal disease is not well established and often not considered in the care of people with kidney disease [2].

Epidemiological characteristics of hepatitis C in hemodialysis patients

Since the discovery of HCV in the late 1980s, a number of investigators reported a high prevalence of anti-HCV antibody in hemodialysis patients. The "silent epidemic" is now receiving much of the attention it deserves [3]. Risk factors for spread include a history of transfusions, number of transfused blood products, and number of years on hemodialysis therapy. Although HCV transmission through blood products transfusion previously was a significant source of infection, current HCV transmission is believed mainly to be caused by nosocomial exposure in dialysis units. Effective screening of blood products virtually eliminated HCV transmission by blood transfusion a decade ago, and a subsequent decline in HCV incidence and prevalence within dialysis units in developed countries was noted [4]. The prevalence of anti-HCV antibodies among hemodialysis patients in the United States was 7.8% in 2002 compared to the prevalence of 10.4% in 1995 [5]. There is considerable variation in the prevalence of anti-HCV, and the incidence of new cases among dialysis centers. A European survey including northern and eastern countries reported seroconversion rates of 1% to 16% in dialysis units [6]. The frequency of hemodialysis patients seropositive for HCV is much higher in developing countries. The

seroprevalence in seven dialysis units in the Cairo area was 80% [7] and in dialysis unit in Saudi Arabia was 57% [8]. Current recommendations to control the spread of HCV in dialysis units include routine serological testing and surveillance, implementation of additional infection control measures, additionnal strategies to control the nosocomial transmission of HCV, such as isolation of HCV positive hemodialysis patients on dedicated machines and restriction on dialyser reuse for HCV infected patients, particularly in units with high prevalence of infection.

Natural history and course of hepatitis C

Acute hepatitis C is often mild and associated with few, if any symptoms. Fulminant or severe cases are rare. The major complication of acute HCV infection is chronic hepatitis, which occurs in up to 80% of cases. The major long-term complications of chronic hepatitis C is hepatic fibrosis, which can evolve into cirrhosis, portal hypertension, and hepatic failure. Patients with cirrhosis also are at high risk for development of hepatocellular carcinoma. The development of cirrhosis in published studies has ranged from 2% to 42% [2]. Several factors correlate with a greater rate of fibrosis progression [9]. Viral factors, such as viral genotype and viral serum level, did not appear to be important. Controversially, several host factors are important, including older age, older age at onset of infection, male gender, co infection with human immunodeficiency virus (HIV) or hepatitis B (HBV), chronic alcoholism, and other co morbid conditions, such as hemochromatosis, nonalcoholic steato-hepatitis, obesity and diabetes.

The natural history of HCV in hemodialysis patients remains controversial because the course of HCV infection typically extends over decades, whereas hemodialysis patients have higher morbidity and mortality rates than those without renal disease, limiting long-term follow-up [3]. There are difficulties in attempts to assess the natural history of hepatitis C in hemodialysis patients because of their unique characteristics: (i) levels of alanine aminotransferase (ALT) are frequently normal and appear to be less reflective of the activity of the liver disease in HCV positive hemodialysis patients compared with patients without renal disease; (ii) liver biopsy, the gold standard for assessment of severity of hepatitis C, has not been applied to a large number of hemodialysis patients [10]; (iii) chronic hepatitis C has an insidious and prolonged natural history, and the competing mortality of complications of hemodialysis may obscure the long-term consequences of hepatitis C. Chronic hepatitis C adversely affects survival in hemodialysis patients. Longitudinal studies have suggested a poorer outcome of HCV positive compared to HCV negative hemodialysis patients [11]. Multivariate analysis showed an increased

relative risk (RR) of death in HCV positive hemodialysis patients of 1.78 (95% CI, 1.01–3.14) [12].

