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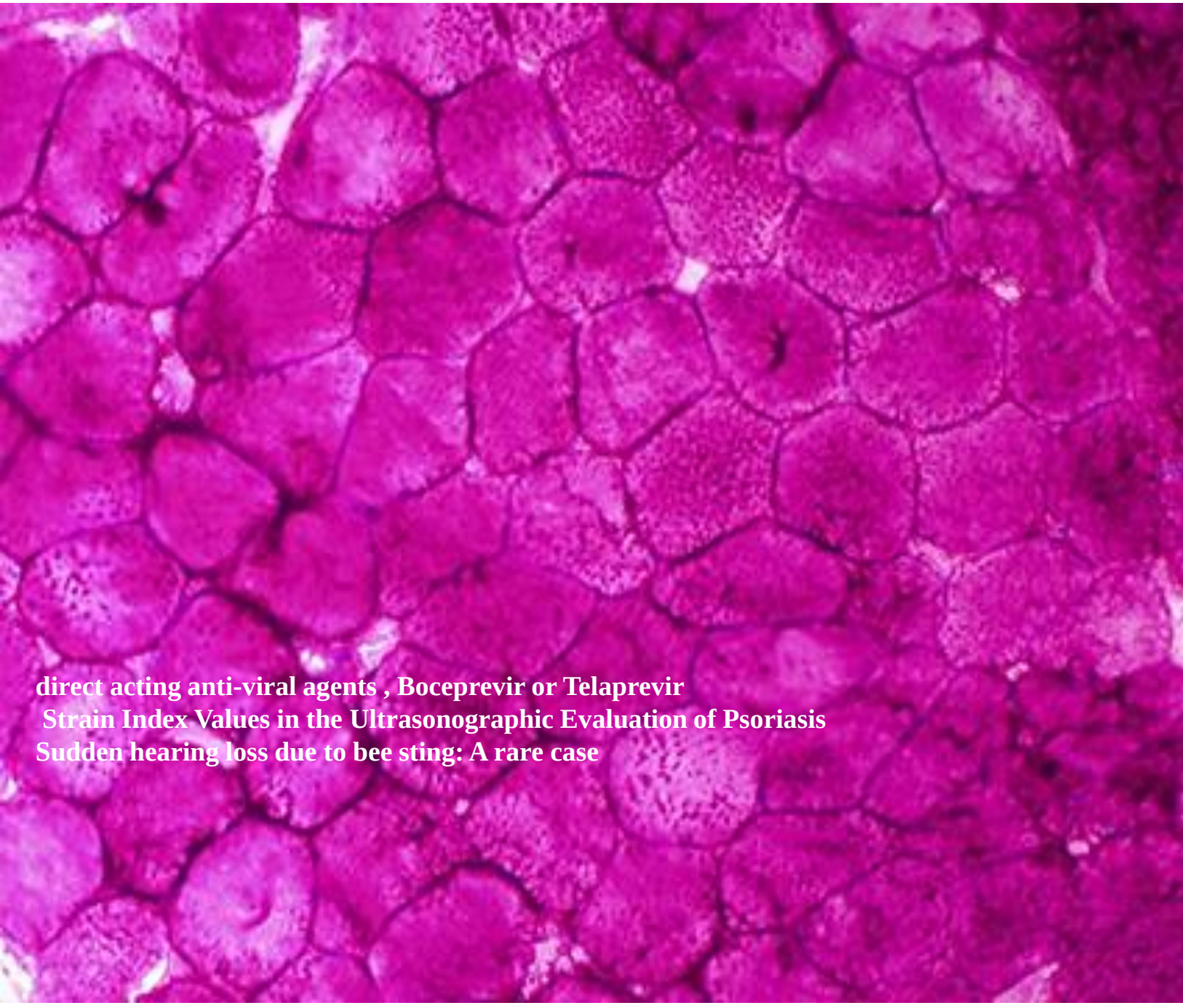

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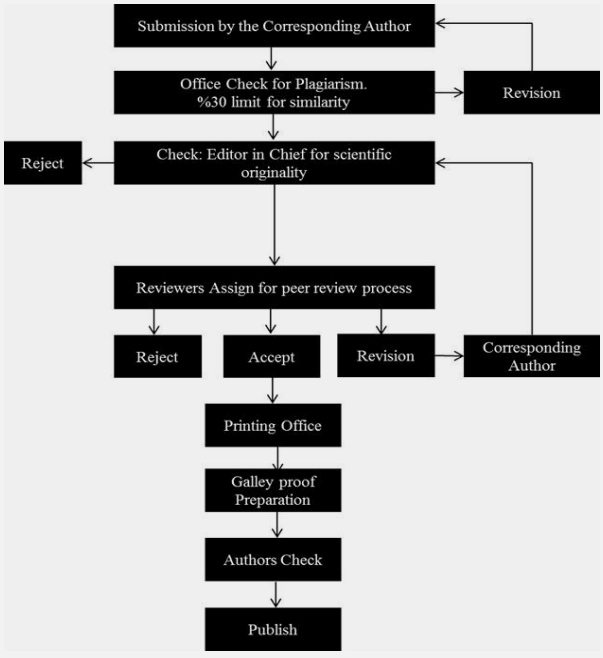

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Review Article Doi: 10.17546/msd.501220

Which of the direct acting anti-viral agents is the better drug in terms of efficacy, cost and safety -Boceprevir or Telaprevir?

