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Management of Hepatitis C Infection
Regional Guideline

HEPATITIS MONTHLY is the monthly bulletin of **Iranian Hepatitis Group**, which will serves as a forum for the exchange of scientific information in the field of liver diseases with a special attention to hepatitis.We aim, in this bulletin, to present the most recent publicaions particulary from Iran and Middle East as well as to provide facility for a scientific communication among researchers who are working on the field of hepatitis and the other liver diseases. You are welcome to help us in this way by sending your recently published papers.

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Management of Hepatitis C Infection

Regional Guideline

Hepatitis C is a major cause of liver-related morbidity and mortality worldwide and represents a major public health problem. HCV infection affects approximately 200 millions in the world. The majority of patients with acute hepatitis C progress to the chronic stage.Of these, 20% will go on to develop cirrhosis over the course 20-25 years, if left untreated. Long-term chronic hepatitis C (CHC) is associated with the risk of decompensated cirrhosis and hepatocellular carcinoma. Liver transplantation is the only treatment available for end stage liver disease resulting from chronic hepatitis C.

Symptoms of hepatitis C are not manifested for 20-30 years in many patients and the rates of diagnosis are relatively low (<20%) even in many developed countries. Together, these factors account for a silent pool of patients who have the potential to unknowingly transmit the virus to other unsuspecting individuals. Although in many patients, the source of infection remains unknown, in developed countries it is estimated that 90% of patients with chronic HCV infection are current or former intravenous drug users and those with a history of transfusion with unscreened blood products. Since screening of blood products was introduced in the early 1990s in most developed countries, the incidence due to blood transfusions dropped dramatically. It seems that its epidemiology has been changing during last decade.

In Iran, it seems that the prevalence of HCV infection in general population is less than 1 percent, which is much lower than the most of regional countries. But the infection is emerging mostly due to problem of intravenous drug use and needle sharing in the country. The prevalence rate of HCV infection is as high as 20% in general population of Egypt and the prevalence in patients with chronic liver disease in Saudi Arabia is 30.4% and in Pakistan is 24%. Two recent consensus conferences on the management of HCV (NIH consensus and French consensus conference) have had a major influence on clinical practice and approach to this disease. New advances have been made in treatment of chronic hepatitis C, with introduction of pegylated interferon(PEG-IFN) which in combination with ribavirin(RBV), gives an overall sustained virological response of 55% (approximately 45% for HCV genotype 1 and 80% for HCV genotype 2 and 3). Improved rates of response to treatment have led to expansion of indications for treatment in hepatitis C to groups such as persons with compensated cirrhosis, patients older than 60 years, patients with normal aminotransferase. Nowadays, eradication of hepatitis C (HCV) is not an unrealistic aim in many chronically infected patients.

Fortunately the information provided to HCV infected individuals has considerably improved, making patients more aware and better placed to participate in the management of their disease. For examples, they ask us about the best treatment and some of them insist to receive curative treatment. The physicians that carring for patients with HCV infection, including internists, specialists in gastroenterology and hepatology and infectious disease need to new information in management strategy for HCV infected patients and this review will support them. We like to answer following questions in our review; which patients should be treated? What are the most appropriate investigations before treatment? What is the most effective therapy for hepatitis C? How should treated patients be monitored and how should the side effects of therapy is managed? How the non-responders patients to standard interferon plus RBV should, be treated? How HCV infected patients on hemodialysis or thallassemic patients should be managed?

This guideline addresses key highlights in management of hepatitis C by emphasis on new drugs in cure of hepatitis C. Many important issues regarding complex cost effective analysis must be taken into account according to socio-economic situations of different countries.

WHICH PATIENTS SHOULD BE TREATED?

Treatment of the HCV-infected patient with anti-viral drugs aims to eradicate the infection and cure the patient from HCV infection. Inhibition of viral replication will decrease the activity of the liver disease, which is believed to be associated with prevention or delay of the progression of liver disease, reduction the risk of HCC and improvement in quality of life.

The introduction of new drugs or new drug combinations with better efficacy may modify the treatment indications in HCV infection. All the patients with chronic hepatitis C infection are potential candidates for antiviral therapy. However, several factors have been shown to have an important impact on the likely response to treatment and should be considered carefully when reaching a treatment decision. These factors include age, quality of life, presence of comorbidity (HIV, neuropsychiatry illness, etc.), intravenous drug users, significant alcohol consumption, and genotype, but the major indication for treatment is largely based on the severity of liver disease. Patients with greater risk of developing cirrhosis, such as persistent ALT elevation, detectable HCV RNA and evidence of fibrosis and at least moderate inflammation on liver biopsy, but other patients that do not meet all of above criteria should refer to specialized units for treatment in the setting of research protocohol. In conclusion, the decision to treat patients with chronic hepatitis C is based upon several factors, including stage of the disease, level of ALT, genotype, and efficacy and adverse effects related to therapy.