One of the principal problems concerning the course of HCV infection in patients with chronic kidney disease is when they are transplanted. The immunosuppressive drugs administered during renal transplantation facilitate HCV replication, aggravating or accelerating hepatic lesions [13]. Several studies have demonstrated that the viral load increased between five and ten times after transplantation. The increase of ALT levels also was notified after transplantation, compared to the hemodialysis period. All these parameters reflect a significant change in the viral status after renal transplantation provoked by the immunosuppressive therapy. After renal transplantation, the use of interferon is restricted because of the risk of acute rejection or renal dysfunction. Therefore it seems important to treat HCV infection in candidates for renal transplantation beforehand, in order to prevent allograft nephropathy and development of cirrhosis [14, 15]

Therapy for hepatitis C

Interferon alpha (IFN-α) had shown activity against chronic hepatitis C in the middle of 1980s and was licensed for treatment of this disease by 1991. The basis of approval was the demonstration that a 24 to 48 weeks course of therapy with interferon could lead to a sustained loss of HCV RNA, normalization of ALT levels, and resolution of the liver disease [15]. Thus, the efficacy of therapy against HCV has been measured by "response" or "sustained response", including viral, biochemical, and histological responses. The definition of sustained viral response (SVR) denotes absence of detectable HCV RNA at least 6 months after completion of therapy. The biochemical response is based upon findings of normal serum aminotransferase values, and histological response is based on the improvement of hepatic disease activity, documented by liver biopsy [16]. A SVR with normal aminotransferase activity currently indicates a "cure" from HCV infection [17]. The SVR rate to interferon therapy was 12% to 20% after 48 weeks course treatment of chronic hepatitis C in patients without renal disease. A major advance in therapy came with the addition of ribavirin (RBV) to interferon therapy, which lead to the increase in SVR rates to as high as 38% to 43% [18]. One important reason for the overall poor sustained response to interferon is its short half-life. To extend the half-life and reduce the frequency of administration, pegylated formulation of interferon alpha (PEG IFN-α) was developed. Peginterferon-alpha-2a (40KD) is a new 'pegylated' subcutaneous formulation of interferon-alpha-2a, that was developed to improve the pharmacokinetic profile and therapeutic efficacy of interferon-

alpha-2a. Peginterferon-alpha-2a was produced by the covalent attachment of recombinant interferon-alpha-2a to a branched mobile polyethylene glycol moiety. It was shown to be significantly more effective than interferon-alpha-2a in interferon-alpha therapy-naive adults with chronic hepatitis C in three nonblind, randomized, multicentre trials [19]. Sustained viral responses were achieved in 44% to 69% of patients with or without cirrhosis after 48 weeks of treatment with PEG IFN-α (180 μg/week). Peginterferon-alpha-2a produced better results than interferon-alpha-2a alone or interferon-alpha-2a plus oral ribavirin on various measures of quality of life in patients with chronic hepatitis C. The combination of PEG IFN-α and RBV has been compared with the combination therapy using standard IFN and RBV. Overall response rates to a 48 week course of combination therapy were 56% using PEG IFN-α and RBV with 44% using standard IFN and RBV [20].

Therapy with interferon has exhibited frequent side effects. The most common side effects of interferon include "flu-like" syndrome, nausea, poor appetite, anxiety, sleep disturbances, and depression. Interferon has also myelosuppressive effects and decreases white blood cell and platelet counts by 30% to 40%. Ribavirin can cause a dose-related hemolysis, which usually results in a 10% to 15% decrease in hemoglobin levels. Combination therapy can also result in serious adverse events, including bacterial infection, introduction of autoimmune disease, and rare cases of renal, pulmonary, cardiac, hepatic, neurological, visual, or auditory injuries [21].

