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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 kilo-base 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 lamivuaine, 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-a 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 - a 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 adversed 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-IFN have been studied for HBV therapy, PEG-IFN α-2a having a large 40 kDa PEG branched and PEG-IFN α-2b with a 12 kDa PEG molecule [27]. Buster and Janssen [22] reported HBV treatment response of 19-35% by administration of peg-IFN. 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. Hepatitic 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-alpha 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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References

1. Awan Z, Idrees M, Rafique S, Rehman I, Akbar H, But S, *et al*: **Hepatitis B virus YMDD-motif mutations with emergence of lamivudine-resistant mutants: a threat to recovery.** *Gastroenterology and Hepatology From Bed to Bench* 2010, **3**:108-114.
2. Lee W: **Hepatitis B virus infection.** *N Engl J Med* 1997, **337**:1733-1745.
3. Ganem D, Schneiden RJ, *et al*: **Hepadnaviridae: the viruses and their replication.** In *Fields Virology*. Edited by: Knipe DM, Howely PM, Griffin DE. Philadelphia: Lippincott-Raven; 2001:292-2969.
4. Klingmuller U, Schallen H: **Hepadnavirus infection requires interaction between the viral pre-s domain and a specific hepatocellular receptor.** *J Virol* 1993, **67**:7414-7422.
5. Sugauchi F, Chutaputti A, Orito E, Kato H, Suzuki S, Ueda R, Mizokami M: **Hepatitis B virus genotypes and clinical manifestation among hepatitis B carriers in Thailand.** *J Gastroenterol Hepatol* 2002, **17**:671-676.
6. Ishikawa K, Koyama T, Masuda T: **Prevalence of HBV genotypes in asymptomatic carrier residents and their clinical characteristics during long-term follow-up: the relevance to changes in the HBeAg/anti-HBe system.** *Hepatol Res* 2002, **24**:1.
7. Westland C, Delaney W, Yang H, Gibbs C, Miller M, Wulfsohn MJ: **Hepatitis B virus genotypes and virologic response in 694 patients in phase III studies of adefovir dipivoxil1.** *Gastroenterology* 2003, **125**:107-116.
8. Sumi H, Yokosuka O, Seki N, Arai M, Imazeki F, Kurihara T, Kanda T, Fukai K, Kato M, Saisho H: **Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease.** *Hepatology* 2003, **37**:19-26.
9. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, *et al*: **A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group.** *Hepatology* 2001, **33**:218-223.
10. Khichi GQK, Channar MS: **Prevalence of hepatitis B carriers among children in Bahawalpur urban slums.** *Pak J Med Sci* 2000, **16**:238-241.
11. Khattak MF, Salamat N, Bhatti FA, Qureshi TZ: **Seroprevalence of hepatitis B, C and HIV in blood donors in northern Pakistan.** *J Pak Med Assoc* 2002, **52**:398-402.
12. Akhtar S, Younus M, Adil S, Hassan F, Jafri SH: **Epidemiologic study of chronic hepatitis B virus infection in male volunteer blood donors in Karachi, Pakistan.** *BMC Gastroenterol* 2005, **5**:26.
13. Abbas Z, Muzaffar R, Siddiqui A, Naqvi SAA, Rizvi SAH: **Genetic variability in the precore and core promoter regions of hepatitis B virus strains in Karachi.** *BMC Gastroenterol* 2006, **6**:20.
14. Gilroy RK, Mukherjee S: **Hepatitis A.** *Kanas Med Centre* 2008.
15. Cammack N, Rouse P, Marr CL, Reid PJ, Boehme RE, Coates JA, Penn CR, Cameron JM: **Cellular metabolism of (-) enantiomeric 2'-deoxy-3'-thiacytidine.** *Biochem Pharmacol* 1992, **43**:2059-2064.
16. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, *et al*: **Lamivudine as initial treatment for chronic hepatitis B in the United States.** *N Engl J Med* 1999, **341**:1256-1263.
17. Lai CL, Chine RW, Leung NWY, Chang TT, Guan R, Tai DI, *et al*: **A one year trial of lamivudine for chronic hepatitis B.** *N Engl J Med* 1998, **339**:61-68.
18. Yuen MF, Fong DY, Wong DK, Yuen JC, Fung J, Lai CL: **Hepatitis B virus DNA levels at week 4 of lamivudine treatment predict the 5-year ideal response.** *Hepatology* 2007, **46**:1695-1703.
19. Qureshi H, Arif A, Alam E: **Treatment of HBV and HDV co-infection using lamivudine.** *J Ayub Med Coll Abbottabad* 2009, **21**:1-3.
20. Zuberi BF, Afsar S, Quraishy MS: **Triple Hepatitis: Frequency and Treatment Outcome of co/super-Infection of Hepatitis C and D Among Patients of Hepatitis B.** *J Coll Physicians Surg Pak* 2008, **18**:404-407.
21. Khokhar N, Gill ML, Alam AY: **Treatment of chronic Hepatitis B with Lamivudine.** *J Coll Physicians Surg Pak* 2005, **15**:78-80.
22. Buster EHCJ, Janssen HLA: **Antiviral treatment for chronic hepatitis B virus infection-immune modulation or viral suppression?** *The Journal of Medicine* 2006, **64**:175-185.
23. Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, *et al*: **Long-term safety of lamivudine treatment in patients with chronic hepatitis B.** *Gastroenterology* 2003, **125**:1714-1722.

