

REVIEW

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An overview of treatment response rates to various anti-viral drugs in Pakistani Hepatitis B Virus infected patients

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Abstract

Hepatitis B virus (HBV) is one of the leading health problem with up to 350 million affected people worldwide including 4.5 million only in Pakistan. It has mortality rate of 0.5 to 1.2 million per year worldwide. Pakistan lies in the endemic region with 3-5% HBV carrier rate in the country. The present article reviews the literature on the treatment response of HBV prevalent in Pakistani population. The average treatment response of Lamivudine and interferon- α is 25.81% and 47.95%, respectively. Peg-Interferon was shown to be not effective against the HBV/HCV (hepatitis C virus)/HDV (hepatitis Delta virus) co-infection. The present study reveals that interferon- α is the most effective therapy available for HBV infection prevalent in Pakistani population. Genotype C & D are the most common HBV genotypes in Pakistan and are associated with increased severity and less response to interferon therapy. This poses a great challenge for physicians and researchers and further studies are needed to describe the outcome of the current therapies recommended against HBV infection in Pakistani population.

Introduction

Hepatitis B virus (HBV) is a crucial health problem with up to 350 million affected people worldwide [1]. HBV is a member of the *Hepadnaviridae* family with 3.2 kilobase pair DNA genome which is partially double-stranded [2,3]. Pre-s domain surface protein is mediates its attachment to the cell membrane [4].

Several previous studies on the association of the HBV genotypes with disease progression reported that genotypes B and C are correlated with severity of liver dysfunction while high viral loads were observed in patients infected with genotype C [5,6], A, and D [7] in some studies but not in others [8,9]. According to WHO, Pakistan has low HBV infection rates of 3%, while studies from Pakistan are more focused towards the HBV prevalence rate [10,11], epidemiological issues [12], genotyping and its core antigen genetic variability [13].

Approved drugs advised for the treatment of HBV include interferon- α , PEG-interferon and antiviral drugs

like lamivudine, adefovir, dipivoxil, entecavir and telbivudine. Hepatitis B antibodies and the HBV vaccine within 12 hours of birth help to prevent the infection [14]. In Pakistan, there are estimated 4.5 million carriers of HBV with a carrier rate of 3-5%. However, studies are limited describing HBV treatment response in Pakistani population. The present article reviews all the available literature on the treatment response to the available therapies against HBV prevalent in Pakistani population (Table 1).

Anti viral efficacy of lamivudine

A nucleoside analogue called lamivudine, has anti-HBV and anti-HIV properties, was approved by the US-FDA in 1998 for the treatment of HBV infections. It is administered orally with concentration of 100 mg/day [15]. Use of lamivudine is reported to decrease the circulating DNA levels of HBV [16,17] while long term decrease has been achieved after one month's therapy [18]. In Pakistani population, the rate of seroconversion against lamivudine was observed to be 16% in HBV/HDV (Hepatitis delta Virus) co-infected patients when administered for 36 months [19], 23 to 38% in HBV infected patients when administered for 12 months and 36 months,

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Table 1 An overview of treatment outcome in Pakistani HBV treated patients

Author	Region	Patients (n)	Etiology	Treatment	Duration (weeks)	Results
Qureshi et al: [19]	Karachi	69	HBeAg, HBV DNA positive patients	100 mg of Lamivudine orally before breakfast till seroconversion	36 months	38% cases were observed to sero-converted.
Qureshi et al: [19]	Karachi	55	HBV DNA positive (wild type) with delta positive	100 mg of Lamivudine orally before breakfast till seroconversion	36 months	16.4% cases in group 2 sero-converted (Wild type of HBV/HDV co-infected cases have a 16% chance of seroconversion)
Naeem et al: [31]	Rawalpindi	50	Chronic viral hepatitis B (HBsAg and HBV DNA positive)	5 mega units of recombinant interferon alfa-2b subcutaneously once daily	4-months	HBV DNA was found negative in 44.0% (22) patients while treatment was ceased in three patients due to severe depression.
Zuberi et al: [21]	Karachi	246	co/super-infection of Hepatitis C and D among patients of HBV	pegylated interferon- α 2a 180 mcg sc weekly	48 weeks	HBV was not cleared in any case
Zuberi et al: [32]	Karachi	52	patients of hepatitis B with hepatitis D	Interferon - α 10.0 MIU sc t.i.w.	48 weeks	51.9% patients had suppressed (< 400 copies/ml) HBV DNA levels
Khokhar et al: [21]	Islamabad	105	positive HBsAg and elevated ALT	lamivudine 100 mg once a day for 12 months	12 months and were followed every 2-3 months with ALT, HBeAg and HBV DNA	HBeAg positive and HBeAg negative patients were found with 23.6% and 80.0% treatment response rate respectively (All the patients were HBsAg positive)

respectively (Table 1) [20,21]. A much higher HBV response rate is being observed in Pakistani population than reported earlier [22]. These studies show that lamivudine monotherapy is a better option for treatment of HBV infection but this therapy require longer durations (up to 36 months) and develop increased resistance (up to 20% after one year and 70% after 5 years of therapy) [23,24], which makes it undesirable for the patients.

