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Resistant Mutations Against Nucleot(s)ide Analogues (NAs) in RT Domain of HBV Genome: A Review

HBV Genomunun RT Alanındaki Nükleotid Analoglarına (NA) Karşı Dirençli Mutasyonlar: Bir Derleme

Zia Ur Rahman, Majid Mahmood

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ABSTRACT

Drug resistance is a significant hurdle in the control and treatment of chronic hepatitis B virus (HBV) infection. This resistance is caused by some mutations in the viral genome which enable alternative ways for viral replication; which otherwise is blocked by nucleot(s)ide analogues (NAs). To overcome this hurdle, the correct drug selection is required because a specific mutation may bestow upon the virus resistance against a particular drug, but it remains susceptible to others. Significant literature has been published on the topic since the start of NAs use as a treatment option for chronic HBV patients. This review summarizes all the literature published on resistant mutations in the reverse transcriptase domain of the HBV genome, most of which have been reported. After a detailed screening, 36 studies were included in the final review. It is concluded that the most frequent mutations related to resistance are rtM204V/S/I/Y, rtM180C/L/I/T, rtN236T, rtA181T/V/S and rtV173L. Mutations rtT184S, rtN238D/S/R, rtA194T, rtL80V/G/I, rtS202I/G/C, rtV214A/T/I, rtV207L/M, rtI169T/P, and rtM250V/I/L are less common but are also reported to be associated with viral resistance.

Keywords: HBV resistance, HBV RT domain, resistant mutations, nucleot(s)ide analogues

ÖZ

İlaç direnci, kronik hepatit B virüsü (HBV) enfeksiyonunun kontrol ve tedavisinde büyük ve zorlu bir engeldir. Bu dirence, viral replikasyona alternatif yollar sağlayan viral genomdaki bazı mutasyonlar neden olur, aksi takdirde nükleotid analogları (NA) tarafından bloke edilir. Bu engelin üstesinden gelmek için doğru ilaç seçimi gereklidir, çünkü belirli bir mutasyon virüse belirli bir ilaca karşı direnç kazandırabilir ancak diğer bazı ilaçlara karşı duyarlı olmaya devam edebilir. NA'ların kronik HBV hastalarında tedavi seçeneği olarak kullanılmaya başlanmasından bu yana konuyla ilgili pek çok literatür yayınlanmıştır. Bu derleme, HBV genomunun ters transkriptaz alanındaki dirençli mutasyonlar hakkında yayınlanmış ve çoğunun rapor edildiği tüm literatürü özetlemektedir. Ayrıntılı bir taramanın ardından 36 çalışma nihai incelemeye dahil edildi. Dirençle ilgili en sık görülen mutasyonların: rtM204V/S/I/Y, rtM180C/L/I/T, rtN236T, rtA181T/V/S ve rtV173L olduğu sonucuna varılmıştır. rtT184S, rtN238D/S/R, rtA194T, rtL80V/G/I, rtS202I/G/C, rtV214A/T/I, rtV207L/M, rtI169T/P ve rtM250V/I/L mutasyonları daha az yaygındır ancak aynı zamanda viral dirençle ilişkili olduğu da bildirilmektedir.

Anahtar Kelimeler: HBV direnci, HBV RT alanı, dirençli mutasyonlar, nükleotid analogları

Introduction

Hepatitis B virus (HBV) is a pathogen infecting human liver cells and is a member of the hepadnaviridae family, of viruses (1). Undesirable effects caused by HBV include liver degeneration, liver cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (2). worldwide, approximately 257 million people are chronic carriers of HBV. The annual number of deaths caused by HBV-related infections was estimated to be 887,000 in 2015 (3).

Different types of interferon and nucleot(s)ide analogues (NAs) are clinically available treatments for chronic HBV patients. Interferon reduces the hepatitis B surface antigen level from blood while also having immunomodulatory effects, but it poses many adverse side effects. The process of reverse transcription is

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targeted by NAs acting on the reverse transcriptase (RT) domain of the viral genome, stopping the production of DNA from pre-genomic RNA (1,4). NAs therapy reduces the level of HBV-DNA to very low or untraceable amounts, which reduces the possibility of death and HCC (3). Lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (Ldt), and tenofovir (TDF) are NAs approved and used to date for chronic HBV treatment. NAs therapy is considered to be more convenient and has fewer side effects than interferon (5).

As mutations occur at a high rate in the HBV genome, due to the lack of a proofreading mechanism, complications are also associated with long-term NAs therapy. Some mutations in the HBV genome give resistance to the virus against the NAs (2). Resistant mutations in viral genomes change the interaction of HBV polymerase and NAs, causing inhibitory effects on drug action. To restore replication activity, primary mutations occur in addition to compensatory and secondary mutations, thus increasing the viral resistance against the drug (5,6). RT domain mutations have specific names according to a continuous numbering system introduced by Stuyver et al. (7). In the current analysis, we aimed to compile the literature available on resistance-related mutations related to NAs in the RT domain of the polymerase region in the HBV genome.

Methodology

We conducted a literature search using databases like "Google Scholar", "PubMed", "Scopus", and "Web of Science" using keywords: "resistant mutations", "NAs", "HBV", "LAM", "TDF", "ETV", "adefovir", "Ldt". The inclusion criterion was set as a study analyzing resistant mutations in the HBV RT domain of treatment non-responders. We initially identified 269 records from the databases. Studies in languages other than English were not included in this review (n=4). Records that did not have full access were also excluded (n=121). A total of 30 studies were excluded, having been found to be duplicates on screening. A total of 114 full-text articles were accessed for eligibility. After full text assessment, 67 studies were excluded because they did not report the mutational analysis of the RT domain, while 11 articles were excluded because they reported mutations from treatment-naive patients and not from treatment non-responder patients. After completing the exclusion process (Figure 1), a total of 36 studies were included in the current review.

Review

A total of 36 studies fulfilling all inclusion criteria were finally selected in the current review (Table 1). In these 36 studies, 14 were found from China (8,9,10,11,12,13,14,15,16,17,18,19,20, 21), 4 from different states of the USA (22,23,24,25), 3 each from Australia (26,27,28), and Korea (2,29,30), 2 from Germany (31,32), and one from each of Iran (33), Iraq (34), Turkey (35), Cyprus (36), Italy (37), Sweden (38), Argentina (39), Hong Kong (40), Pakistan (41), and Japan (1) (Figure 2, Table 1).

Common Mutations Associated with HBV Resistance

Very much frequent mutations were reported on positions rt204 and rt180 of HBV genome in literature. The most frequent mutation associated with viral resistance was found to be rtM204I/V/S/Y, which was reported by 29 studies from different countries included in the current review (Figure 2, Table 1). It was found to be associated primarily with LAM and Ldt resistance; however, it is suspected to have some role in viral resistance against all other NAs too, i.e., adefovir, ETV and TDF. The mutation rtL180M/L/C/I/T was reported in 25 studies included in the current review (Figure 2, Table 1). This mutation has been reported to be primarily associated with LAM and Ldt resistance, but it is assumed that it also has some role in viral resistance against adefovir, ETV and TDF.

According to the reviewed literature, mutations at rt236, rt181, and rt173 are also commonly found in the RT domain of the HBV genome, but their frequency is slightly lower than the mutations at rt204 and rt180. Mutations rtN236T, rtA181T/V/S and rtV173L were reported by 13, 11 and 10 studies respectively, included in this review (Figure 2, Table 1). Mutations rtN236T and rt181T/V/S are reported to be generally associated with resistance against ADV therapy, while rtV173L is generally associated with resistance against LAM and Ldt therapy.

Apart from the above-mentioned common mutations at positions rt204, rt180, rt236, rt181, and rt173, which are now well known for their role in HBV resistance to NAs treatment, some mutations have also been reported in many studies from different parts of the world with a possible role in viral resistance. These mutations are: rtN238D/S/R, rtS202I/G/C, rtA194T and rtM250V/L/M, which are reported in 8, 6, 6 and 6 studies respectively (Figure 2, Table 1). Mutation rtN238D/S/R is commonly found to be associated with ADV resistance, while the mutation rtS202I/G/C has been reported to have an association with ETV resistance. Mutation rtA194T is reported to have a probable role in resistance against TDF, while the mutation rtM250V/L/M is reported to have an association with resistance to all NAs (Table 1).

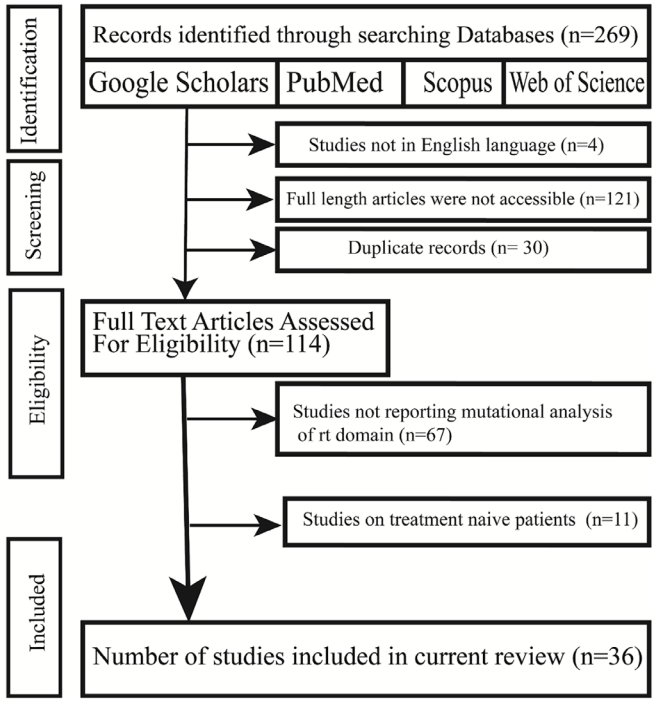


Figure 1. Flow chart of study methodology with detail of the articles included and excluded

Each of the mutations rtL80I/G and rtA184S has been reported in five studies (Figure 2) rtA184S was found to be associated with ETV resistance, while rtL80G/I is reported to be associated with

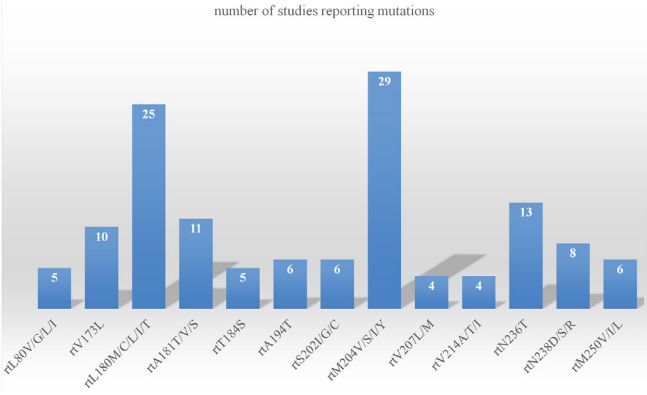


Figure 2. Detail of major resistant mutations in HBV RT domain with number of studies for each mutation reporting the particular mutation

LAM and Ldt resistance. Mutations rtV214A/T/I and rtV207L/M were each reported in four studies (Figure 2). these mutations are thought to have some association with resistance to all NAs, i.e., LAM, Ldt, adefovir, ETV, and TDF.

Overall, 13 mutations in the RT domain of the HBV polymerase region are reported in different studies from the samples of patients non-responders to different NAs (Figure 2). More commonly reported of these 13 are rtM204I/V/S/Y, rtL180M/L/C/I/T, rtN236T, rtA181T/V/S and rtV173L, which have been reported by at least 10 studies included in this review. Mutations less commonly reported include rtN238D/S/R, rtS202I/G/C, rtA194T, rtM250V/L/M, rtL80I/G, rtA184S, rtV214A/T/I and rtV207L/M, which are reported in less than 10 studies. The role of less common mutations in resistance is still to be established completely.

NAs used for the treatment of chronic HBV are not equally resistant to the virus. Some of these drugs have more mutations to resist while some have much fewer. A brief review of each is given below.