Recommendations

1 Patients with active histology i.e. Total Histological Activity Index (HAI) >= 5 or stage more than 2 should be treated.
2 Patients with persistently elevated ALT especially those with severe fibrosis on liver histology (>F1 ,Metavir).
3 Patients who wish to be treated in any case especially those with genotype 2 and 3 may be treated even with normal serum ALT.

WHAT ARE THE MOST APPROPRIATE INVESTIGATIONS BEFORE TREATMENT?

A detailed history and physical examination on the initial patient-physician encounter, will provide the most important early information leading to the therapeutic plan, and ultimately aid in managing the potential side effects of treatment. Furthermore, significant co-morbidities, such as congestive heart failure and uncontrolled depression, which would be contraindications to treatment, also are identified by the initial patient history. Patients who are considered for treatment first should have a virological proof of HCV RNA in serum. Lab studies are also necessary for establishing a pretreatment baseline, identifying advanced liver disease, or contraindications to treatment. Recommended baseline tests consist of complete blood count(CBC), aminotransferase level (ALT, AST), alkaline phosphatase, liver function tests (blirubine , protrombin time and serum albumin), renal function tests, thyroid function tests, and alpha fetoprotein .Evaluation for other types of liver disease should also be obtained;

especially HBV and Hemochromatosis.Other medical conditions should be investigated. Special attention should be paid to diabetes mellitus, congestive heart failure, epilepsy, extrahepatic manifestations, psychological disorders, HIV coinfection, excessive alcohol consumption and excess body weight. Patients with a history of psychiatric disorders are particularly at risk for the development of the neuropsychiatric side effects of IFN. History of significant or severe psychiatric disease is a contraindication to initiating therapy. A psychiatric evaluation should be obtained for patients who have a significant past or present history of depression, and most notably those with a history of hospitalization or a suicide attempt .For the patients with active depression first treat with appropriate psychotropic drugs, before initiating IFN therapy.

The nucleotide sequence of HCV varies considerably from one isolate to another, forming the basis for at least six known genotypes and 30 subtypes. Genotypes have been of considerable epidemiological interest and their prevalence varies considerably in different parts of the world. Knowledge of the genotype may be useful in the predicting the likelihood of a favorable response to therapy. Patients infected with genotype 2 and 3 are more likely to respond to combination therapy than those with genotype 1. Thus, because of the strong influence of HCV genotype on predicting response and influencing the duration of therapy, HCV genotyping prior to treatment has been suggested.

Many physicians feel that a liver biopsy should be a part of the work-up of any individual with chronic hepatitis C infection and is generally recommended before treatment. The biopsy is still the best way of evaluating fibrosis and therefore, the outcome (prognosis) of the liver disease.

It helps to determine the natural history of disease, identify cirrhosis and concomitant liver diseases such as non alcoholic steatohepatitis. Considering the high treatment efficacy in some HCV genotypes and biopsy refusal by some patients, liver biopsy should not be mandatory when the decision to treat has already been taken and will not be affected by the histological results. In patients who infected by genotype 2 or 3, patients with symptomatic cryoglobulinemia, HCV/HIV co- infected patients and women who wishing to avoid the (low) risk of transmitting HCV to their child in their future pregnancy, without liver biopsy treatment are possible.

Routine pregnancy testing prior to treatment is mandatory for patients or patients of childbearing potential, because of the teratogenicity of RBV.

A baseline retinal examination, at the time of the initial physical examination, should be done; IFN-associated retinopathy has rarely reported to occur during treatment.

Recommendations

1 Complete blood count (CBC), aminotransferase level (ALT, AST) , alkaline phosphatase, liver function tests(blirubine,protrombin time and serum albumin), renal function tests, thyroid function tests, fasting blood sugar, and alpha fetoprotein as a base line tests should be done.

2 Ultrasonographic studies for evaluation of liver morphologic changes, ascites, splenomegaly and portal hypertension signs in all cases is recommended.

3 Liver biopsy is necessary and is still the best way of evaluating severity of liver disease, but can be withdrawn in special circumstances.

