Proceeding S.Z.P.G.M.I. Vol: 29(1): pp. 1-4, 2015.

Pegylated Interferon and Ribavirin For Post Liver Transplant HCV Recurrence

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ABSTRACT

Pakistan has a very high HCV prevalence[1] with majority being genotype 3. A high number of patients with cirrhosis undergo liver transplantation. HCV recurrence following transplant is universal[2]. Interferon free therapy has recently become available and preliminary studies show 70% SVR in post transplant patients[8]. Since genotype 3 has a high response to pegylated Interferon 3, it remains a competitive agent. **Aims & Methods:** The aim of this study was to determine the efficacy of pegylated interferon plus ribavirin in the treatment of recurrent hepatitis C following liver transplantation. 15 patients with recurrent hepatitis C following liver transplantation were included in the study, 13 males and 2 females. Mean age was 52 years. 13 had genotype 3 disease, one genotype 2 and one genotype 1. 11 were living donor and 4 were cadaveric grafts. 13 were on tacrolimus & MMF, one on tacrolimus alone and one on cyclosporine & MMF. 6 patients were treated within 2 years of transplant and remaining 9 were treated 3-5 years after transplant. Liver biopsy was done prior to therapy in 6 patients. All patients received pegylated interferon α2a 180μg weekly plus ribavirin 15mg/kg daily for 48 weeks. **Results:** 14 out of 15 patients (93.3%) achieved SVR. This included all 13 Genotype 3 patients (100%) and the single genotype 2 patient. One patient, genotype 1, was nonresponder to treatment. Treatment was stopped at 22 & 36 weeks in 2 patients due to anaemia. Both achieved SVR. 11 patients were administered erythropoietin for anemia. 7 patients required ribavirin dose reduction for anemia, and achieved SVR despite dose reduction. **Conclusion:** Pegylated interferon and ribavirin is an extremely effective combination for treatment of patients with recurrent genotype 3 hepatitis C after liver transplantation. The main side effect is anaemia, which can be managed with erythropoietin supplementation and ribavirin dose reduction without any reduction in response rate.

Keywords: erythropoietin, genotype 3, liver transplantation, Pegylated interferon, recurrence of hepatitis C, ribavirin dose reduction

INTRODUCTION

Pakistan has a very high HCV prevalence with majority being genotype 3[1]. Liver transplantation started in Pakistan 4 years ago. We are dealing with a large number of patients who have undergone liver transplant either locally or in neighbouring countries (India and China) and now have recurrent hepatitis C. Recurrence of hepatitis C following liver transplant is universal[2]. Approximately half of the patients transplanted for HCV related liver disease develop chronic hepatitis within a year of transplantation whereas cirrhosis develops in about 30% of these cases after 5 years[3]. Hepatitis C follows an accelerated course following liver transplantation and is a major cause of graft loss. Early treatment is recommended as soon as active disease is confirmed with serological markers with or without histological confirmation. Until now the standard of care has been pegylated interferon in combination with ribavirin for the management of such patients with recurrent disease[4, 5, 6, 7]. Various

factors such as HCV genotype and early virological response to treatment predict success of treatment[3]. Oral, interferon-free, therapy has only recently become available and preliminary studies have showed a 70% SVR rate to oral therapy (sofosbuvir plus ribavirin) in the post liver transplant population with HCV recurrence[8]. Since genotype 3 has a very favourable response to pegylated interferon plus ribavirin, we believe that this will still have a role considering the high cost of interferon free oral regimes. As Pakistan is one of the worst hit countries with HCV related liver disease[7], the management of recurrent HCV in the few patients who can afford to undergo liver transplant is vital.

AIMS

The aim of this study was to determine the efficacy of pegylated interferon plus ribavirin in the treatment of recurrent hepatitis C following liver transplantation.