Table 1. List of studies included in the review along with the reported mutations associated to be resistance against NAs

Study reference	Country/state	Sample size	Drug	Non responder percentage	RT mutations reported
Westland et al. (22)	California	467	ADV	14%	S119A, H133L, V214A/T/I, H234Q
Angus et al. (26)	Australia	1	ADV	100%	N236T, N238D
Delaney et al. (23)	New Jersey	216	ADV	22%	V173L, L180M,204V
Tenney et al. (27)	Australia	500	ETV	NR	L18M, S78T, I169T, V173L, L180M, T184S/G, S202I, M204V, M250V
Pai et al. (34)	Turkey	1	LAM	100%	L180C, M204I
Marrone et al. (37)	Italy	14	LAM	57%	L180M, M204V/I,
Burnelle et al. (24)	California	NR	LAM, ADV	NR	L180 M, M204V, N236T
Sheldon et al. (31)	Germany	43	TDF	53%	A194T, L180M, M204V
Colonno et al. (25)	Wallingford CT	673	ETV, LAM	16%	L180M/L/I, S202G, M204I/V
Warner et al. (28)	Australia	1376	LAM	37%	L180M, M204I/V
Libberecht et al. (40)	Hong Kong	80	LAM	25%	L80V/I, V173L, L180M, M204V/I,
Malmström et al. (38)	Sweden	5	LAM	100%	L180M, M204I/V
Cassino et al. (39)	Argentina	1	ETV, ADV, TDF, LAM	100%	L180M, M204V
Qin et al. (8)	China	5	ADV	60%	M204Y, N238R, N248H
Lei et al. (9)	China	179	LAM, ADV, LdT	89%	M204I, L80I/V, L180M, N236T
Jiang et al. (10)	China	79	ADV	63.29%	L180M, A181T, T184L, M204V, 207M/L/I, S213T, V214A, Q215S, N236T, P237H, N238T, M250L
Wang et al. (11)	China	3	ADV	100%	A181V, N236T,
Hua et al. (12)	China	620	LAM, ADV, LdT	2.7%	L180M, A181T, 204I/V, N236T
Yin et al. (13)	China	26	LdT	61%	L180I/V, M20I
Kim et al. (29)	Korea	83	ADV, LAM	NR	L180M, A181T, 204I/V, N236T
He et al. (14)	China	84	LAM, LdT, ADV, ETV	52.94%	V173L, L180M/I, A181T, M204I/V, V207M, S213T, V214A, N236A/T, N238T
Motahar et al. (33)	Iran	64	TDF	20%	A194T
Zhao et al. (15)	China	269	LAM, LdT, ADV	8.9%	L180M, T184G, S202I, 204V/I, M207I, N236T, M250V
Qian et al. (16)	China	139	LAM, LdT, ADV, ETV	41.7%	L80I/V, V173L, L180M/I, A181V/G, A194G, S202N, 204I/V, N236T, M250L/V

Table 1. Continued

Study reference	Country/state	Sample size	Drug	Non responder percentage	RT mutations reported
Fan et al. (17)	China	300	LAM, TDF, LdT, ADV, ETV	51.7%	L80V, V173L, V191I, A194T/S, L199V, A200V/S, V207L/M/I, A211S, K212R, V214A L220I/N, Y221H/S, A222S, L228I, I235I, P237H, N238T, T240I, R242S
Zhang et al. (18)	China	46	ADV, ETV	8.7%	R15Q, D134N, L145M/S, F151Y/L, P177G, A181T/V, A194T, M204I/V, S223A, N236T, F249A, D263E
Shirvani-Dastgerdi et al. (32)	Germany	2	TDF, ETV	100%	S78T
Mahmood and Anwar (41)	Pakistan	20	LAM, LdT, ETV, ADV	65%	L80G, Y135, I169P, V173L, L180M, A181V, T184Y, M204V, N248H
Yamada et al. (1)	Japan	70	ETV	50%	V173L, L180M, M204, N238H, L269I
Marhoon et al. (35)	Iraq	20	LAM, ETV, ADV, LdT, TDF	NR	L80I/V, V173L, L180M, A181S, A194T, S202I, M204V/I, N236T, M250L/V
Jiang et al. (19)	China	1	LAM, ETV, ADV	100%	L180M, T184L, A200V, M204V
Arikan et al. (36)	Cyprus	100	LAM, ETV, ADV	37%	L91I, Q149K, V173M, Q215H/P/S, N238D
Choe et al. (2)	Korea	232	ETV, TDF	16.7%	M204I
Zhang et al. (20)	China	435	ADV, LAM, ETV, TDF	54.7%	L180M, A181T, T184S M204I/V, I224V, N238H, F221Y
Hong-tao et al. (21)	China	406	ADV, LAM, ETV	NR	L180M, A181S, S202I, M204V/I, N236T, M250L/V, V207L/M/I
Park et al. (30)	Korea	2	TDF	100%	S106C, H126Y, D134E, D204I/V, L269I

RT: Nucleot(s)ide analogues, RT: Reverse transcriptase, NR: Not reached, ETV: Entecavir, TDF: Tenofovir, LAM: Lamivudine, ADV: Adefovir, Ldt: Telbivudine

LAM Associated Resistance

LAM was the first NA approved for oral use in 1998 for chronic hepatitis B (CHB) at a dosage of 100 mg/day. It was found to be effective in the recovery of CHB complications by inhibiting the activity of the RT enzyme, adding deoxycytidine triphosphate to the growing DNA chain, during viral replication. However, the major drawback associated with LAM was treatment resistance in patients, which was attributed to some mutations in the rt domain of the virus (4,6). The current review included 21 studies published from different parts of the world with different numbers of patients reporting mutations associated with LAM therapy (Table 1). The most frequent mutations reported to be associated with viral resistance against LAM are rtL180M and rtM204I/V (Table 1). Moreover, the mutations rtL80I/V and rtV173L are also reported to be associated with LAM resistance. In 2005, three studies were published reporting the mutations rtL180M and rtM204I/V from the patients having no response against LAM from Turkey (35), Italy (37), and California (24). In 2006 and 2007, four studies, including two with a larger number of patients, reported mutations rtL180M and rtM204I/V in the patients who were resistant to LAM (25,28,38,40). Additionally, the mutations rtL80I/V and rtV173L were also found in one of these studies 40 from the patients resistant to LAM therapy (Table 1). In 2011, mutations rtL180M and rtM204I/V were identified in a patient who was a non-responder to LAM, from Argentina (39). In 2013, mutations rtL80I/V, rtL180M, and rtM204I/V were found in another non-responder patient against LAM, along with another mutation rtN236T from patients who had developed resistance to Ldt and ETV (9). In 2015, three studies reported the mutations rtL180M, rtM204I/V and rtV173L from the patients having no response against LAM therapy from China (12,14), and Korea (29) while the mutations rtA181T, rtV207M, rtS213T, rtV214A, rtN236A/T and rtN238T were also found from the patients resistant against Ldt, ADV and ETV (Table 1). In 2016, three studies reporting mutations rtL80I/V, rtL180M, rt204I/V, and rtV173L from patients not responding to LAM treatment were published from China (15,16,17). Moreover, mutations rtV191I, rtA194T/S, rtL199V, rtA200V/S, rtS202N, rtV207L/M/I, rtA211S, rtK212R, rtV214A, rtL220I/N, rtY221H/S, rtA222S, rtL228I, rtL235I, rtP237H, rtN238T, rtT240I, rtR242S, rtN236T, rtA181V/G were also reported in these studies associated with adefovir, ETV, Ldt and TDF resistance (Table 1). In 2017, resistant mutations rtL80I/V, rtL180M, rt204I/V, and rtV173L were reported from the patients not responding to LAM therapy in a study from Pakistan (41). Additionally, the mutations rtY135, rtI169P, rtA181V, rtT184Y, and rtN248H were also reported in patients resistant to Ldt, adefovir, and ETV (Table 1). In 2018, a study from Iraq reported mutations rtL80I/V, rtV173L, rtL180M and rtM204V/I in patients treated with LAM who did not respond (34). In 2019, two studies from China (19,20) and one from Cyprus (36) reported mutations rtL180M, rtM204I/V and rtV173L with association to resistance against LAM. Some other mutations like rtL91I, rtQ149K, rtA181T, rtT184S, rtA200V, rtQ215H/P/S, rtN238D, rtI224V, rtN238H, and rtF221Y were also found in these studies associated with resistance to ETV, adefovir, and TDF (Table 1).

ADV Associated Resistance

ADV is an adenosine monophosphate NA, approved in 2003 for treating CHB at a dose of 10 mg/day. It was proved to significantly improve histological, virological, and biochemical parameters, and it was also effective against patients resistant to LAM (6). ADV inhibits elongation of the viral DNA strand by inhibiting the addition of deoxyadenosine triphosphate to the viral primer. Thus, the reverse transcription of the virus is stopped (4). However, soon

after its approval as a improved therapy for chronic HBV patients, reports of resistant mutations against it began to emerge. The current review included 23 studies reporting mutations associated with ADV therapy (Table 1). The mutations rtN236T/A, rtN238T, and rtA181T were most commonly reported to be associated with ADV resistance. Other putative mutations reported to be associated with ADV resistance were rtS119A, rtH133L, rtH234Q, rtN248H, and rtS213T (Table 1). In 2003, three studies including two with larger sample size reported the mutations rtN236T, rtN238D, rtS119A, rtH133L, rtV214A/T/I, rtH234Q, rtV173L, rtL180M and rtM204V in the patients having no response against ADV from California (22), Australia (26), and New Jersey (23). In 2005, rtN236T was detected in a patient from California, who was a non-responder against ADV (24). Additionally, the mutations rtL180M and rtM204V were found in association with LAM resistance (Table 1). In 2011, resistant mutations rtL180M and rtM204V were reported in patients from Argentina who were non-responders to ADV along with other drugs (39). In 2013, two studies from China reported the resistant mutations rtN236T, rtN238, and rtN248H from non-responder patients against ADV therapy (8,9). Additionally, the mutations rtM204I, rtL80I/V and rtL180M, associated with LAM and Ldt resistance, were also reported in the studies. Mutations rtL180M, rtA181T, rtT184L, rtM204V, rt207M/L/I, rtS213T, rtV214A, rtQ215S, rtN236T, rtP237H, rtN238T, and rtM250L were detected in a non-responder patient from China against Adefovir, in 2014 (10). In 2015, four studies reported the mutations rtA181T, rtS213T, rtV214A, rtN236A/T and rtN238T in the patients having no response against ADV therapy from China (11,12,14), and Korea (29) while the mutations rtV173L, rtL180M and rtM204I/V were also detected in the study from the patients non-responder to LAM, ETV and Ldt (Table 1). In 2016, four studies were published from China reporting mutations rtI235I, rtP237H, rtN238T, rtT240I, rtR242S, rtN236T, and rtA181V/G in patients who were non-responders to ADV (Table 1) (15,16,17,18). In 2017 and 2018, resistant mutations rtA181V, rtN236T, rtM250L/V and rtN238T were reported against ADV from Pakistan (41), and Iraq (34). In 2019, four studies including three from China (19,20,21), and one from Cyprus (36) reported the mutations rtA181T, rtV207L/M/I, rtN238D, rtI224V and rtN238H, from the patients non-responder against ADV therapy (Table 1). In conclusion, the most frequently reported mutations from patients unresponsive to ADV therapy are present on positions rt238, rt236, and rt181, which have been found in many studies from different parts of the world.

ETV Associated Resistance

ETV is a carboxylic analogue of guanosine and was approved in 2005 with a dosage of 0.5 mg/day and 1 mg/day for treatment naïve and LAM resistant CHB patients, respectively. Inside the cell, phosphorylation occurs at its active 5'triphosphate metabolite. ETV inhibits HBV-DNA polymerase by competing with its natural substrate guanosine triphosphate (6). This review included 16 studies published in different parts of the world, with different numbers of patients reporting mutations associated with ETV resistance (Table 1). The most frequently associated with resistance against ETV are rtI169P/T, rtT184S/G/F/C/A/L/M/S, and rtS202I/G/C. Moreover, the mutations rtS78T, rtP177G and rtD263E were also reported by some studies to have an association with ETV resistance (Table 1). In 2004, a study from Australia reported mutations rtL18M, rtS78T, rtI169T, rtV173L, rtL180M, rtT184S/G, rtS202I, rtM204V, and rtM250V from a patient who was a non-responder to ETV therapy (27). This was the first report on resistance against ETV. In 2006, another study, conducted in Wallingford CT on 673 patients, reported the mutation rtS202I associated with ETV resistance mutations (Table 1) (25). In 2011, resistant mutations rtL180M and rtM204I/V were also reported from patients who were non-responders against ETV, in a study from Argentina (39). In 2015, a study from China on 84 patients reported the mutation rtV207M and rtS213T to be associated with ETV resistance (14). Three more studies were published from China in 2016 on mutations associated with ETV resistance (16,17,18). These studies found rtS202N, rtP177G, and rtD263E from the patients having no response to ETV therapy (Table 1). Two studies in 2017, including one with a larger number of patients, reported mutations rtV173L, rtL180M, rtI169P, rtT184Y, rtM204, rtN238H and rtL269I in the patients who were resistant to ETV (1,41). Five studies, including three from China (19,20,21), one from Cyprus (36), and one from Korea (2) were published in 2019 on mutations from patients having no response to ETV. These studies reported mutations rtQ215H/P/S, rtT184S, rtA200V, rtS202I, and rtM250L/V associated with ETV resistance (Table 1).