Nucleotide and nucleoside analogues are shown to be associated with minimum side effects as compared to the standard INF and PEG-INF therapies. These include short term adverse effects like myopathy, neuropathy and lactic acidosis [25]. These include side effects like abdominal pain, headache, cough, nasopharyngitis, pyrexia, diarrhea and fatigue [26].

Anti viral efficacy of Peg-Interferon

Interferon is supplemented with polyethylene glycol (PEG) which prolongs its half-life resulting in sustained antiviral response rates. Two types of PEG-INF have been studied for HBV therapy, PEG-INF α -2a having a large 40 kDa PEG branched and PEG-INF α -2b with a 12 kDa PEG molecule [27]. Buster and Janssen [22] reported HBV treatment response of 19-35% by administration of peg-INF. However, administration of pegylated interferon- α 2a for 4 months failed to treat the HBV, HDV and HCV co-infection in Pakistani population [20] and is associated with adverse effects like depression, flu-like symptoms, neuropsychiatric disorders and suppression of bone marrow [28].

This shows that peg-interferon is not effective against HBV when administered in HBV/HDV/HCV co-infected patients. However, there is no study describing the use of peg-interferon against HBV infected Pakistani population.

Anti viral efficacy of Interferon- α (IFN- α)

IFN- α was approved in 1992 after being extensively studied. It is reported to increase hepatitis B surface antigen (HBsAg) expression by hepatocytes and inhibit packaging of pre-genomic viral RNA into the core particles [29]. Currently, many different types of interferon are available but available data is limited to support advantage of one therapy to be more effective than the others. However, the response rate of 30-40% was reported by the administration of IFN- α for 6-12 months as compared to 10-20% in controls. Patients with lower ALT and/or higher HBV viral loads and immunosuppressed patients are the risk factors that result in decreased response to IFN treatment. Hepatic flares are shown to predict sustained virological response during interferon treatment [30]. Naeem and coworkers [31] reported that administration of 5MIU of recombinant IFN- α -2b for four months lead to response in 44% of Pakistani patients. On the other hand, Zuberi and colleagues [32] described an increased treatment response of 51.9% after administration of 10.0 MIU of IFN- α in HBV infected patients for the same period of 16 weeks. IFN- α is also shown to be associated with the development of side effects like insomnia, fatigue,

alopecia and anorexia [33,34]. However, further studies on the treatment response and follow up of patients are needed to understand the effectiveness of INF- α against HBV infection in Pakistani population.

HBV genetic heterogeneity and Antiviral Therapy

HBV has been classified into 9 genotypes (A-I) based on 8% or more inter-group divergence in full length genomic sequence [35-38] and its antiviral treatment response rate is highly affected by genetic variability as well as by various host and viral factors.

The most recent study conducted throughout Pakistan has reported that HBV genotype C is the most prevalent genotype in Pakistan with 26.7% prevalence, followed by genotype B (18%), A (14.3%), D (13%), mixed genotypes (14.6%) and 10.3% were found untypable [38]. While genotypes E (0.6%) and F (1.3%) have been reported recently in Pakistan. A very high prevalence of HBV genotype D (60-100%) were also reported from different regions of Pakistan [39-44,13]. It is well understood that both genotype C & D are less responsive to interferon therapy and associated with more severe disease than genotype A and B [45,46]. Moreover, these genotypes are reported to be less frequently related to HBeAg clearance rates than genotypes A and B when treated with pegylated interferon [47]. Another study revealed that antiviral response rate against IFN- α was higher in genotype F as compared to genotypes E and G [48].

The high prevalence of HBV genotype D and C in Pakistani population and its association with increased severity of the disease and resistance to the present therapies demands more consistent preventive measures like mass vaccination and awareness programs at national level.

Conclusion

This review explains that interferon- α is the most effective available drug against the HBV prevalent in Pakistan with up to 47.95% treatment response rate. Moreover, treatment of the resistant but most prevalent HBV genotypes C and D is a challenge for clinicians and scientists in our region. However, further studies are needed to fully describe the treatment response and the risk factors of the currently recommended therapies against HBV infection especially combination therapy of interferon and lamivudine in Pakistani isolates. These future prospects will enable the virologists to focus drug designing in this part of the world.

Authors' contributions

LA and MA reviewed the literature, and wrote the manuscript. MI reviewed the manuscript. IR, AH, SA, SB, SS, SM and SB helped LA & MA in literature review. All the authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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