OPERATIONAL DEFINITIONS

HCV recurrence: Recurrence of HCV disease was diagnosed by the presence of biochemical graft dysfunction evident with elevated serum transaminases and with detectable viral RNA by polymerase chain reaction (PCR) with or without concomitant liver biopsy (showing features consistent with recurrent HCV, including portal or lobular infiltration by mononuclear cells with piecemeal necrosis, hepatocellular fatty change, and/or fibrosis in the absence of other specific causes such as cellular rejection).

HYPOTHESIS

Pegylated interferon plus ribavirin is an effective treatment for patients with recurrence of hepatitis C following liver transplantation.

Study Design:

Non-randomized open label clinical trial

Setting:

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Duration:

1 year

Sample Size

15 patients

METHODS

A total of 15 patients with recurrent hepatitis C following liver transplantation were included in the study. Eleven were living donor and 4 were cadaveric grafts. Thirteen male and 2 female patients. Mean age was 52 years. Thirteen patients had genotype 3 disease, one was genotype 2 and one was genotype 1. Thirteen patients were recieving tacrolimus and mycophenolate mofetil (MMF). One patient was recieving tacrolimus alone and one was recieving cyclosporine with MMF. 6 patients were treated for HCV recurrence within 2 years of undergoing transplant. The remaining 9 were treated in the 3-5 years after transplant. Liver biopsy was done prior to therapy in 6 patients while the remaining 9 were started on therapy on confirmation of virus activation on detection of viral RNA by polymerase chain reaction (PCR) and elevated transaminases. All patients were scheduled to receive pegylated interferon α2a 180μg weekly plus ribavirin 15mg/kg daily for 48 weeks.

RESULTS

Fourteen out of fifteen patients (93.3%) achieved sustained virological response (SVR) as evidenced by non detectable viral RNA 12 months after end of treatment with pegyated interferon. This included all 13 Genotype 3 patients (100%) and the single genotype 2 patient. One patient, genotype 1, was a non responder to treatment.

Eleven patients were administered erythropoietin for anemia. The dose of erythropoietin varied between 4000 units subcutaneusly once to twice weekly. Seven patients required ribavirin dose reduction for anemia. These patients achieved SVR despite dose reduction in ribavirin.

Two patients were unable to complete the full 48 weeks of thrapy. Treatment was stopped at 22 & 36 weeks in these two patients due to anaemia

which was non responsive to ribavirin dose reduction and subcutaneous erythropoietin. Both of these patients also achieved SVR.

CONCLUSION

Pegylated interferon plus ribavirin is an extremely effective combination for treatment of patients with recurrent genotype 3 hepatitis C after liver transplantation. The main side effect is anaemia which is attributed to ribavirin. Pegylated interferon causes leucopenia and thrombocytopenia. However the occurrence of the latter two side effects is less than anaemia, as is observed in patients receiving both drugs. It must be noted that ribavirin is also an essential component of the all oral regime for treatment of HCV i.e sofosbuvir and ribavirin. The side effect of anaemia is thus shared by both old and new regimes which incorporate ribavirin. The basic recommended strategies for dealing with ribavirin induced anemia are the same in both groups, namely administration of erythropoietin with or without reduction in the dose of ribavirin. Erythropoietin supplementation usually allows maintaining full dose ribavirin. In certain cases, reduction in dose of ribavirin can be done when hemoglobin levels continue to fall despite high dose ertyhropoietin. This combination proves effective in most cases. However in certain patients, as was also the case with two in our study, no strategy proves effective and treatment needs to be stopped. For these patients, the only effectivbe soltion would be ribavirin free regimes which are currently unavailable in Pakistan and will remain so for the forseeable future.

The side effect of anemia (plus any others that may arise during therapy) requires close follow up with the treating clinician. This means closely spaced visits in many cases to assess hemoglobin levels and other laboratory parameters to assess a response to supplementary drugs such as erythripoietin in this case as well as to see the response to reduction in drug doses as with ribavirin in outr study.

We are fortunate to have a very low prevalence of genotype 1 amongst our HCV patients. This genotype has a far less response to therapy with inteferon plus ribavirin. These patients plus those of genotype 3 who are non-responders will benfit from new regimes which incorporate directly acting antiviral agents such as sofosbuvir.

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