Ldt Associated resistance

Ldt (L-deoxythymidine) is a NA of L-thymidine approved in 2006 for the treatment of CHB patients at the dosage of 600 mg/day. The stoichiometric structure of L-nucleoside is different from natural nucleoside, as the sugars and base moieties are arranged in L configuration rather than the D configuration. It inhibits the synthesis of the positive strand of HBV-DNA by competing with thymidine 5'-triphosphate. With the incorporation of Ldt , the nascent chain of HBV-DNA is terminated (4,6). This review included 9 studies published from different parts of the world with different numbers of patients reporting the mutations associated with Ldt (Table 1). The most frequent mutation reported to have an association with resistance against Ldt is rtM204V/I, with or without rtL80I/V and rtL180M. Moreover, the mutations rtV173L were also reported to have an association with Ldt resistance (Table 1). In 2013, a study from China (9) reported the mutations rtL180M and rtM204I/V from the patients having no response against Ldt therapy. Moreover, three studies from China in 2015 also reported the mutations rtV173L, rtL180M, and rtM204I/V in the patients having no response to Ldt therapy (Table 1) (12,13,14). In the next year (2016), three more studies were published from China who reported mutations rtL80I/V, rtL180M, rt204I/V and rtV173L from the patients non-responders to Ldt confirming the role of these mutations in Ldt resistance (15,16,17). Same mutations (rtL80I/V, rtL180M, rt204I/V and rtV173L) were again reported in 2017 from Pakistan (41), and in 2018 from Iraq (34) in the patients not responding to Ldt (Table 1). The role of mutations rtL80I/V, rtL180M, rt204I/V, and rtV173L in Ldt-associated resistance has been confirmed by many reports.

TDF Associated Resistance

TDF is an acyclic NA {9-[(R)-2-(phosphonomethoxy)-propyl] adenine} which undergoes phosphorylation to competitively inhibit the natural substrate deoxyadenosine 5'triphosphate. TDF has been available since 2002 for HIV treatment. It was approved for

the treatment of CHB in 2008 at the dosage of 300 mg/day. It was found to be superior to other NAs in terms of suppression of HBV-DNA and normalization of alanine transaminase (4,6). Few reports exist on mutations associated with TDF resistance. The current review included 9 studies reporting mutations possibly associated with TDF therapy (Table 1). Three mutations are frequently reported to have an association with resistance against TDF. These are: rtA194T, rtS78T and rtM204V/I. Moreover, the mutations rtS106C, rtH126Y, rtD134E, rtD204I/V, rtL269I, were also suspected to have a role in TDF resistance (Table 1). In 2005, a study reported the mutations rtA194T, rtL180M, and rtM204V in the patients who showed no response to TDF therapy, from Germany (31). In 2011, a study from Argentina reported that mutations rtL180M and rtM204V also have some association with TDF resistance in addition to their association with resistance against LAM, ETV, and ADV (Table 1) (39). Mutation rtA194T was also found in non-responder patients against TDF in Iran in 2016 (33). In 2017, another study from Germany on two patients reported that mutation rtS78T is associated with resistance against TDF (32). A study from Iraq in 2018 reported the mutations rtA194T and rtM204V/I in non-responder patients against TDF (34). Three more studies were published in 2019, reporting mutations that may have some association with TDF resistance. One of these studies from Korea (2) reported that the mutation rtM204I is associated with both TDF and ETV resistance, while the second study from Korea (30) reported the mutations rtS106C, rtH126Y, rtD134E, rtD204I/V and rtL269I from patients who were non-responders for TDF. The third study in 2019 reported the mutations rtL180M, rtA181T, rtT184S, rtM204I/V, rtI224V, rtN238H and rtF221Y from the patient non-responder of a patient from China against adefovir, LAM, ETV and TDF. It was suggested in the study that any of these mutations might also have a role in resistance against TDF (Table 1). The exact mutations conferring resistance against TDF therapy are, however, still to be confirmed.

Conclusion

The most frequent mutation associated with viral resistance was found to be rtM204I/V/S/Y and then the mutation rtL180M/L/C/I/T, both of which are considered to be associated with almost all of the NAs but primarily associated with LAM and Ldt resistance. Mutations rtN236T, rtA181T/V/S, and rtV173L are also commonly found in the RT domain of the HBV genome with a slightly lower frequency than the mutations at rt204 and rt180. Mutations rtN236T and rt181T/V/S are associated with ADV resistance, while rtV173L is generally associated with resistance against LAM and Ldt therapy. Relatively less common mutations are rtN238D/S/R, rtS202I/G/C, rtA194T, and rtM250V/L/M. Of these, the first three are associated with adefovir, ETV and TDF resistance respectively, while the lattermost is thought to be associated with resistance to all NAs. Mutations rtL80I/G, rtA184S, rtV214A/T/I, and rtV207L/M were also reported in a smaller number of studies with their association with different NAs.

Footnotes

Authorship Contributions

Concept: M.M., Design: M.M., Data Collection or Processing: Z.U.R., Analysis or Interpretation: M.M., Literature Search: Z.U.R., Writing: Z.U.R., M.M.

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Research Article

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Evaluation of Acute Hepatitis B Patients Epidemiologically and Clinically

Akut Hepatit B Hastalarının Epidemiyolojik ve Klinik Olarak Değerlendirilmesi

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ABSTRACT

Objectives: Hepatitis B virus (HBV) is a DNA virus that can cause acute and chronic hepatitis, liver failure, and liver cancer. It is a widespread public health problem that can be prevented by vaccination. This study aimed to evaluate the demographic, clinical, and laboratory data of patients with acute hepatitis B who were hospitalized in our clinic.

Materials and Methods: Twenty-three patients diagnosed with acute hepatitis B who were hospitalized and followed up in the infectious disease service between 2021 and 2023 were included in the study. Our study was designed as a retrospective cohort study.

Results: The patients had an average age of 51.3±12.6 years, with 21 (91.3%) being male. Twelve (52.1%) of 23 patients had chronic diseases, which prolonged hospital stays. All patients involved in the study were not vaccinated for HBV. An examination of the transmission routes showed that 3 (13%) patients were infected through intravenous drug use or tattooing, 6 (36%) through dental procedures, and 14 (61%) through sexual contact. Patients who contracted the virus sexually stayed longer in the hospital. Antiviral treatment was started in 7 out of 23 patients (30.4%) because of international normalized ratio elevation (above 1.5) during hospitalization. One patient was referred to a liver transplantation clinic. Other patients were recovered and discharged. All 14 patients who regularly attended outpatient follow-ups had negative hepatitis B surface antigen.

Conclusion: This study demonstrated that acute HBV infection continues to be observed in individuals over 50 years of age who were not routinely vaccinated in our country. The findings underscore the importance of adult vaccination and the implementation of methods to prevent sexually transmitted infections.

Keywords: Acute hepatitis, hepatitis B, vaccination

ÖZ

Amaç: Hepatit B virüsü (HBV), akut ve kronik hepatite, karaciğer yetmezliğine ve karaciğer kanserine neden olabilen bir DNA virüsüdür. Aşılama ile önlenebilen yaygın bir halk sağlığı sorunudur. Bu çalışma kliniğimizde akut hepatit B tanısıyla yatırılan hastaların demografik, klinik ve laboratuvar verilerini değerlendirmek amacıyla yapıldı.

Gereç ve Yöntemler: Çalışmaya 2021-2023 yılları arasında enfeksiyon hastalıkları servisinde yatarak takip edilen akut hepatit B tanısı almış 23 hasta dahil edildi. Çalışmamız retrospektif kohort çalışması olarak tasarlandı.

Bulgular: Hastaların ortalama yaşı 51,3±12,6 yıldı ve 21'i (%91,3) erkekti. Yirmi üç hastanın 12'sinde (%52,1) hastanede kalış süresini uzatan kronik hastalıklar mevcuttu. Çalışmaya katılan hastaların tamamı Hepatit B aşısı olmamıştı. Bulaş yollarının incelenmesi, 3'ünün (%13) intravenöz uyuşturucu kullanımı veya dövme yoluyla, 6'sının (%36) diş prosedürleri yoluyla ve 14'ünün (%61) cinsel temas yoluyla enfekte olduğunu gösterdi. Virüsü cinsel yolla kapan hastalar hastanede daha uzun süre kaldı. Yirmi üç hastanın 7'sine (%30,4) yatış sırasında INR yüksekliği (1,5'in üzerinde) nedeniyle antiviral tedavi başlandı. Bir hasta karaciğer nakli merkezine sevk edildi. Diğer hastalar iyileşip taburcu edildi. Düzenli olarak ayaktan hasta takiplerine katılan 14 hastanın hepsinde hepatit B yüzey antijeni negatifti.

Sonuç: Bu çalışma, ülkemizde rutin olarak aşılanmayan 50 yaş üstü bireylerde akut HBV enfeksiyonunun görülmeye devam ettiğini göstermektedir. Bulgular, yetişkin aşılamasının ve cinsel yolla bulaşan enfeksiyonları önlemeye yönelik yöntemlerin uygulanmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Akut hepatit, hepatit B, aşılama

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Introduction

Hepatitis B virus (HBV) is a DNA virus that causes infection through parenteral, sexual, and vertical (from mother to baby) transmission routes (1). In our country, HBV infection is a common public health issue worldwide, and it is preventable with vaccination. According to World Health Organization 2019 data, there are 296 million HBV carriers worldwide and approximately 1 million deaths per year (2). In addition to causing severe liver damage, it is considered a leading cause of liver cancer.

The incubation period for acute hepatitis B infection ranges from 28 to 180 days, with most infections typically showing symptoms within a period of 60 to 110 days (3). During the incubation period, patients are generally asymptomatic, which increases the risk of transmission (4). Most cases are subclinical, and the course of the disease varies significantly. Although acute hepatitis B usually resolves in immunocompetent individuals, it becomes chronic in 90% of newborns, 30-50% of children under 5 years old, and 5-10% of adults (5).

Hepatitis B surface antigen (HBsAg) and anti-HBs, HBeAg and anti-HBe, and anti-HBc immunoglobulin M (IgM) and IgG are virological biomarkers of hepatitis B infection (6). Biochemical parameters indicating liver damage include aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total and direct bilirubin, serum albumin, gamma globulin, complete blood count, and prothrombin time (PT). Increased AST and ALT levels indicate the degree of liver fibrosis. When biochemical parameters are insufficient, invasive and non-invasive methods are preferred to determine the degree of liver damage.

Acute hepatitis B infection is usually managed with supportive therapy, whereas direct antiviral therapy is recommended in the presence of severe liver disease, coagulopathy, and prolonged jaundice (7). The hepatitis B vaccine is a safe and effective vaccine that has been in use worldwide since 1981 (8). In our country, the hepatitis B vaccine has been included in the routine vaccination schedule since 1998 (9).

Materials and Methods

Our study was designed as a retrospective cohort study. Patients diagnosed with acute hepatitis B who were hospitalized and followed up in the infectious disease department between 2021 and 2023 were included in the study. The demographic data of the patients, routes of transmission, accompanying comorbidities, clinical data, biochemical, microbiological, and serological laboratory parameters, medical imaging, and treatment management were examined. The patient data were scanned retrospectively from the hospital information database. Our study was reviewed and approved by the Clinical Research Ethics Committee of İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital (approval number: 2022/0719, date: 21.12.2022).

Statistical Analysis

In the case of categorical variables, descriptive characteristics are presented along with frequencies, percentages, means, and standard deviations (SDs). Several statistical techniques, including the t-test, analysis of variance (One-Way ANOVA), and Pearson correlation analysis, were utilized. A p-value 0.05 was considered statistically significant.

Results

The study included 23 patients. The gender distribution of the patients was as follows: 21 males (91.3%) and 2 females (8.7%). The patients' ages were found to have a mean of 51.3±12.6 years. In total, 12 (52.1%) of the 23 patients had accompanying chronic diseases, while 11 patients (47.9%) did not have any accompanying chronic diseases. All patients were unvaccinated against HBV. Analysis of the transmission routes revealed that 14 patients (61%) acquired the virus through sexual contact, 6 patients (36%) through dental procedures, and 3 patients (13%) through intravenous (IV) drug use or tattooing.

The symptoms at the time of the patients' emergency department admissions were fatigue (61%), jaundice (57%), nausea (43%), dark urine (35%), light-colored stool (17%), and fever (9%) (Table 1).

Regarding the distribution of symptoms, fatigue was the predominant symptom, representing 27% of the cases. The percentage distribution of symptoms at admission is shown in Figure 1.