4 Evaluation for associated viral disease (HBV and HIV) should be done.

5 HCV genotyping and HCV RNA by qualitative PCR for all cases (and if possible HCV RNA level by quantitative PCR for those with genotype 1 and 4) must be determined before treatment.

6 A psychiatric evaluation should be obtained for

patients who have a significant past or present history of depression, for the patients with active depression first treat with appropriate psychotropic drugs, before initiating IFN therapy.

7 Eye examinations before therapy as the base and in follow up; especially in patients with diabetes and hypertension is recommended.

8 Pregnancy testing prior treatment is mandatory.

WHAT IS THE OPTIMAL TREATMENT ?

The established treatment of chronic hepatitis C is with alpha IFN. The anti-viral effect of alpha IFN is well demonstrated. Until 1998, alpha IFN (monotherapy) was the only approved treatment for HCV infection. Now, combination therapy with IFN and RBV should be considered as the initial treatment of choice among patients with chronic hepatitis C who are deemed suitable candidates. Treatment with RBV alone reduces serum ALT concentrations, but not serum HCV RNA levels, and RBV alone is not recommended.

The optimal response to antiviral therapy is called a virologic sustained response (SVR), which define as absence of detectable HCV RNA by using RT-PCR assay 6 months after stopping the treatment.Most of these patients will remain in remission with no detectable HCV RNA in the blood and liver.

The overall SVR with combined alpha IFN plus RBV for 48 weeks is about 40%. However, the SVR for patients infected with genotype 2 and 3 are 60% and for genotype 1 is 30%.

The recent NIH Consensus Conference of the Management of Hepatitis C has concluded that on the basis of available data the highest response rates to antiviral therapy for the treatment of chronic hepatitis C have been achieved by using the combination of PEG-IFN plus RBV, at least for patients infected with genotype 1 and such regimen has been therefore proposed as the new therapy for chronic hepatitis C.

Combination therapy with PEG-IFN plus RBV is preferred in which countries which it is available. Although in the three large pivotal randomized trials pegylated IFN plus RBV was more effective than standard IFN-RBV combination or PEG-IFN alone, but among patients with genotypes 2 or 3, SVRs with standard IFN and RBV were comparable to those with pegylated IFN and RBV (60-76% versus 76-86%) and thus we recommend standard IFN and RBV in treating naïve patients with genotype 2 or 3. It has been shown that genotype is one of the key factors influencing treatment modalities.

Data from the treatment individualization study with pegylated INF plus ribavirin indicate that treatment duration should be related to HCV genotype. Patients with hepatitis C genotype 2 or 3 can be effectively treated with pegylated IFN plus low-dose RBV (800mg) for only 24 weeks, while patients with genotype 1 require pegylated IFN plus standard-dose RBV (1000-1200mg) for a full 48 weeks. Patients with genotype 1 and high viral load (>2 million copies/ml or >800,000 IU/ml) are considered populations with poor response to treatment (difficult to treat patients) and maximum SVR of 40-45% in this group is attained with pegylated IFN and 1200mg ribavirin (for 48wk) while with standard IFN and ribavirin the SVR is less than 15%.

The standard protocohol for IFN administration is to be injected 3 MU, three times in a week (TIW) for 24-48 weeks.

The current recommended dose for RBV is 800-1200 mg /d orally, depends upon the patientís body weight. In patients who weigh more than 75 kg, the dose is increased to 1200 mg/d. The standard dose in PEG-IFN 2a is 180 micro grams/ weekly. Length of treatment depends upon genotype: 48 weeks for genotype 1 and 24 weeks for genotype 2 or 3.

Ribavirin warning : RBV has been shown to be teratogenic. Women of childbearing age

and female partners of male patients who are taking RBV must use at least two reliable forms of effective contraception during treatment and during the six-month post treatment follow-up period. Because of the drug`s long half-life, pregnancy is contraindicated for 24 weeks after its discontinuation.

Treatment with IFN plus RBV is more likely to clear HCV if a person has a genotype other than 1, a low HCV viral load (less than two million copies / ml), has been infected with HCV for a shorter time, has mild to moderate disease, is female, and is of a younger age. After twelve weeks of antiviral treatment, a 2-log drop in viral load or elimination of virus predicts a successful response at the end of treatment.

The evidence suggests that the majority of patients with a sustained virological response (SVR) will remain HCV RNA negative by sensitive RT-PCR for years after stopping therapy. These patients show a decrease in necro-inflammatory activity and show some decrease in the reversible components of fibrosis. Most of patients with SVR will have a favorable long-term biochemical and histological outcome.