The first controlled trial concerning IFN-α treatment in hemodialysis patients with chronic hepatitis C was done by Ellis ME and colleagues in Saudi Arabia [22]. It was a double blind, placebo, controlled and cross-over study on 13 patients with histological and biochemical documentation of chronic non-A, non-B hepatitis. Patients received 3 MU of IFN-α subcutaneously, 3 times weekly after hemodialysis session over a 6 months period. Ten out of thirteen (77%) patients achieved complete biochemical remission during IFN-α treatment. The mean level of ALT decreased significantly during the treatment (74.7 U/L before treatment *vs.* 37.6 U/L during treatment, $p < 0.005$). Histological improvement was apparent for interlobular inflammation, mean score 3.3 for biopsies prior to IFN treatment, compared to 1.8 after IFN treatment. Five out of thirteen (39%) and two out of thirteen (15%) patients had complete resolution of piecemeal necrosis and interlobular inflammation, respectively. A meta-analysis identified 14 trials (269 patients) of interferon therapy of chronic hepatitis C in hemodialysis patients [23]. The summary estimate for SVR and dropout rate were 37% (95% CI, 28–47%) and 17% (95% CI, 10–28%), respectively. The most frequent side effects requiring interruption of treatment were "flu-like" symptoms (21%), neurological (21%), and gastrointestinal symptoms (18%). This systematic review suggested that the response rate to

interferon monotherapy in hemodialysis patients with chronic hepatitis C is higher than in patients without renal disease, but tolerance is lower. It is not fully understood why the response to interferon is better in hemodialysis patients than in the general population, but factors that might be involved are: the length and severity of HCV infection is probably lower in hemodialysis patients than in other situations, and the pharmacokinetics of interferon in hemodialysis patients are different from that in the general population, with a significantly higher area under the concentration time-curve [24]. Impaired clearance of interferon in the hemodialysis patients, their older age, and high frequency of co morbid conditions may explain the frequency of side effects leading to interferon discontinuation.

Pegylated formula of interferon alpha-2a is excreted via the liver, but pharmacokinetic studies have shown that serum concentrations of pegylated interferon alpha-2a were greater in patients with reduced renal function. A dose of 135 μg of pegylated interferon alpha-2 in hemodialysis patients gave similar serum concentration to a dose of 180 μg in patients without renal disease [20]. The two most recent studies of treatment of chronic hepatitis C in hemodialysis patients with pegylated interferon alpha-2a gave contradictory response rates. In the study of Kokoglu *et al*. [25], twelve hemodialysis patients were treated with PEG-IFN alpha-2a at a dose of 135 μg weekly for 48 weeks. The SVR was observed in 75% (nine out of twelve patients). Noted side effects were anemia (75%), fatigue (58.3%), thrombocytopenia (33.3%) and leucopenia (33.3%), but they did not impose discontinuation of treatment. Sporea I. *et al*. [26] treated ten HCV positive hemodialysis patients with PEG-IFN alpha-2a (180 μg weekly) for 48 weeks. Intention-to-treat analysis showed that 3 out of 10 patients (30%) had SVR. Side effects occurred in most of the patients (flu-like syndrome, thrombocytopenia or leucopoenia), but they did not impose the discontinuation of treatment. In our study [27], fourteen hemodialysis patients with chronic hepatitis C received 135 μg PEG-IFN alpha-2a subcutaneously, once a week, after dialysis session for a period of 48 weeks. In the intention-to-treat analysis, sustained viral response was present in 36% of the patients (five out of fourteen patients) at the end of the follow up period. The biochemical response with normalization of serum ALT levels during the treatment was observed in all treated patients (83 ± 20.1 U/L at base line *vs.* 23.4 ± 4.6 U/L after the 48 weeks; $p < 0.01$). The most common adverse events were "flu-like" syndrome, myalgia, arthralgia, and pancytopenia, but those side effects were manageable and there was no need for discontinuation of treatment.

Clinicians have so far been reluctant to use combined therapy (IFN and RBV) in hemodialysis patients with chronic hepatitis C, due to development of dose dependent hemolytic anemia. The elimination rate of ribavirin in patients with impaired renal function is reduced, and only a small fraction of the drug is eliminated during dialysis session. In the concentration-controlled safety study,

Bruchfeld *et al*. [28] used combined therapy in six hemodialysis patients. The SVR rate was 17% (one out of six patients). The target ribavirine concentration was reached with average daily doses of 170-300 mg ribavirin. The usual dose of ribavirin in patients with normal renal function is 1000–1200 mg per day. Ribavirin-induced anemia was successfully treated with high doses of erythropoietin (20 000–30 000 IU per week). The successful management of ribavirin-induced anemia in hemodialysis patients has been also presented by Mousa *et al.* [29]. They treated nine hemodialysis patients with biopsy-proven hepatitis C, with combined therapy of IFN and RBV (200 mg three times a week) for 24 weeks. The SVR rate was 66% (six out of nine patients), and the main side effect was ribavirin induced anemia. These results indicate that ribavirin could be administrated in hemodialysis patients, but only in low doses and with aggressive support for the hemolyisis and anemia.