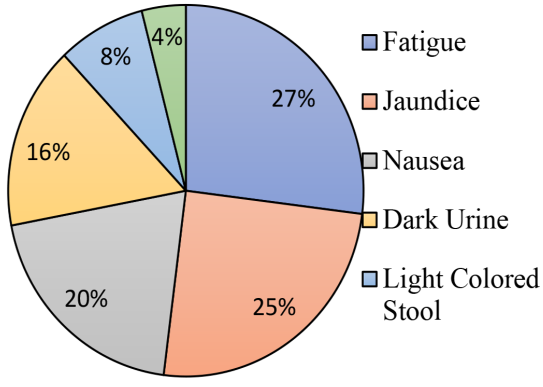


Figure 1. Percentage distribution of symptoms at admission

Table 1. Duration and percentage distribution of symptoms at admission

Symptom duration	Jaundice	Fever	Dark urine	Light-colored stool	Nausea	Fatigue
Acute (0-7 days)	9	1	3	3	7	4
Subacute (7-14 days)	4	1	5	1	2	5
Long-term (14>days)	0	0	0	0	1	5
Total	13	2	8	4	10	14
Percentage	57%	9%	35%	17%	43%	61%

The average HBV-DNA level of the patients at initial admission was determined to be 2719165-3187990 IU/mL. The average AST level was 1664-829 U/L, ALT level was 2332-1151 U/L, ALP level was 289-145 U/L, and GGT level was 272-100 U/L. The mean total bilirubin level is 11.2-6.3 mg/dL; direct bilirubin level is 8.7-5.1 mg/dL. The international normalized ratio (INR) was 1.27 with a SD of 0.1.

Patients' AST and ALT values peaked on the first day of hospitalization. The peak AST value was determined to be an average of 1861-827 SD U/L, and the peak ALT value was an average of 2480-1192 SD U/L. While total bilirubin reached its peak value on the 4th day of hospitalization, with a peak value average of 14.7-6.5 SD mg/dL, INR reached its peak value on the 3rd day of hospitalization, with an average peak value of 1.38 SD ±0.2.

When patients' age, initial ALT, and HBV-DNA data were examined using descriptive statistical methods, younger patients generally had higher ALT values but lower average HBV-DNA values. Conversely, older patients had higher HBV-DNA levels but lower ALT levels. The correlation between age, HBV-DNA, and ALT levels upon admission is shown in Figure 2.

When examining the correlation between the initial AST-ALT values and the hospitalization duration, we observed that as the liver function test values increased, the hospitalization duration also increased. The correlation between AST, ALT, and length of hospital stay is shown in Figure 3.

All patients had positive anti-Hbc-IgM and anti-IgG antibodies. Five out of 23 patients (21.7%) had positive anti-HBs values. Sixteen patients (70%) had positive HbAg values, whereas 14 patients (61%) had positive anti-Hb values. All patients tested positive for anti-Hbc-IgM and anti-Hbc-IgG (Table 2).

Ultrasonographic examination revealed hepatomegaly in 10 patients (43.4%), grade 1-2 hepatosteatosis in 8 patients (34.7%), and thickening of the gallbladder wall in 11 patients (47.8%). During hospitalization, 30.4% (7 out of 23) of the patients were prescribed antiviral therapy. Specifically, 3 patients were given entecavir and 4 patients were given tenofovir disoproxil fumarate. This treatment was initiated due to an increase in INR levels above 1.5.

The average length of hospital stay was 9.48-4.4 SD days. The number of patients with and without chronic diseases and the average length of hospital stay is presented in Table 3. The t-test indicated that the hospital stay duration was significantly longer for patients with chronic diseases than for those without chronic diseases (p=0.014).

The correlation between patient age and length of hospital stay is presented in Table 4. Pearson correlation analysis showed a significant increase in hospital stay duration with increasing age (p=0.013).

The correlation between hepatitis B transmission routes and length of hospital stay is presented in Table 5. Statistical analysis using the One-Way ANOVA test showed that the mode of transmission had a significant effect on the length of hospital stay, with sexually transmitted infections having the most significant impact (p=0.004).

One patient was referred to a liver transplantation center due to the development of severe liver disease and progression to hepatic failure. The remaining patients recovered and were discharged. During follow-up, 15 patients attended control visits within 1 to 6 months. Among these patients, 6 continued to have positive

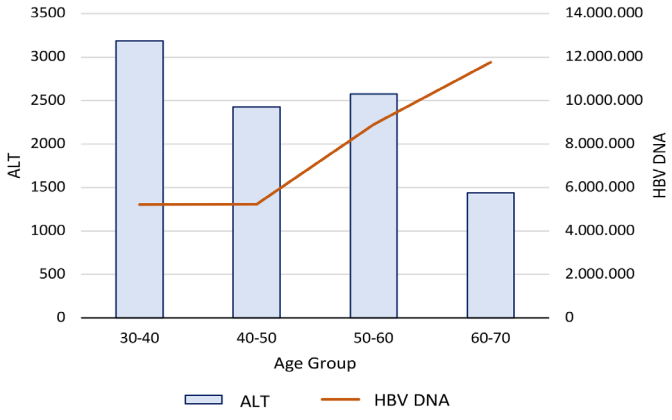


Figure 2. Correlation between age, HBV-DNA, and ALT levels at admission
HBV: Hepatitis B virus, ALT: Alanine transaminase

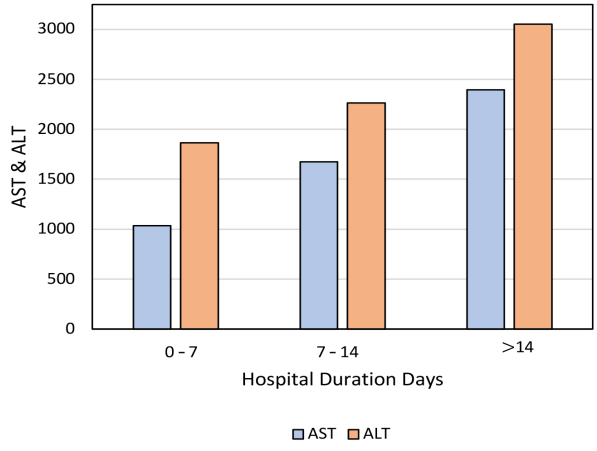


Figure 3. Correlation between AST, ALT, and length of hospital stay
AST: Aspartate aminotransferase, ALT: Alanine transaminase

Table 2. Percentage distribution of serological tests

	Anti-Hbs		HbeAg		Anti-Hbe		Anti-Hbc-IgM, IgG	
	Count	Percentage	Count	Percentage	Count	Percentage	Count	Percentage
Positive	6	26%	16	70%	14	61%	23	100%
Negative	17	74%	7	30%	9	39%	0	0%
Total	23	100%	23	100%	23	100%	23	100%

Anti-Hbs: Hepatitis B surface antigen, HbeAg: Hepatitis B e-antigen, anti-Hbe: Anti-hepatitis B e-antigen, IgM: Immunoglobulin M, IgG: Immunoglobulin G

Table 3. The number of patients with and without chronic diseases and the average length of hospital stay

Chronic Disease	Count	Average length of hospital stay
Yes	12	11.67
No	11	7.09
Total	23	9.48

Table 4. Correlation between patient age and length of hospital stay

Age	Count	Percentage	Average length of hospital stay (days)
30-40	7	36.00	7.29
40-50	5	47.40	7.80
50-60	3	54.33	11.67
60-70	8	66.25	11.63
Total	23	50.21	9.48

Table 5. Correlation between hepatitis B transmission route and length of hospital stay

Hepatitis B transmission route	Count	Percentage	Average length of hospital stay (days)
Sexually transmitted	14	61%	11.79
Dental procedures	6	26%	6.33
IV drug use/tattoos	3	13%	5.00
Total	23	100%	9.48

IV: Intravenous

HbsAg levels, while 9 were found to be HbsAg-negative. During the 6-12 month follow-up, seroconversion to negative HbsAg was detected in 5 out of 6 patients who were initially found to be HbsAg-positive at the first outpatient visit, while the HbsAg status of 1 patient could not be determined due to a loss of follow-up. In 6 patients, HBV-DNA was negative during the 1- to 6-month follow-up, while 1 patient continued to have positive HBV-DNA. For the patient with positive HBV-DNA, the 6-12 months data showed that HBV-DNA had become negative.

Discussion

This study examined the demographic characteristics, clinical findings, transmission routes, laboratory parameters, treatment, and follow-up outcomes of patients with acute hepatitis B infection. In studies conducted in different regions of Turkey, the prevalence of HbsAg positivity is higher in males (10). The majority of the 23 patients included herein were male, suggesting that HBV transmission may be associated with gender and age.

Since 1998, routine vaccination against hepatitis B has been implemented in Turkey. Vaccination coverage has been increasing in recent years, with vaccination rates rising from 64% in 1999 to 98% in 2016. As a result, the incidence of acute HBV infections in the young population has significantly decreased (11). In a study on the epidemiology of acute viral hepatitis conducted by Karacaer et al. (12) in 2018, it was observed that the ages of patients with acute HBV were mostly between 20 and 40. Considering that hepatitis B vaccination was included in the routine vaccination program in Turkey in 1998, the average age of patients indicates that most of them were not included in Turkey's national vaccination program, suggesting that unvaccinated individuals are at high risk (12).

In a study conducted by Miao et al. (13), a 57.31% decrease in the incidence of acute hepatitis B was observed between 2005 and 2019 in China following the widespread adoption of hepatitis B vaccination. In our study, the high mean age of the patients supported the effectiveness of hepatitis B vaccination in Turkey. The absence of HBV vaccination among the patients we followed also underscores the importance of adult immunization.

When examining transmission routes, we found that most patients acquired the virus through sexual contact and had longer hospitalization periods. These data confirm that unprotected sexual intercourse is a significant risk factor for HBV transmission. In addition, dental procedures and IV drug use/tattooing were identified as contributing factors to transmission routes. In a study conducted by Wu et al. (14) in China, out of 164 patients diagnosed with acute hepatitis B, 33 (20.12%) acquired the virus through sexual transmission and 21 (12.80%) acquired it after dental procedures. The hepatitis B vaccination rate among these patients was only 5.49%.

The most common symptoms of acute viral hepatitis are abdominal pain, nausea, and/or vomiting; dark urine or clay-colored stools; fatigue; fever; jaundice; joint pain; and loss of appetite (15). In our study, when symptoms were examined, patients commonly experienced typical hepatitis symptoms, such as fatigue and jaundice, upon presentation. Looking at the correlation between liver function tests and HBV-DNA according to the age groups of patients at admission, it is observed that liver function tests are high in the younger age group, while HBV-DNA was low, whereas the opposite was true in the older age group. This suggests that inflammation and hepatocyte damage are predominant in young patients, whereas the viral replication burden is higher in older individuals.

Chronicity occurs in 5-10% of individuals who have had acute hepatitis B infection in adulthood, but it is observed in 90% of cases in the newborn period and in 20-50% of cases in childhood (16). In our study, all 14 patients who attended follow-up visits had negative HbsAg values. For patients with severe acute HBV clinical and laboratory findings (INR≥1.5 and/or PT longer than 4 seconds above the upper limit of normal and jaundice period >4 weeks), oral antiviral therapy (OAT) is recommended (17). Fulminant hepatitis occurs in less than 1% of jaundiced cases of acute infections. (18).

A meta-analysis to determine the efficacy of nucleoside analogs (NA) compared with placebo or no intervention to treat acute primary HBV infection revealed that there is insufficient evidence to suggest that NA has superior efficacy compared with placebo/standard care in patients with acute viral hepatitis (19). In our study, OAT was preferred for patients with severe liver disease and elevated INR. Among the 7 patients who received OAT, one progressed to liver failure despite antiviral treatment and was referred to a liver transplantation center. The remaining patients were discharged, and follow-up revealed negative HBsAg levels.

When examining the relationship between hospitalization duration and liver function, patients with high liver function values had longer hospital stays.

Upon reviewing the medical histories and vaccination records of the patients, it was found that none had been vaccinated against HBV, highlighting the importance of vaccination for preventing HBV infection. Unprotected sexual contact was the most common route of transmission for acute hepatitis B, emphasizing the importance of safe sexual practices.

Study Limitations

The limitations of this study include a small number of patients, irregular attendance at follow-up visits, and data obtained from a single center. Future studies with larger sample sizes and data from different centers may provide more comprehensive results.

Conclusion

In conclusion, this study demonstrated that acute hepatitis B infection continues to occur in individuals over 50 years of age in our country, where routine vaccination is not implemented, emphasizing the importance of adult vaccination and prevention methods against sexually transmitted infections.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Clinical Research Ethics Committee of İstanbul Medeniyet University, Göztepe Prof. Dr. Süleyman Yalçın City Hospital (approval number: 2022/0719, date: 21.12.2022).

Informed Consent: Informed consents were not obtained due to the retrospective design of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ç., H.V., R.G., M.B.U., Y.Ç., Concept: H.Ç., Design: H.Ç., H.V., Y.Ç., Data Collection or Processing: H.Ç., H.V., R.G., M.B.U., Analysis or Interpretation: H.Ç., H.V., Literature Search: H.Ç., H.V., R.G., M.B.U., Y.Ç., Writing: H.Ç., H.V., Y.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research Article

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Investigation of Anti-HCV, Anti-HIV, and Anti-HAV IgG Seroprevalence in HBsAg-positive Patients

HBsAg Pozitif Hastalarda Anti-HCV, Anti-HIV, Anti-HAV IgG Seroprevalansının Araştırılması

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ABSTRACT

Objectives: The objective of this study was to evaluate serologic markers anti-hepatitis C virus (anti-HCV), anti-hepatitis A virus immunoglobulin G (anti-HAV IgG), anti-human immunodeficiency virus antibody (anti-HIV)] associated with HCV, HAV, and HIV in individuals with hepatitis B virus infection, with a view to contributing to the development of preventive strategies for disease control.