Severe HAV and HBV infections have been reported in people co-infected with HCV. It is strongly recommended that people with HCV get vaccinated against HAV and HBV if they are not already immune.

Recommendations:

1 Those who are indicated for treatment should receive combination therapy with standard alpha IFN 3 MU three times in a week plus RBV 800-1200 mg/daily according to weight, and if available PEG-IFN 2a 180 microgram per week plus RBV 800-1200 mg/daily.

2 The benefit of using PEG-IFN instead of standard IFN in combination with RBV were not uniform in different patients groups: PEG-IFN improved significantly SVR in patients with genotype 1 and high viral load. By the way non- responder to standard IFN and RBV have no other choice than using PEG-IFN with RBV. Also combination of PEG-IFN plus RBV may be used as initial therapy for those patients who themselves intend to receive this combination.

3 The dose of RBV should be decided according genotype and body weight. Patients with genotype 2 or 3 should be given a fixed dose of 800 mg daily of RBV and patients with high titer viremia (2-3 million copies/ml) and genotype 1 should be given full dose of RBV (1000-1200 mg daily) based on body weight less than or greater than 75 kg.

4 Duration of therapy depends on genotype: 24 weeks for genotype 2 or 3 and 48 weeks for genotype1.

5 Patients with contraindication for RBV should be given 48 weeks of IFN 3 MU three times in a week.

6 Check the HCV RNA after three month in genotype 1 (patients with genotype 2 and 3 do not need to this request).

7 Positivity or less than 2 log drop of the HCV RNA titer after 12 weeks of therapy in genotype1 has a 98% negative predictive value for SVR, so in this circumstance therapy can be shifted from standard INF to PEG-IFN.

8 Continue if HCV-RNA at three months is detectable in combination therapy with pegylated IFN with RBV(or decrease less than 2 log in HCV RNA titer) and check the HCV RNA at 24 weeks and continue it to 48, if seroconvert to negative.

9 Hepatitis B vaccination in patients who are not immune is recommended.

10 Alcohol consumption seems to be associated with increased viral replication and

How to monotor the patients?

Patients should be tested on regular basis to monitor side effects and to make sure that they are responding to therapy. If a person has not responded after three months of treatment, further therapy is unlikely to clear the virus; many physicians recommend stopping the medication at this time current treatment options can have many undesired side effects and treatment success cannot be achieved in everyone. But one should bear in mind that continuing treatment in these patients can result in histologic improvement and HCC protection, even in the absence of virological response.

Recommendations

1 Patients should be seen two weeks interval in first month so that blood counts are performed to look for Hemolysis. Thereafter patients should be seen every 4-6 week until therapy is finished.

2 Patients need continued support and encouragement and side effects must be monitored.

How to manage the side effects?

Combination therapy with IFN and RBV has a proven efficacy in treatment of HCV infection. However this therapy is associated with numerous adverse effects that should cautiously evaluated through rigorous monitoring. Most of adverse effects are dose dependent and often reversible. The most common of these are a flu-like syndrome, muscle and joint pain, nausea, headache, loss of appetite, fever rigors and arthralgia, which occurs in the first 4 weeks of therapy and that generally, resolves on its own. After the first month of therapy, late adverse effects, such as fatigue, headache and neuropsychiatric changes, may occur. Depression is also a common adverse effect of IFN therapy, and patients with a history of depression must be carefully monitored while undergoing therapy. Other less common adverse events include hypothyroidism, hyperthyroidism, arthralgia, rash and reversible alopecia.

IFN has myelosuppresive effects resulting in reduced granulocyte, platelet and red cell counts. The reductions are usually mild and well tolerated unless there are hypersplenism. Neutropenia and especially thrombocytopenia may be managed through dose reduction. Some people may develop thyroid dysfunction while on treatment with IFN. Thyroid function should be closely monitored prior to starting treatment and then every three months during therapy. In most people, thyroid function returns to normal once therapy discontinued, but some people may develop irreversible thyroid problems that will require replacement therapy medications. Common adverse effects of RBV include anemia, irritability, rash, pruritus, cough, shortness of breath and insomnia. RBV must be used with caution in patients with coronary artery disease. The main adverse effects of RBV are Hemolysis. A decrease in hemoglobin levels (2-3 gms/dl on average) may be expected in 30% of patients and occurs generally within the first weeks of therapy.