Conclusion

Therapy for hepatitis C has advanced considerably in the last 10 years, but the applicability of the current regimen for hemodialysis patients remains unclear. Results indicate that sustained responses can be achieved in hemodialysis patients, and these responses are likely to be clinically significant. The complications of chronic hepatitis C, also can be prevented by antiviral therapy. The challenge in therapy of hepatitis C in hemodialysis patients is to identify the optimal and safe regimen. At present, therapy for hepatitis C should be considered in hemodialysis patients with significant liver disease, minimal other co morbidities, and a reasonable likelihood of prolonged survival or if renal transplantation is planned. Prospective and controlled clinical trials should be conducted to assess efficacy and safety of different ribavirin doses in hemodialysis patients.

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Р е з и м е

НОВ ПРИСТАП ВО ЛЕКУВАЊЕТО НА ХЕПАТИТОТ Ц КАЈ БОЛНИТЕ НА ДИЈАЛИЗА

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Пациентите со бубрежна слабост се изложени на зголемен ризик од инфекција со вирусот на хепатитот Ц, бидејќи имаат честа потреба од трансфузија со крв, како и можност за инфекција преку опремата за хемодијализа. Преваленцата на хепатитот Ц кај болните на хемодијализа варира помеѓу 5–10% во земјите на развиениот свет, и 10–70% во земјите во развој.

Акутниот хепатит Ц има блага клиничка слика која се манифестира со мали или никакви симптоми. Главната компликација на акутниот хепатит Ц претставува хроничниот хепатит, којшто се јавува кај 80% од заболените.

Долгорочните последици од хроничниот хепатит се: цирозата, портална хипертензија, хепаталната инсуфициенција и хепатоцелуларниот карцином. Интерферонот алфа покажа делотворност во лекувањето на хепатитот Ц. Лекувањето во текот на 24–48 недели може да резултира со негативизирање на ХЦВ-РНК во серумот на болните, нормализација на аланин аминотрансферазата и резолуција на хепаталната лезија. Стабилен вирусолошки одговор се постигнува кај околу половината од лекуваните болни. Лекувањето со интерферон е асоцирано со појава на неколку несакани ефекти: грипозен синдром, невролошки и гастроинтестинални симптоми, анемија, изнемоштеност, тромбоцитопенија, леукопенија. Напредок во лекувањето претставуваше додатокот на рибавиринот кон интерферонската терапија. Пегинтерферонот алфа 2а (40 кд) претставува нова, пегилирана форма на интерферонот алфа 2а. Тој беше создаден со цел да го подобри фармакокинетскиот профил и да ја зголеми тераписката ефикасност на интерферонот алфа 2а.

Во нашата студија, четиринаесет пациенти на хемодијализа со хроничен хепатит Ц беа лекувани со 135 μg пегинтерферон алфа 2а, аплициран супкутано, еднаш неделно по хемодијализа, во текот на 48 недели. Стабилен вирусолошки одговор беше постигнат кај 5 болни, односно кај 36% од лекуваните. Биохемиски одговор, со нормализација на серумските вредности на аланин аминотрансферазата, беше постигнат кај сите лекувани пациенти (83 ± 20,1 U/L на почеток на лекувањето, споредено со 23,4 ± 4,6 U/L на крајот од лекувањето; $p < 0,01$). Засега, лекувањето на хепатитот Ц треба да се примени кај болните на дијализа со значајна хепатална лезија, присуство на минимални коморбидни состојби, веројатност за долго преживување, или при планирана бубрежна трансплантација.

Клучни зборови: хронична бубрежна слабост, хепатит Ц, хемодијализа, интерферон, рибавирин.

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