Materials and Methods: The study population comprised hepatitis B surface antigen (HBsAg)-positive adult patients admitted to the hospital between January 2015 and January 2024. Patients with complete anti-HCV, anti-HIV, and anti-HAV IgG tests were included in the study. The results were then subjected to retrospective analysis. Results identified as borderline and reactive in the anti-HIV test were referred to the National HIV-acquired immunodeficiency syndrome Confirmatory Reference Centre for confirmation by additional testing.

Results: In the present study, 733 patients were HBsAg-positive. Among these patients, anti-HAV IgG was detected in 23.1% (170/733), anti-HCV in 0.81% (6/733), and anti-HIV in 0.13% (1/733). Of the 733 patients who tested positive for HBsAg, 53% were male and 47% were female. The mean age of the cohort was found to be 50.49 (±14.32) years. The mean age of patients who tested positive for anti-HAV IgG was found to be 49.42 (±14.14) years. Among anti-HAV IgG positive patients, 89 (52.4%) were male and 81 (47.6%) were female.

Conclusion: HAV seroprevalence should be investigated in HBsAg-positive patients due to the risk of a more severe HAV infection. Anti-HCV and anti-HIV tests should also be evaluated in HBsAg-positive patients because they have common transmission routes and increase mortality and morbidity. Guidelines recommend hepatitis A vaccination in seronegative cases and especially in the

ÖZ

Amaç: Bu çalışmanın amacı, hepatit B virüs enfeksiyonu olan bireylerde; hepatit C virüsü (HCV), hepatit A virüsü (HAV) ve insan bağışıklık yetmezliği virüsü (HIV) ile ilişkili serolojik belirteçleri (anti-HCV, anti-HAV IgG, anti-HIV) değerlendirmek ve hastalıkların kontrolü için önleyici stratejilerin geliştirilmesine katkıda bulunmaktır.

Gereç ve Yöntemler: Çalışma popülasyonu, Ocak 2015 ile Ocak 2024 tarihleri arasında hastaneye başvuran hepatit B yüzey antijeni (HBsAg)-pozitif yetişkin hastalardan oluşmaktadır. Anti-HCV, anti-HIV ve anti-HAV IgG test sonuçları eksiksiz olan hastalar çalışmaya dahil edilmiştir. Sonuçlar daha sonra retrospektif analize tabi tutulmuştur. Anti-HIV testinde sınırda ve reaktif olarak tanımlanan sonuçlar, ek testlerle doğrulanması için Ulusal HIV-edinilmiş bağışıklık yetmezliği sendromu Doğrulama Referans Merkezine iletilmiştir.

Bulgular: Çalışmamızda 733 HBsAg pozitif hasta olup; bu hastalarda anti-HAV IgG %23,1 (170/733), anti-HCV %0,81 (6/733) ve anti-HIV %0,13 (1/733) oranında pozitif saptandı. HBsAg pozitif saptanan 733 hastanın %53'ünün erkek, %47'sinin kadın ve yaş ortalamasının 50,49 (±14,32) olduğu görüldü. Anti-HAV IgG pozitif olan hastaların yaş ortalaması 49,42±14,14 yıl olup, %52,4'ü erkek (n=89) ve %47,6'sı kadın (n=81) olarak tespit edildi.

Sonuç: HBsAg pozitif hastalarda HAV seroprevalansı, klinik olarak daha şiddetli bir HAV enfeksiyonu riski nedeniyle araştırılmalıdır. HBsAg pozitif hastalarda, ortak bulaşma yollarına sahip olmaları ve mortalite ve morbiditeyi artırmaları nedeniyle anti-HCV ve anti-HIV testleri de değerlendirilmelidir. Kılavuzlar seronegatif olgularda ve özellikle hepatit B, hepatit C ve alkolik hepatit gibi kronik karaciğer hastalığı varlığında hepatit A aşılamasını önermektedir. Çalışmamızın bulguları bölgesel verilere katkı sağlayacaktır. Her

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presence of chronic liver disease such as hepatitis B, hepatitis C and alcoholic hepatitis. The findings of our study will contribute to regional data. Collecting seropositivity data from each center will significantly help understand the real prevalence in our country.
Keywords: Hepatitis B, hepatitis A, hepatitis C, HIV/AIDS, HBV co-infection

merkezden seropozitiflik verilerinin toplanması ülkemizdeki gerçek prevalansın anlaşılmasına önemli ölçüde yardımcı olacaktır.
Anahtar Kelimeler: Hepatit B, hepatit A, hepatit C, HIV/AIDS, HBV ko-enfeksiyon

Introduction

Viral hepatitis is a prevalent hepatic disorder predominantly triggered by classical hepatitis viruses (A, B, C, D, E). The condition may be complicated by cirrhosis, liver failure, and hepatocellular carcinoma (HCC), which can result in morbidity and mortality (1). In the context of liver disease, viral hepatitis, particularly that attributable to hepatotropic viruses, has been observed to exhibit a propensity for more severe clinical presentations (2). Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infections can be observed concurrently because of shared modes of transmission (percutaneous transmission through blood and body fluids, sexual transmission via semen and vaginal secretions). This treatment has been shown to increase morbidity and mortality in patients. Hepatitis A virus (HAV), an acute and self-limiting infection of the liver, is transmitted through the primary fecal-oral route (3). According to the World Health Organization (WHO), the global prevalence of chronic hepatitis B (CHB) infection was estimated at 254 million in 2022. The study also reported that the annual incidence of new cases was 1,2 million, while 1,1 million deaths were attributed to cirrhosis and HCC associated with HBV infection (4). According to the WHO estimates, the global mortality rate from hepatitis A in 2016 was 7,134. This represents approximately 0.5% of viral hepatitis-related deaths (1). HAV superinfection exacerbates underlying liver disease in patients with chronic liver disease. Epidemiological studies conducted in Turkey demonstrated that hepatitis B surface antigen (HBsAg) seropositivity rates obtained from studies conducted with blood donors ranged from 2% to 7% (5). In 2015, it was reported that 71 million people, 1% of the global population, lived with HCV infection, 399,000 people died from cirrhosis or HCC caused by HCV infection, and 1,75 million new HCV infections developed (6). In the context of Turkey, the prevalence of HCV seropositivity exhibits a range of variation, with estimates ranging from 1% to 1.9%. (7). The issue of HIV infection as a significant public health problem persists, insofar as the condition has the capacity to affect individuals across all segments of society, reduce healthy life expectancy, and be transmitted from person to person. According to recent reports, the global prevalence of HIV is estimated to be 39 million (33,1 million to 45,7 million) (8). In the given country, the number of individuals with HIV and acquired immunodeficiency syndrome (AIDS) cases who were reported with positive confirmation tests between 1985 and November 8, 2023 was 39,437 and 2,295, respectively (9). It is recommended that serological markers associated with HCV, HIV, and HAV be assessed in individuals with HBV infection (10,11,12). The identification of co-infected cases is of paramount importance in the context of reducing mortality and morbidity, determining treatment strategies, and ascertaining the necessity for immunization and the development of preventive strategies for disease control. The present study aimed to ascertain the seroprevalence of anti-HCV, anti-HIV, and anti-HAV IgG in HBsAg-positive patients.

Materials and Methods

In the present study, the results of anti-HCV, anti-HIV, and anti-HAV IgG tests of patients admitted to the hospital between January 1, 2015, and January 1, 2024 and found to be HbsAg-positive were analyzed retrospectively from the hospital information management system. In the present study, we sought to ascertain the most effective approach to the inclusion of test results to ensure the integrity of the study findings. To this end, a query was initiated within Microsoft Excel 2021, the objective of which was to identify and exclude patients who had repeated tests within the same year or between years. To exclude repeated patients from the study, a query was made with the Microsoft Excel 2021 program based on patient identity separately for positive and negative patient results, and repeated data were deleted. At the conclusion of the study, test results exceeding the reference value were designated as positive. Samples from patients who were found to be anti-HIV reactive in the enzyme-linked immunosorbent assay device were sent to the National AIDS Verification Center and Viral Hepatitis Laboratory of the General Directorate of Public Health for confirmation testing. In this facility, samples that were positive as a result of the HIV1/2 anti-body differential rapid confirmatory test were considered positive.

For this study, permission was obtained from Clinical Research Ethics Committee Balıkesir University Faculty of Medicine (date: 31.01.2018, approval number: 27).

Statistical Analysis

IBM Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 statistical package program (IBM SPSS Corp.; Armonk, NY, USA) was used for data evaluation and analysis. Categorical variables are presented as frequency (n) and percentage (%), whereas numerical variables are presented as mean ± standard deviation. For comparison of categorical variables between the two independent groups, χ^2 and Fisher's exact test were applied. The independent sample t-test and Mann-Whitney U test were used to compare continuous variables between the two independent groups. The statistical significance level was set as $p<0.05$.

Results

In the present study, 733 patients with HBsAg positivity were included in the analysis. Among the included patients, 388 (52.9%) were male and 345 (47.1%) were female, with a mean age of 50.49 years (±14.32). Furthermore, the study revealed that 23.1% (170/733) of patients exhibited positive anti-HAV IgG, 0.81% (6/733)

demonstrated positive anti-HCV, and 0.13% (1/733) exhibited positive anti-HIV. The mean age of patients positive for anti-HAV IgG was 49.42 years (±14.14), 89 (52.4%) of whom were male and 81 (47.6%) of whom were female. No statistically significant findings were identified in the distribution of anti-HAV IgG and anti-HCV seropositivity according to age or gender (p=0.270, p=0.232, p=0.863, p=1, respectively). The seropositivity rates according to age and sex, along with the p-values, are presented in Figure 1, Tables 1 and 2.

Discussion

Viral hepatitis and HIV infection continue to be a global public health problem. It is estimated that approximately 296 million people worldwide are chronic carriers of HBV (4). In accordance with international guidelines, screening for HBV, HIV, and HAV co-infection is recommended for individuals with HBV infection, given the similarity of the transmission routes for these pathogens (10,11,12). HBV/HCV is important for the detection of HBV/HIV co-infection and for altering the natural course of chronic HBV infection. It is also imperative to be aware of HAV serology in patients with HBV to avoid the potentially fatal consequences of possible HAV infection and in light of the necessity for immunization. The present study was undertaken with the objective of determining the frequency of co-infection in individuals with HBV, eliminating any deficiencies that may occur during the diagnostic process and subsequent follow-up, and increasing awareness. The prevalence of co-infection varies geographically, with different regions exhibiting distinct endemicity patterns for the respective viruses. According to data provided by the WHO, Turkey is classified as an intermediate-endemic region for HBV. These data were primarily obtained from studies on blood donors (13). The prevalence of HBsAg positivity exhibits variability across diverse populations and geographical regions. Research findings have indicated that the global prevalence of chronic HBV infection, as indicated by the presence of HBsAg, is approximately 3.6%, with elevated rates observed in certain regions, including Africa (8.8%) and the Western Pacific (5.2%) (14). In a study conducted in the Central African Republic, the prevalence of HBsAg among 801 students was 15.5% (15). A number of epidemiological studies conducted in Turkey have demonstrated that the prevalence of HBsAg positivity ranges from 4% to 5% within the general population (16). It is imperative to acknowledge the significance of these rates and to take them seriously. Screening tests and seroepidemiological data are instrumental in guiding the management of patients with this disease, with the aim of reducing morbidity and mortality. In patients with hepatitis B, the investigation of hepatitis A is of two types. First, preventing the mortality of acute HAV co-infection. Second, determining the need for immunization in seronegative patients. A study conducted in Thailand reported fulminant liver failure and 25-55% mortality rates in HBsAg carriers with superinfection by acute hepatitis A (2). Chu and Liaw (17). found that the risk of developing fulminant liver failure in the event of acute infection with other hepatotropic viruses was approximately nine times higher in HBsAg carriers than in non-carriers. Hepatitis A seroprevalence exhibits significant interpopulation and interregion variability, with factors such as vaccination coverage, sanitation, and socioeconomic conditions playing a pivotal role in its distribution. For instance, a study conducted in Korea on patients with chronic viral liver disease revealed that 80% of those with chronic HBV infection were also infected with hepatitis A (18). A study conducted in Italy found that the levels of this substance were higher in the southern part of the country than in the northern part of the country. The researchers