24. Pawlotsky JM, Dusheiko G, Hatzakis A, Lau D, Lau G, Liang TJ, *et al*: **Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach.** *Gastroenterology* 2008, **134**:405-415.
25. Sonneveld MJ, Janssen HLA: **Pros and cons of peginterferon versus nucleos(t)ide analogues for treatment of chronic hepatitis B.** *Curr Hepatitis Rep* 2010, **9**:91-98.
26. Chang T, Gish RG, de-Man R, Gadano A, Sollano J, Chao Y, *et al*: **A Comparison of Entecavir and Lamivudine for HBeAg-Positive Chronic Hepatitis B.** *N Engl J Med* 2006, **354**:1001-10.
27. Craxi A, Cooksley WG: **Pegylated interferons for chronic hepatitis B.** *Antiviral Res* 2003, **60**:87-89.
28. Chang T, Suh DJ: **Current approaches for treating chronic hepatitis B: when to start, what to start with, and when to stop.** *Hepatol Int* 2008, **2**: S19-S27.
29. Lau JYN, Bain VG, Naomov NV, Smith HM, Alexander GJ, Williams R: **Effect of interferon-a on hepatits B viral antigen expression in primary hepatocyte culture.** *Hepatology* 1991, **14**:9759.
30. Guan R: **Interferon monotherapy in chronic hepatitis B.** *J Gastroenterol Hepatol* 2000, **15**:34-40.
31. Naeem MA, Khan I, Waris J, Usman M: **Efficacy of Interferon therapy in patients of chronic hepatitis B viral infection treated at MH Rawalpindi.** *Professional Med J* 2008, **15**:380-386.
32. Zuberi BF, Quraishy MS, Afsar S, Akhtar N, Kumar A, Dodani SK: **Treatment outcome in patients of hepatitis B with hepatitis D: Experience of 4 years at a tertiary care centre in Pakistan.** *J Coll Physicians Surg Pak* 2007, **17**:320-322.
33. Okushin H, Ohnishi T, Morii K, Uesaka K, Yuasa S: **Short-term intravenous interferon therapy for chronic hepatitis B.** *World J Gastroenterol* 2008, **14**:3038-3043.
34. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, Chutaputti A, Chang WY, Zahm FE, Pluck N: **Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B.** *J Viral Hepat* 2003, **10**:298-305.
35. Okamoto H, Tsuda F, Sakugawa H, Sastrosoewinjo RI, Imai M, Miyakawa Y, Mayumi M: **Typing hepatitis B virus by homology in nucleotide sequence: comparison of surface antigen subtypes.** *J Gen Virol* 1988, **69**:2575-2583.
36. Huy T, Ngoc T, Abe K: **New complex recombinant genotype of hepatitis B virus identified in Vietnam.** *J Virol* 2008, **82**:5657-5663.
37. Yu H, Yuan Q, Ge SX, Wang HY, Zhang YL, Chen QR, Zhang J, Chen PJ, Xia NS: **Molecular and phylogenetic analyses suggest an additional. Hepatitis B virus genotype "I".** *PLoS One* 2010, **5**:9297.
38. Awan Z, Idrees M, Amin I, *et al*: **Pattern and Molecular Epidemiology of Hepatitis B virus genotypes circulating in Pakistan.** *Infect Genet Evol* 2010, **10**:1242-1246.
39. Ahmed CS, Wang ZH, Bin Z, Chen JJ, Kamal M, Hou JL: **Hepatitis B virus genotypes, subgenotypes, precore, and basal core promoter mutations in the two largest provinces of Pakistan.** *J Gastroenterol Hepatol* 2009, **24**:569-73.
40. Baig S, Siddiqui A, Chakravarty R, Moatter T: **Hepatitis B virus subgenotypes D1 and D3 are prevalent in Pakistan.** *BMC Research Notes* 2009, **2**:1.
41. Noorali S, Hakim ST, McLean D, Kazmi SU, Bagasra O: **Prevalence of Hepatitis B virus genotype D in females in Karachi, Pakistan.** *J Infect Developing Countries* 2008, **2**:373-378.
42. Hakim ST, Kazmi SU, Bagasra O: **Seroprevalence of hepatitis B and C genotypes among yung apparently healthy females of Karachi-Pakistan.** *Libyan J Med* 2008, **3**:66-70, AOP: 071123.
43. Alam MM, Zaidi SZ, Shaukat S, Sharif S, Angez M, Naeem A, *et al*: **Common Genotypes of Hepatitis B virus prevalent in Injecting drug abusers (addicts) of North West Frontier Province of Pakistan.** *Virology J* 2007, **4**:63.
44. Baig S, Siddiqui AA, Ahmed W, Qureshi H, Arif A: **The association of complex liver disorders with HBV genotypes prevalent in Pakistan.** *Virology J* 2007, **4**:128.
45. Kao JH, Wu NH, Chen PJ, Lai MY, Chen DS: **Hepatitis B genotypes and the response to interferon therapy.** *J Hepatol* 2000, **33**:998-1002.
46. Wai CT, Chu CJ, Hussain M, Lok AS: **HBV genotype B is associated with better response to interferon therapy in HBeAg-positive chronic hepatitis than genotype C.** *Hepatology* 2002, **36**:1425-30.
47. Janssen HLA, Senturk H, Zeuzem S, Akarka U, Cakalluglu Y, Simon K, *et al*: **Peginterferon alfa 2b and lamivudine combination therapy compared withpeginterferon alfa 2b for chronic HBeAg positive hepatitis B: randomized controlled trial in 307 patients.** *Hepatology* 2003, **38**:1323.
48. Erhardt A, Gobel T, Ludwig A: **Response to antiviral treatment in patients infected with hepatitis B virus genotypes E-H.** *J Med Virol* 2009, **81**:1716-1720.

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