The frequency of most adverse effects of combination therapy with RBV and either one of the two available interferons (conventional IFN and PEG-IFN) are not statically different. Neutropenia, thrombocytopenia and inflammation in injection site are a little more common with PEG-IFN groups. The most important factor in attaining sustained virologic response (SVR) is adherence to therapy. Receiving less than 80% of prescribed treatment and premature

discontinuation and dose reduction decreases the SVR. Published data indicates that 32-42% of patients on pegylated interferon compared to 27-34% of patients on standard interferon required dose reduction do to adverse events. The most frequent indication for dose reduction is laboratory abnormalities such as anemia, neutropenia and thrombocytopenia. Near 25% of patients require at least one dose reduction for these abnormalities.

Table 1: Major Side Effects of Combination Therapy with Interferon-a and RBV

Common side effects usually caused by interferon-a

- Fatigue, malaise, myalgia, headache, poor appetite.
- Depression, irritability, anxiety, emotional lability.
- Difficulty concentrating, forgetfulness, sleeplessness.
- Bone marrow suppression, thrombocytopenia, and neutropenia
- Accentuation of INF bone marrow suppression

Common side effects caused by RBV

- Hemolysis, hemoglobin decrease of 20 to 30 g/l
- Gastrointestinal upset
- Nasal congestion, sore throat, cough, dyspnea
- Pruritus, skin rash

Uncommon, serious side effects

- Bacterial infections
- Induction of autoantibodies and autoimmune disease
- Severe depression, psychosis, suicide
- Relapse in substance abuse
- Seizures
- Vision or hearing loss, tinnitus
- Acute renal or heart failure

Constitutional Symptoms: Fatigue, fever and myalgia the so called influenza like symptoms are the most frequent side effects.

In practice almost all patients experience at least one of these symptoms during therapy. Frequency and severity of these symptoms decrease with time. Simple measures such as adequate hydration, light to moderate regular exercise, altering schedule of injection to days with lighter work loads are very effective but are usually neglected .Acetaminophen or ibuprofen before or at the time of injection may prevent these symptoms. COX 2 inhibitors may have effect but the data are scant and the drugs are more expensive.

Anemia: Both interferon (by suppression of hematopoiesis) and RBV (by Hemolysis) may induce anemia. This effect is greater with PEG-IFN. RBV produces hemolytic anemia to some extent in almost all patients and is dose dependent.

There is usually a drop of approximately 2-3 mgs/dl in the first 2-4 weeks of treatment in combination therapy.

In near 9% of patients, hemoglobin drops to levels that mandating dose reduction. The initial response should be reduction of the RBV dose unless there is concomitant neutropenia or thrombocytopenia.

Neutropenia: Decrease in neutrophil counts is more marked in the first 2 weeks of the therapy and is usually stabilized in the next 4-6 weeks. In about 5% of these patients severe neutropenia (<500 cell/mm3) occurs. No increased instance of infections had been shown in these patients except for those suffering from cirrhosis in which the incidence of infectious complications is probably increased in the presence of neutropenia. Current recommendation is decreasing the dose of interferon if neutrophil counts drop to below 750 cell/mm3 although lower limits may be also well tolerated.

Regarding neutrophil kinetics it is the best to measure neutrophil count just before the injections rather after .With this approach improper dose reduction would be avoided.

Thrombocytopenia:

The platelet count is decreased by 10-50% on interferon therapy. The nadir is usually reached within 8 weeks of therapy and the count would be stabilized for the whole length of therapy at this low level. After discontinuation of the drug the count would return to normal within 4-8 weeks. Dose reduction or drug discontinuation is usually not needed. In cirrhotic patients with low base line counts of platelet it is best to avoid further decrease of count to below 50000 cell/mm3. Rare instances of immune mediated thrombocytopenia have been reported with profound decrease in platelet count. This complication should be treated with corticosteroids and discontinuation of interferon.

Table 2: Dose adjustment of IFN and RBV

Absolute neutrophil counts (cells/mm3)

- < 1000 but > 750 reduce to 1.5 MU in Conventional IFN and to 135 microgram in PEG-IFN
- < 750 but > 500 stop treatment until > 750 cells/mm3 and then resume with low dose

Platlets counts (cells/mm3)

- < 100 000 but > 50,000 Reduce to half dose
- Stop treatment until > 50,000 cells/ mm3 then resume with low dose

Hemoglobin (gm/l)

- < 10 but > 8.5 reduce RBV dose to 400-600 mg / day
- < 8.5 stop RBV until > 8.5 gm/l resume the RBV in low dose

Neuropsychiatric symptoms:

Serious neuropsychiatric side effects to IFN can occur and include depression, paranoia, severe anxiety, and psychosis. In patients with a history of substance abuse, the psychiatric changes can lead to a disastrous relapse in drug abuse. There is an increased incidence of depression in patients with chronic hepatitis C infection even before treatment. The reason for this observation is not clear but may be related to excess fatigue, uncertainty about prognosis and higher rates of substance abuse among these patients .It is mandatory to evaluate these patients before starting antiviral therapy for the presence of psychological disturbances which may need their own management. Suicidal thoughts or attempts and severe bipolar disorders are contraindications for interferon therapy. Currently there is a trend in expanding eligible patients for antiviral therapy in chronic HCV infection. Even active drug abuse is no longer considered as absolute contraindication for therapy and there are reports of success even in this high risk group without adverse neuropsychiatric events.

Interferon based regimens can induce a variety of neuropsychiatric adverse reactions including depression, irritability, emotional liability, aggressive behavior and panic reactions. The incidence of depression has reported to be as high as 30%. Depression usually occurs in the first half of the treatment period .PEG-IFN had lower incidence of depression compared to standard IFN. Treatment of depression with antidepressants is recommended in this situation .Speculative mechanism of depression in these patents involves serotonin depletion so serotonin reuptake inhibitors (SSRI) are considered drug of choice in these patients. SSRIs are effective and safe in patients with liver disease. Tricyclic antidepressants should generally be avoided due to their anticholinergic and sedative side effects. If antidepressants are started they should be continued 6-12 months after stopping antiviral therapy. Regarding high rates of depression in these patients some investigators have proposed prophylactic treatment with SSRIs but this is not recommended by most authorities.

Thyroid Disease: Some patients with chronic HCV infection have thyroid disease before antiviral therapy. Up to 31% of women with chronic hepatic C infection have autoantibodies to thyroglobulin and thyroid microsomal antibodies and 5 to 17% of them have hypothyroidism before treatment. The incidence is much lower in male with only 2% incidence of autoantibodies and very low incidence of hypothyroidism. Presence of autoantibodies before treatment has been linked to the development of thyroid disease during interferon therapy. While 38.5% of women with thyroid autoantibodies developed hypothyroidism on interferon the incidence in the whole group was only 7.8% in one series. The effect of interferon on thyroid is not always reversible. A subset of patients who develop autoantibodies on interferon therapy progress to chronic thyroiditis even after discontinuation of the drug. Measurement of autoantibodies before or during therapy is not cost effective because not all patients with these antibodies progress to clinically significant thyroid disease but TSH should be tested before and every 12 weeks while on therapy and once after completion o treatment. There should be high index of suspicious to hypothyroidism during therapy. Subtle complaints such as excessive fatigue might be the only clue. Hypothyroid patients should receive hormone replacement. Usually antiviral therapy could be continued. Hyperthyroidism may also occur. This could be a presentation of grave's disease or a stage of thyroiditis so thorough evaluation before starting antithyroid drugs in these patients is very important. Referring the patient to endocrinologist is recommended.

Other adverse effects

Autoantibodies to adrenal cortex and pancreatic islet cells have been reported during interferon therapy. There are reports of new onset of type one diabetes in these patients. Uncontrolled hyperglycemia in previously well controlled diabetics is not an uncommon problem during interferon therapy which needs more aggressive monitoring and treatment in these patients. There is a large list of other side effects of interferon most as case reports with no documented cause and effect relation. These include pulmonary, ocular, neurologic, dermatologic, renal and cardiovascular events. Even if they are really related to interferon they are area and only close monitoring during therapy is enough to detect them.

Recommendations

1 Contraindications to combination therapy should consider such as: include Hemolysis, anemia, bone marrow suppression, coronary and cerebro-vascular disease, neuropsychiatric condition, active alcohol or substance abuse, renal transplantation and autoimmune disease.

2 Before treatment patients should be informed about possible side effects and plans for their monitoring and managements during therapy.

3 Proximity and availability of medical support during treatment is essential.

4 To avoid constitutional symptoms during therapy, adequate hydration, light to moderate regular exercise altering injection schedules to days with lighter work loads and receiving either acetaminophen or ibuprofen just before injections are helpful.

5 CBC should be done on weeks 2, 4 and thereafter every 4-6 weeks till the end of treatment. The test should be checked before injection. If hemoglobin drop to less than 10 g/dl but more than 8.5 g/dl, RBV dose should reduced to lower dose and stop in less than 8.5 g/dl, thrombocytopenia less