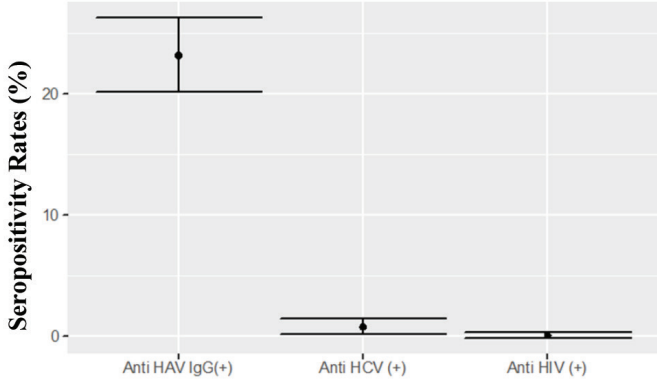


Figure 1. Anti-HCV, anti-HIV, and anti-HAV IgG seropositivity in HBsAg-positive patients

HBsAg: Hepatitis B surface antigen, HAV IgG: Hepatitis A virus immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Table 1. Prevalence of anti-HCV, anti-HIV, and anti-HAV IgG seropositivity in HBsAg-positive patients

	n	% (95% CI)
Anti-HAV IgG (+)	170	23.2 (20.14-26.26)
Anti-HCV (+)	6	0.8 (0.16-1.44)
Anti-HIV (+)	1	0.1 (-0.13-0.33)

HBsAg: Hepatitis B surface antigen, HAV IgG: Hepatitis A virus immunoglobulin G, CI: Confidence interval, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Table 2. Distribution of anti-HCV, anti-HIV, and anti-HAV IgG seropositivity in HBsAg-positive patients according to age and sex

	Total (n=733)	Anti-HAV IgG (+) (n=170; 23.2%)	Anti-HCV (+) (n=6; 0.8%)	Anti-HIV (+) (n=1; 0.1%)	p-value*	p-value**
Age (year)	50.49±14.32	49.42±14.14	57.33±12.30	49	0.270†	0.232µ
Sex						
Male	388 (52.9%)	89(52.4%)	3 (50%)	1 (100%)	0.863¶	1•
Female	345 (47.1%)	81 (47.6%)	3 (50%)	0 (0%)		

*: Anti-HAV IgG (+), **: Anti-HCV (+)
†: Independent samples t-test, µ: Mann-Whitney U test, ¶: Chi-square test, •: Fisher's exact test
HBsAg: Hepatitis B surface antigen, HAV IgG: Hepatitis A virus immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

attributed this discrepancy to the higher socioeconomic standards in the north and the lower consumption of raw or partially cooked shellfish in the region (19). In a multicenter study conducted in Turkey, 4,793 CHB patients were examined, and the anti-HAV IgG positivity rate was found to be 93.5%. The study reported that 26.2% of patients were under the age of 19, 15.5% were in the 20-25 age group, and 12.5% were in the 26-29 age group. All patients were HAV seronegative (20). In a further study conducted in our country, the data of 137 adult male patients (aged ≥20 years) who were HBsAg-positive and had not received HAV vaccination were analyzed. The study revealed that 83.2% (114/137) of the serum samples from the study group were anti-HAV IgG positive, with higher percentages observed in the Marmara Region (61.5%, 8/137), the Aegean Region (83.3%, 10/12), and the Central Anatolia Region (81.3%, 13/16). The lowest percentages were found in the Black Sea Region (66.7%, 8/12), Eastern Anatolia region (87.5%, 21/24), and Southeastern Anatolia region (94.1%, 32/34) (21). In the study by Kepenek et al. (22), the presence of anti-HAV IgG was examined in a cohort of 923 patients who were monitored for HBsAg positivity between 2010 and 2019. The overall positivity rate was 89.9% (830/923), indicating a high prevalence of the infection (22). In a separate study, the presence of anti-HAV IgG was identified in 105 (94.6%) of 111 patients diagnosed with CHB (23). In the present study, the anti-HAV IgG positivity rate was 23.2%. The results of a study conducted on a smaller sample from the same center in 2018 yielded similar outcomes, and this rate was found to be lower than that of other studies conducted in our country. Consequently, it was hypothesized that the level of awareness regarding hepatitis A vaccination among the study population was inadequate. Conversely, the low rate of anti-HAV IgG positivity may be attributable to disparities in socioeconomic status, hygienic practices, sanitation infrastructure, and familial size across different regions (24). In the United States, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices recommends hepatitis A vaccination in seronegative cases and in the presence of chronic liver disease, especially hepatitis B, hepatitis C, and alcoholic hepatitis (25). In consideration of the data obtained from our own research, it was recommended that patients with a hepatitis B infection who were seronegative for hepatitis A should receive vaccination as initial controls.

In comparison with patients infected with HBV alone, those with HBV/HCV, HBV/HIV, and HBV/HAV infection demonstrated a more unfavorable prognosis with regard to elevated HBV replication, frequent and rapid progression to cirrhosis, the development of HCC, and fulminant liver failure (2,26,27). It has been established that patients suffering from both HBV and HCV infections face an elevated risk of progressive liver disease, cirrhosis, and HCC when compared with individuals who are infected with a single virus (27,28). Therefore, it is recommended that anti-HCV be requested during the diagnostic process and throughout the treatment phase. As a general rule, these patients should be treated for the virus during its replication phase. However, it is important to note that treatment of HCV with direct-acting antivirals may result in the reactivation of HBV. Consequently, in cases of co-infection, the prescription of direct-acting antivirals should be accompanied by the administration of a nucleotide analog, provided that the patient fulfills the treatment criteria for CHB. In patients with chronic HBV infection, the concurrent administration of direct-acting antivirals and a nucleotide analog is recommended, with treatment continuing for a period of up to 12 weeks following the cessation of direct-acting agent therapy (29,30). In the event of co-infection, a comprehensive evaluation is imperative to ascertain the necessity of treatment and prophylaxis. The anti-HCV seroprevalence rate in HbsAg-positive patients has been the subject of investigation in various populations. In a study conducted in China between 2018 and 2020, 44 (0.4%) of 10,560 HbsAg-positive patients were found to be anti-HCV-positive (31). A study conducted in China found that 14.9% of 712 HBV patients exhibited HCV co-existence (32). In a separate study, Chu and Lee (33) discovered that HCV was present in 2-10% of individuals who were carriers of HBV. In their report, Benvegnù et al. (34) stated that the 10-year cumulative risk of developing HCC was 45% in patients with cirrhosis with co-infection and 16% in patients with HBV-related cirrhosis. Consequently, the potential for HCV infection should be assessed in patients with HBV-related chronic liver disease. A comprehensive study was conducted in 15 centers to investigate the prevalence of HBV/HCV co-infection in our country. The prevalence rate was approximately 0.974% (974/100,000) (28). In the present study, the anti-HCV seroprevalence rate was 0.8% in HBsAg-positive patients, which is consistent with the findings of previous studies. Despite the absence of a vaccine against the HCV, the low prevalence observed in our country and within our patient group appears to be advantageous.

The prevalence of HIV infection has increased worldwide, which has resulted in a concomitant increase in the number of studies investigating HBV and HIV co-infection (26). It is important to note that HBV and HIV can occur in parallel due to the similarity of their respective transmission routes. In patients with HBV and HIV infection, both types of infection should be treated, irrespective of CD4 levels. The combination of tenofovir disoproxil fumarate and tenofovir alafenamide has proven efficacious in combating both HIV and HBV and is therefore recommended for incorporation into therapeutic regimens. However, it is crucial to emphasize that discontinuation of treatment can lead to HBV reactivation, emphasizing the necessity for strict adherence to treatment guidelines. It is imperative to emphasize that treatment should aim to be suppressive and lifelong (29,30). In a study conducted in Taiwan, 57 (18.9%) of the anti-HIV-positive sample group consisting of 301 intravenous drug users were found to have HBV/HIV co-infection (35). A recent meta-analysis of HBV infection among people with HIV reported that the prevalence of HBV/HIV co-infection was highest in the Western Pacific region (11.4%) and sub-Saharan Africa (10.0%) and lowest in Europe (6.7%) and the Americas (5.3%) (36). The prevalence of hepatitis B infection and HIV in Senegal was 8.8% in a study conducted in the region (37). In Turkey, the prevalence of HBV and HIV co-infection was reported to be 4.2% and 4.4%, respectively (38,39). In the present study, the anti-HIV seroprevalence rate was 0.13% among patients positive for HBsAg. The risk of developing CHB infection increases by up to 23% in the presence of HIV infection (40). While studies investigating HBV and HIV co-infection have predominantly concentrated on HBV in HIV-positive individuals. Consequently, co-infection may be detected at a higher rate in patients with HBV

than in studies investigating HIV. This underscores the necessity of incorporating risk factors and specific population demographics when evaluating co-infection rates.

In the present study, no statistically significant difference was identified between the distribution of anti-HAV IgG and anti-HCV seropositivity according to age (p=0.270, p=0.232) and gender (p=0.863, p=1.00). These findings underscore the importance of hepatitis A vaccination, particularly among older seronegative patients. In Turkey, hepatitis A and B vaccinations are included in the childhood vaccination schedule. A Turkish study conducted among a cohort of children born after 1998, when the national programme for free hepatitis B vaccination was initiated, and who had received cancer treatment, found that HBsAg positivity was not observed in 100 children (41). Although the present study was conducted in a cohort of patients with hepatitis B, it is nevertheless incumbent upon us to eradicate the virus. The decline in HBsAg positivity in Turkey is a significant public health achievement, which can be attributed to the success of vaccination campaigns targeting high-risk groups, public health initiatives, and the commitment of healthcare workers to combat HBV transmission (42).

The objective of this study was to contribute to the regional data. It is acknowledged that seropositivity rates may vary among countries, regions, and even centers. The collection of seropositivity data from each center will facilitate a more comprehensive understanding of the actual prevalence in our country. From a clinical perspective, in the presence of co-infection, HAV seroprevalence should be investigated in HBsAg-positive patients because of its severe course, and seronegative cases should be vaccinated. It is hypothesized that enhancing public awareness regarding the modes of transmission, augmenting knowledge concerning vaccination, and undertaking further research into immunization will result in a substantial decline in the incidence of these infections.

Study Limitations

This study is subject to several limitations. Due to its retrospective nature, the study did not achieve a sufficient sample size, and the available data were limited in scope. To contribute to the epidemiological data of our country, it is thought that the study needs more patients and should be supported by a multicenter study.

Conclusion

In conclusion, individuals living with HBV must undergo meticulous monitoring for co-infections. Co-infections are of particular significance due to their capacity to increase morbidity and mortality. Relevant tests should be requested and followed up to determine disease management and treatment priorities. It is recommended that each center evaluate its own epidemiological data and raise awareness.

Ethics

Ethics Committee Approval: For this study, permission was obtained from Clinical Research Ethics Committee Balıkesir University Faculty of Medicine (date: 31.01.2018, approval number: 27).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.Ç., E.D., Concept: Y.Ç., E.D., Design: Y.Ç., E.D., Data Collection or Processing: Y.Ç., E.D., Analysis or Interpretation: Y.Ç., E.D., Literature Search: Y.Ç., E.D., Writing: Y.Ç., E.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research Article

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Comparison of Patient Adherence and Treatment Response in Patients with Chronic Viral Hepatitis: Results of a 48-Week Observational Study

Kronik Viral Hepatit Hastalarında Hasta Uyumu ve Tedavi Yanıtının Karşılaştırılması: 48 Hafta Gözlemsel Çalışma Sonucu

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ABSTRACT

Objectives: Viral hepatitis is one of the significant health problems in the world. The main purpose of treatment is virological eradication. There are many factors that determine treatment response. The most important factor that can be affected is treatment adherence. In our study, we aimed to compare compliance with treatment response, which is one of the factors that can be affected in chronic viral hepatitis patients. We highlight that this element should be considered in treatment failures, especially in chronic diseases that require long-term treatment.

Materials and Methods: Chronic hepatitis patients over 18 years of age and under 65 years of age, who were neither co-infected with Human immunodeficiency virusnor pregnant, were prospectively analyzed after receiving ethics committee approval. Treatment adherence was defined as taking the prescribed medication in the required number of doses and for the required duration. Drug count and questionnaires were used in the compliance assessment. Patients' compliance and patients' 12, 24, 36, and 48th-week virological responses were compared.

Results: Seventy-six patients were included in the study. Sixty point five percent of patients had chronic hepatitis B, and 39.5% had chronic hepatitis C. According to the drug count data, it was determined that 83.9% of the patients did not take their treatment during at least one visit. At the end of the treatment (48th-week follow-up), 89.4% of all chronic hepatitis patients were compliant and 92.6% of the compliant patients responded to the treatment. Five out of eight non-compliant patients, accounting for 62.5%, were able to respond to the treatment. Response rates of

ÖZ

Amaç: Viral hepatitler dünyadaki önemli sağlık sorunlarından biridir. Hepatit tedavisinde ana amaç virüs eradikasyonun sağlanmasıdır. Bu hedefe ulaşmada tedavi yanıtın etkileyen pek çok faktor mevcuttur. Etkilenebilen en önemli faktör ise hastaların tedaviye uyumlarıdır. Çalışmamızda kronik viral hepatit hastalarında etkilenebilen faktörlerden olan uyum ile tedavi yanıtı karşılaştırılarak özellikle uzun dönem tedavi gerektiren kronik hastalıklarda tedavi başarısızlıklarında bu öğenin de akılda tutulması gerektiğine dikkat çekmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamıza 18 yaş üstü ve 65 yaş altı yeni tedavi başlanması planlanan kronik hepatit B ve hepatit C hastaları alındı. İnsan bağışıklık yetmezliği virüsü ile ko-enfekte ve gebe hastalar çalışma dışı bırakıldı. Çalışma öncesi etik kurul onayı alınarak hastalar 48 hafta prospektif olarak izlendi. Tedaviye uyum, reçete edilen ilacı reçete edildiği gibi uygun doz ve sürede almış olmak olarak tanımlandı. Uyum belirlenirken ilaç sayımı ve anket yöntem kullanıldı. Hastaların uyum ile 12., 24., 36. ve 48. hafta virolojik yanıtları karşılaştırıldı.

Bulgular: Çalışmaya 76 hasta dahil edildi. Hastaların %60,5 kronik hepatit B, %39,5'i kronik hepatit C hastası idi. İlaç sayım verilerine göre hastaların %83,9'unun en az bir vizitte ilaçlarını almayı unuttuğu tespit edildi. Kırk sekiz haftalık izlem sonunda hastaların %89,4'ünde uyum tespit edildi. Uyumlu hastaların ise %92,6'sında tedaviye cevap mevcut idi. Uyumsuz tespit edilen hastaların ise %62,5'inde tedaviye cevap alındı. Tedaviye uyumlu ve tedaviye uyumsuz hastaların tedavi cevap oranları istatistiksel olarak anlamlı bulundu.

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compliant and non-compliant patients to treatment were found to be statistically significant.
Conclusion: Non-adherence to treatment in chronic viral hepatitis is infrequent. Given the increased risk of virological failure in poorly adherent patients, clinicians should keep in mind adherence issues in every patient treated for viral hepatitis.
Keywords: Adherence, hepatitis B, hepatitis C

Sonuç: Kronik viral hepatit hastalarında tedavi uyumsuzluk çok sık görülen bir durum olmamasına rağmen, düşük uyumlu hastalarda virolojik cevabın yetersizliği riski yüksek olmasından dolayı hekimler tüm tedavi alan kronik hepatit hastalarında tedaviye uyum faktörünü aklında bulundurmalıdır.
Anahtar Kelimeler: Uyum, hepatit B, hepatit C

Introduction

Viral hepatitis is one of the common health problems all over the world. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are viruses that can cause an infection progressing from acute to cirrhosis and hepatocellular carcinoma. Achieving virological eradication and slowing this progression are among the goals of treatment. Today, there are many therapeutic agents used in the treatment of viral hepatitis. There are many factors that canbe changed in treatment response. Viral load, genotype, and race of the patient are traits that can affect the sustained response but cannot be changed. The most important factor that can be changed is the patient's adherence to treatment. Adherence to treatment can be defined under two subheadings, and for a successful treatment, both should be:

Compliance: Compliance to patient's appointments, medical recommendations such as medication and regulation of living conditions as required by the disease and treatment,

Cooperation (Adherence): Taking prescribed medication as required (in number and at appropriate time) and attending the health institution appointments without interruption (1).

Compliance becomes more important in patients with chronic diseases, which are costly and require long-term treatment. This study aimed to investigate the effect of treatment compliance on a virological response in hepatitis, a chronic disease that requires long-term treatment.

Materials and Methods

Our study was conducted in an infectious disease's out patient clinic in Trabzon from July 2012 to July 2014. Chronic hepatitis patients, who were over 18 years of age and under 65 years, who weren't co-infected with Human immunodeficiency virus and not pregnant, were prospectively analyzed after receiving ethics committee approval. A follow-up form was created and virological, biochemical and serological responses were evaluated at the 12th, 24th, 36th and 48th weeks from the beginning of treatment. Fourth-week response was also evaluated in chronic hepatitis C (CHC) patients. This study approval was received from the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval number: 74, dated: 12.02.2013). A patient informed consent form was obtained. Publication approval has been given.

Hepatitis B medication regimens were defined as pegylated-interferon (PEG-IFN) α2a or -α2b, the nucleos(t)ide analogues including lamivudine, adefovir, entecavir, tenofovir disoproxil fumarate and telbivudine (2).

Medication regimens for hepatitis C were defined as combination therapy, including PEG-IFN α2a or -α2b combined with ribavirin and triple therapy with protease inhibitors boceprevir and telaprevir (3,4).

Patient adherence was assessed by the monthly number of prescribed antiviral drugs and compliance questionnaire, The questionnaire comprised two sections designed to understand treatment behaviors. Section 1 consists of 6 questions with yes or no answers adapted from Turkish modified Morisky questions, whose validity and reliability were confirmed by Vural et al. (5). Second section includes questions focusing on treatment regimen, doses and patient perceptions.The survey results were given as percentages.

Treatment response in CHC was defined as normal liver function tests, HCV-RNA becoming negative in the 4th week of treatment (rapid virological response), HCV-RNA becoming negative or a 2-log decrease in the 12th week of treatment (early virological response), and RNA becoming negative end of treatment and thereafter (6). Treatment response in chronic hepatitis B (CHB) patients was defined as the normalization of liver function tests, the decline of HBV-DNA to an undetectable level, and the maintenance of these levels (7).

Full compliance is defined as not having a forgotten dose; moderate compliance is forgetting 1 dose in the last 4 days or on the weekend; incompatibility is defined as forgetting more than one dose in the last 4 days or more than one dose on the weekend (8). Compliance percentage is obtained by subtracting the forgotten amount from the amount of medication prescribed to the patient and dividing the result by the amount of medication that should be taken daily multiplied by the duration. And multiplying it by 100 (9).

Statistical Analysis

IBM SPSS Statistics for Windows. Version 22.0 (Statistical Package for the Social Sciences, IBM Corp. Armonk, NY, USA) was used for data analysis. For categorical variables, descriptive statistics include numbers(n) and percentages (%); for numerical variables, descriptive statistics include mean and standart deviations. Risk factors affecting adherence were identified by univariate analysis, the chi-square test was used for qualitative data. Analysis results were presented as p-value estimated relative risk (odds ratio) and 95% confidence interval. Statistical significance level was accepted as $p<0.05$. Variables found to be statistical significant in univariate analysis were subjected to further detailed multivariate analysis using the logistic regression technique.

Results

Seventy-six patients were included in the study. Sixty point five percent (n=46) of patients were CHB patients, and 39.5% (n=30) were CHC patients. Forty-two point one percent of the patients were women. The mean age of the patients was 45.18±13.2 years. Thirty-nine point five percent of the patients had comorbid diseases, and 26.3% of these patients used an additional drug.

According to the survey, all CHB patients received oral treatment. No patient received interferon. Ninety-three percent

of CHB patients disrupted their treatment for at least one visit. Thirty-two percent stated that they forgot to take their medication on weekends. The most common reason for non-adherence was "forgetfulness". Twenty-two percent of them had difficulty remembering to take medications because they were using multiple medications. Twenty-five percent of them used the telephone setting methods to remember medication. Twenty percent of them considered stopping treatment because they thought that their disease was stable.

Twenty percent of CHC patients were given triple treatment. Six point six percent of patients disrupted their treatment for at least one visit. The most common reason for this was drug side effects. It was observed that 12% of CHC patients had difficulty remembering medications. The telephone setting method was the most common recall method. All our patients stated that they take their treatment with them when they travel. According to drug count data, at the end of the 48-week treatment follow-up, 89.4% of all chronic hepatitis patients had compliance and 92.6% of compatible patients responded to the treatment. Sixty-two point five percent of the eight incompatible patients were able to respond to treatment. Response rates of compliant and incompatible patients to treatment were statistically significant (p=0.034).

The average compliance percentage of CHB patients at 48-week follow-up was 90.9%. At the 4th week follow-up, 28.2% (n=13) of patients were fully compliant, while 56.5% (n=26) were moderately compliant and 15.2% (n=7) of patients were incompatible. At the 12th week, 19.5% (n=9) of patients were fully compliant, 65.2% (n=30) were moderately compliant, and 15.2% (n=7) of patients were incompatible. Sixty-six point six percent (n=6) of fully compliant, 53.3% (n=16) of moderately compliant patients, and 28.6% (n=2) of incompatible patients responded to treatment.

At 24th week, 36.9% (n=17) of patients were fully, 43.4% (n=20) were moderately compliant and 19.5% (n=9) of patients were incompatible. Response was achieved in 70.6% (n=12) of fully compliant, 60% (n=12) of moderately, and 22.2% (n=2) of incompatible patients.

At the end of a 48-week follow-up after treatment, 13 CHB patients were fully adherent, 25 CHB patients were moderately adherent, and 8 were non-adherent. The viral load became negative in 92.1% of compliant patients and 62.5% of non-compliant patients. This rate was statistically significant (p=0.048). The average compliance rate of CHC patients was 95% at 48-week follow-up. At the 4th week, 63.3% (n=19) of CHC patients were fully compliant, and 36.6% (n=11) were moderately compliant. We had no incompatible patients. Rapid virological response occurred in 94.7% (n=18) of fully compliant patients and 45.5% (n=5) of moderately compliant patients. This rate was statistically significant (p=0.004). At the 12th week, 70% (n=21) of the patients were fully compliant, 26.6% (n=8) were moderately compliant, and one patient was non-compliant. Virological response was observed in 95.2% (n=20) of fully compliant patients and 75% (n=6) of moderately compliant patients.

Virological response could not be achieved in one non-responsive patient. At the 24th week, while 80% of patients were fully compliant, treatment response rates were 95.8% (n=23). Success was achieved in 80% of five moderate patients and the single patient with incompliance. At the end of the 48-week follow-up after treatment, full compliance was observed in 2 patients, and moderate compliance was observed in 28 patients with CHC.

We did not have any incompatible patients. While no response was obtained in 2 patients with compatibility, 28 patients with moderate compatibility showed a 100% response. This rate was statistically significant (p=0.002).

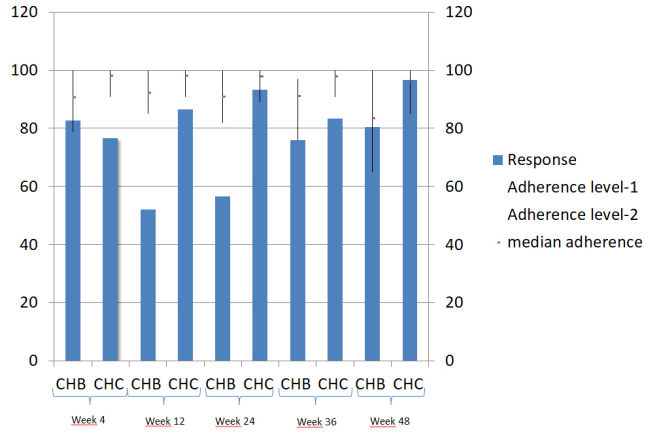
Compliance and response charts according to treatment follow-up weeks, in chronic hepatitis B and hepatitis C patients are given in Table 1.

Graphs of compliance and treatment response by week in CHB and CHC patients are presented in Graph 1.

Table 1. Compliance and response charts in chronic hepatitis B and hepatitis C patients

	Full adherence/ response (%)	Moderate adherence/ response (%)	Incompliance/ response (%)	p-value
CHB				
Week 0-4	28.2 (n=13)/92.3 (n=12)	56.5 (n=26)/84.7 (n=22)	15.2 (n=7)/57.1 (n=4)	
Week 5-12	19.5 (n=9)/66.6 (n=6)	65.2 (n=30)/53.3 (n=16)	15.2 (n=7)/28.6 (n=2)	
Week 13-24	36.9 (n=17)/70.6 (n=12)	43.4 (n=20)/60 (n=12)	19.5 (n=9)/22.2 (n=2)	
Week 25-36	34.7 (n=16)/100 (n=16)	52.1 (n=24)/79.2 (n=19)	13.04 (n=6)/0 (n=0)	
Week 37-48	43.7 (n=20)/90 (n=18)	39.1 (n=18)/83 (n=15)	17.3 (n=8)/50 (n=4)	
Median	28.2 (n=13)/100 (n=13)	54.3 (n=25)/88 (n=22)		
Median	82.6 (n=38)/92.1 (n=35)		17.3 (n=8)/62.5 (n=5)	0.048
CHC				
Week 0-4	63.3 (n=19)/94.7 (n=18)	36.6 (n=11)/45.5 (n=5)	0	0.004
Week 5-12	70 (n=21)/95.2 (n=20)	26.6 (n=8)/75 (n=6)	3.3 (n=1)/0 (n=0)	
Week 13-24	80 (n=24)/95.8 (n=23)	16.6 (n=5)/80 (n=4)	3.3 (n=1)/100 (n=1)	
Week 25-36	73.3 (n=22)/90.9 (n=20)	23.3 (n=7)/57.1 (n=4)	3.3 (n=1)/100 (n=1)	
Week 37-48	73.3 (n=22)/100 (n=22)	23.3 (n=7)/85.7 (n=6)	3.3 (n=1)/100 (n=1)	
Median	6.6 (n=2)/0 (n=0)	93.3 (n=28)/100 (n=28)	0	0.002

CHB: Chronic hepatitis B, CHC: Chronic hepatitis C



Graphic 1. Compliance and treatment response graphs by weeks in hepatitis patients

CHB: Chronic hepatitis B, CHC: Chronic hepatitis C

Discussion

Nowadays, reliable and effective treatments are used to prevent unwanted complications of hepatitis, such as cirrhosis, liver failure, and hepatocellular carcinoma, which is one of the important health problems in the world.Besides drug performance, compliance with treatment is also an important factor in chronic diseases like hepatitis (1-10).

Chronic hepatitis patients are generally asymptomatic, so long-term compliance rates may be suboptimal. Due to the difficulty of measuring adherence, many methods have been developed. Pharmacy filling data, reports provided by patients and doctors, patient compliance questionnaires, and medication count are methods used to measure compliance. In many studies patient reports was used to calculate compliance. However, compliance measurements that were made based on patient statements can yield results higher than the actual compliance rate. Assessing compliance through drug count gives more objective results than other methods. In our study, toevaluate compliance, we used drug counting and adherence questionnaires. In recent studies on CHB and compliance, the compliance range has been reported to be 81-99% (10). We found a 90% compliance rate in CHB patients, consistent with the literature. It is estimated that the single daily dose used in the treatment, good tolerance and minimal side effects are reasons for this high rate of compliance in CHB (12).

The average compliance rates vary between 54.1% and 95% in CHC patients in recent studies. In our study, we found the average compliance is over 95% in CHC patients. Wide range of compliance rates is attributed to many factors such as changing methods in calculating compliance, duration of follow-up, socio-cultural status, economic characteristics, and the different side effects of drugs in each patient. In addition to these reasons, in our study, reasons such as close following up and knowing patients that they would bring their medications boxes with them may have caused these high average compliance percentage. Tolerance to CHC treatment may vary among individuals. Sometimes serious side effects may occur. These side effects are the main reason for dose reduction and disruption in the treatment of CHC. Dose reduction or treatment interruptions due to side effects, in CHC treatment may be confused with patient-induced noncompliance. Dose reduction or skipping by the doctor should not be considered unresponsiveness to treatment. Joint evaluation of dose reduction by doctor and patient in CHC can be another reason for the wide range of compliance observed among CHC patients (13). When the compliance in CHB treatment is compared with the compliance in CHC treatment, the compliance of CHC patients to treatment is higher. The reasons for this may be closer follow-up due to side effects, providing motivation after frequent patient-doctor communication (10-14). Additionally, the long treatment of CHB leads to a decrease in patient compliance due to decreased interest in medication and the patient's motivation (12).

In a few studies on CHB, although the virological testing varies, the effect of compliance on virological response is variable. Some studies have found that compliance is not a predictor for HBV-DNA negativity (14). In our study, compliance and response rates were variable, too, which support this view.

Adherence of >85% to treatment in CHC patients was associated with increased early virological outcomes (15). In our study, good treatment responses were obtained with high compliance rates in first 12 weeks of treatment. At week 24, high compliance and high response rates were also correlated in our patients, consistent with the literature (16). The fact that our incompatible patients also responded to treatment suggests that other factors, such as the structure of the virus can be effective in the response to treatment. In practice, medication side effects are seen as a major cause of non-compliance (19). According to compliance survey questions, while we found similar results in CHC patients (18), the most common reason for non-compliance in CHB patients was "forgetfulness" in line with the literature (17). The reason for this may be that drug side effects are rare in CHB patients (12). Furthermore, "Feel better already and do not think it is necessary to continue," and "Multiple medications are taken daily," were other reasons that impact regular medication use in patients, unlike the findings of Giang et al. (12).The main drawback of this study was that adherence was assessed by patients' self-reports, although medication enumeration was also performed. Although self-reported adherence is the most appropriate method for evaluating adherence to a medication, it is subject to overestimation (20). Additionally, due to the small sample size, these findings are not generalizable. Nevertheless, these results could help in understanding patients' treatment behaviors and highlight areas to improve adherence. In addition, the success of treatment in hepatitis patients who was considered incompatible in our study indicates that the definitions of compatible and incompatible in drug counting should be reconsidered in further studies. In the future, more objective results will be obtained in compliance evaluations with current and new treatment approaches by contacting patients one-on-one, such as through home health services using technology.

Conclusion

In conclusion, while compliance is important in chronic diseases that require long-term treatment, this situation has become even

more important with the newly developed oral antiviral agents in hepatitis. In CHB patients, as in CHC patients, shortening the treatment period with newly developed drugs can lead to higher treatment success by increasing the compliance rate.

Ethics

Ethics Committee Approval: This study approval was received from the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval number: 74, dated: 12.02.2013).

Informed Consent: A patient informed consent form was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S.Y., İ.K., Concept: S.S.Y., İ.K., Design: S.S.Y., İ.K., Data Collection or Processing: S.S.Y., İ.K., Analysis or Interpretation: S.S.Y., F.K.B., İ.K., Literature Search: S.S.Y., F.K.B., Writing: S.S.Y., F.K.B., İ.K.

Conflict of Interest: No conflict of interest was declared bythe authors.

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Case Report

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Hepatitis B and Hepatitis C Co-infection: Treatment Approaches and A Case Report

Hepatit B ve Hepatit C Ko-enfeksiyonu: Tedavi Yaklaşımları ve Bir Olgu Sunumu

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ABSTRACT

Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection is a significant health issue worldwide and can accelerate liver damage when they occur together. This study presents the treatment process of a 52-year-old female patient with HCV and HBV co-infection. The patient was initiated on direct-acting antiviral therapy (glecaprevir and pibrentasvir) for HCV infection and entecavir for HBV reactivation. As a result of treatment, both HCV-RNA and HBV-DNA became negative, and a sustained virologic response was achieved for HCV. Our study highlights the effectiveness of modern treatment approaches for patients with HBV and HCV co-infection.

Keywords: Chronic hepatitis C, chronic hepatitis B, chronic hepatitis B and C, direct-acting antiviral

ÖZ

Hepatit B virüs (HBV) ve hepatit C virüs (HCV) ko-enfeksiyonu, dünya genelinde önemli sağlık sorunları arasındadır ve birlikte oldukları durumlarda karaciğer hasarının ilerlemesini hızlandırabilir. Bu çalışmada, 52 yaşındaki bir kadın hastanın HCV ve HBV ko-enfeksiyonu ile tedavi süreci sunulmuştur. Hastaya, HCV için doğrudan etkili antiviral tedavi (glekaprevir ve pibrentasvir) ve HBV reaktivasyonu için entekavir başlanmıştır. Tedavi sonucunda hem HCV-RNA hem de HBV-DNA negatifleşmiş ve HCV için kalıcı viral yanıt elde edilmiştir. Çalışmamız, HBV ve HCV ko-enfeksiyonu olan hastalarda modern tedavi yaklaşımlarının etkinliğini vurgulamaktadır.

Anahtar Kelimeler: Kronik hepatit C, kronik hepatit B, kronik hepatit B ve kronik hepatit C, direkt etkili antiviral

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are important causes of morbidity and mortality worldwide. Chronic HBV and HCV co-infection occurs when both viruses cause infection simultaneously, with a prevalence of approximately 1-15% globally (1). The presence of both HBV and HCV can accelerate the progression of liver disease and increase the risk of complications such as cirrhosis and hepatocellular carcinoma (HCC) (2). The treatment of HBV and HCV co-infections is an important clinical experience for physicians. For this reason, we considered sharing our case as a practical contribution. Informed consent for this case report was obtained from the patient.

Case Report

A 52-year-old female patient with no known comorbidities was referred to our clinic after routine tests conducted prior to surgery for benign breast disease revealed positive anti-HCV and hepatitis B surface antigen (HBsAg) results. The patient's family history did not include hepatitis or cirrhosis, and she had no history of intravenous drug use or previous surgical interventions. It was noted that she had multiple regular sexual partners.

Laboratory tests showed negative anti-human immunodeficiency virus, anti-hepatitis B core immunoglobulin M, anti-hepatitis B e antigen (anti-HBeAG), anti-HBe, negative hepatitis delta virus Ag (HDV Ag), and negative HDV-RNA. Liver function tests indicated aspartate aminotransferase (AST): 23 IU/L, alanine aminotransferase (ALT): 18 IU/L; total bilirubin: 0.3 mg/dL, international normalized ratio: 1.2, platelet count: 280,000/mm^3, and hemoglobin: 13.8 g/dL. Thyroid function tests and autoantibodies were within normal limits. The patient's HCV-RNA and HBV-DNA levels were 4,270,000 and 7,950 IU/mL, respectively. HCV genotype analysis revealed genotype 1B. Abdominal ultrasound did not reveal any pathological findings

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except for "mild granulation in the liver parenchyma". Liver biopsy results showed fibrosis stage 2/6 and HAI score of 8/18.

In the treatment planning, direct-acting antiviral (DAA) therapy was initiated for HCV, along with a nucleoside/nucleotide inhibitor for HBV prophylaxis. The treatment regimen for the treatment-nave, noncirrhotic genotype 1B patients included a combination of glecaprevir (100 mg) and pibrentasvir (40 mg) administered 1x3/day for 8 weeks. Additionally, entecavir 0.5 mg/day was started for HBV. At the 4th week of treatment, follow-up tests showed HBV-RNA-negative, HBV-DNA at 484 IU/mL, AST at 32 IU/L, and ALT at 24 IU/L. Twelve weeks after initiating treatment, both HCV-RNA and HBV-DNA were negative, indicating that no viral genome was detected. The 24th week of follow-up showed a sustained virologic response.

Discussion

HBV and HCV co-infection can lead to a more complex clinical picture and faster progression of liver diseases compared with mono-infection. Co-infection often results in a more aggressive disease course and increased risk of complications. The presence of both HBV and HCV elevates the risk of liver fibrosis and cirrhosis and increases the risk of developing HCC. In particular, the co-existence of both viruses complicates treatment and monitoring processes, necessitating a multidisciplinary approach (3).

Co-infections typically manifest in three ways: co-dominant, HBV-dominant, and HCV-dominant. In our case, the HCV-RNA copy number was significantly higher than that of HBV-DNA, indicating HCV-dominant coinfection, and treatment was conducted according to protocols recommended for HCV mono-infected patients. This approach has shown successful results when HCV is more dominant than HBV (4,5).

In recent years, interferon-based treatments have been replaced by DAA drugs, and these drugs have provided a revolutionary development in the treatment of HCV. DAAs such as glecaprevir and pibrentasvir have high efficacy rates and provide high treatment success in coinfected patients. As observed in this case, the HCV-RNA of the patient treated with the combination of glecaprevir and pibrentasvir turned negative as of the 4th week, and a sustained viral response was achieved at the end of the treatment. The low side effects and high effectiveness of these treatment protocols have made them the primary choice for HCV treatment (6).

However, the risk of HBV reactivation increases with HCV treatment. Therefore, before initiating HCV treatment, prophylactic treatment should be initiated against the risk of HBV reactivation. Prophylaxis for HBV should be administered during DAA treatment for at least 12 more weeks after treatment ceased (7). In this case, entecavir treatment was initiated successfully to prevent HBV reactivation. At the end of the treatment period, HBV reactivation was not observed.

This case demonstrates the effectiveness and safety of DAA treatment in patients with HBV-HCV co-infection and highlights the points that should be taken into consideration for the management of the risk of HBV reactivation. In patients with HBV and HCV co-infection, it is vital to carefully monitor the viral load and to take precautions against possible complications during treatment.

Conclusion

Chronic HBV and HCV co-infection leads to a more complex clinical picture and a more aggressive disease course compared with mono-infections. DAAs have replaced traditional interferon-based therapies, particularly in HCV-dominant HBV/HCV co-infected patients, due to their lower side effects and high treatment success rates. However, the risk of HBV reactivation after DAA treatment should be considered, and patients should be monitored with appropriate prophylaxis. Treatment selection in co-infected patients should be based on the dominant virus type and side effect profile.

Ethics

Informed Consent: Informed consent was obtained from all participants.

Acknowledgments

This case report presented as a poster in Infectious Diseases and Clinical Microbiology Specialty Society of Turkey 2022 congress, Antalya.

Footnotes

Autorship Contributions

Surgical and Medical Practices: M.B., T.D., Concept: M.B., T.D., Design: M.B., T.D., Data Collection or Processing: M.B., T.D., Analysis or Interpretation: M.B., T.D., Literature Search: M.B., T.D., Writing: M.B., T.D.

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