Mark Aziz[1]*

Abstract

Objective: Hepatitis C virus can cause chronic hepatitis with 20-30% of those infected are developing liver cirrhosis and some developing hepatocellular carcinoma. It is a global health problem with 130-170 million people infected worldwide. Current treatment uses pegylated interferon and Ribavirin. As of 2011, two new drugs have been approved in the U.S.A and Europe, the protease inhibitors Boceprevir and Telaprevir. The aim of this structured review is to investigate which of these two new drugs is better in terms of efficacy, safety and cost. A literature search was conducted using various primary and secondary sources. A database search was conducted to find three journals for critical review.

Conclusion: The articles showed that the two drugs are equally effective and more effective than standard therapy. Boceprevir is potentially significantly cheaper. Boceprevir may also have a slightly better adverse effects profile. However, it is evident that direct clinical trials comparing the two drugs are required.

Keywords: HCV, Boceprevir, Telaprevir, Review

Introduction

History: In 1975, serological tests found a hepatitis virus, which was neither hepatitis A or B, named the non-A non-B hepatitis virus (1, 2). It was estimated that the virus was caused by up to 10% of transfusions. It was also responsible for 75% of cases of transfusion associated hepatitis with only 25% caused by hepatitis B (3). The condition was associated with chronic infection of the liver and progression to liver cirrhosis.

The hepatitis C virus (HCV) was molecularly identified in 1988. In 1990, blood tests became available for the virus. This enabled screening of blood transfusion products and proved a link between HCV and the development of hepatocellular carcinoma (1, 2). Due to the amount of blood transfusions occurring in 1990, it was estimated that the ability to screen blood products for HCV, prevented 40,000 infections at the time, or 111 infections per day (4).

Virology: HCV belongs to the hepacivirus genus, only member of that genus, and to the flavivirus family (5). 7 genotypes, named from 1 to 7, and a number of subtypes (abcd...etc) have been identified. The genome consists of a single RNA positive strand, consisting of approximately 9600 bases. The genome contains of a single open reading frame, which codes for a 3000 amino acids polyprotein, that is then cleaved by proteases into at least 10 proteins.

One third of these proteins form the structural proteins of the virus, while 2 thirds are involved in the viral replication process. The structural proteins are the core protein and the envelope proteins E1 and E2 and the non-structural proteins are the NS2-NS5 proteins. In addition, there is a small p7 protein. The non-translated regions, which flank the open reading frame contain an internal ribosome entry site that is used to help in the translation of the viral RNA (6-9).

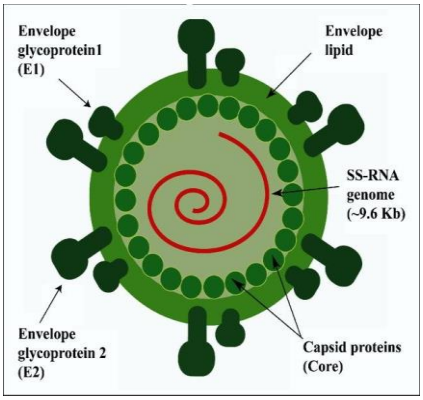

Figure 1: Structure of the HCV. Sharma SD. Hepatitis c. Molecular biology & current therapeutic options. Indian Journal of medical research (9)

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1 Hull University Teaching Hospitals NHS Trust, Hull, HU3 2JZ, UK
*** Corresponding Author:** Mark Aziz **E-mail:** markaziz@gmail.com **Phone:** +44 07846479991

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Replication: The virus enters host cells by binding to glycoaminoglycans and LDL receptors. Specialised cellular structures called the membranous webs, which are derived from the endoplasmic reticulum, are involved in forming a replication complex. Some of the non-structural proteins are involved in the formation of this replication complex.

The RNA is then used as a template for the virus replication and translation (6-10).

Epidemiology: The current global prevalence of HCV is around 2.35% of the world's population (11). Estimates vary but are in the range of 130-170 million people worldwide (12). The variation in these estimates stems from the fact that the majority of acute infections are asymptomatic; however, 80% of these patients will go on to develop chronic HCV infection (12). HCV has been implicated in 27% of cases of liver cirrhosis and 25% of cases of hepatocellular carcinoma (13). The prevalence rates vary from one region to another. The majority of the infected population lives in central/southeast Asia and in the western pacific region. The global epidemiology of the HCV can be seen in Figure 2. (12).

There are regional differences in prevalence rates, which can range from less than1% of the population in northern European countries to 15% of the population in Egypt (11). In Egypt, where the highest prevalence of HCV is found, the infection was spread by bad injection practice during mass public health campaigns to treat schistosomiasis in the 1960s (8, 12). The common transmission routes of the HCV are percutaneous exposure to blood, cross-contamination during injections, sexual transmission and vertical transmission. The risk factors are listed in table 1. Transmission through sexual intercourse, needle-stick injuries and vertical transmission are not as common (8, 13)..

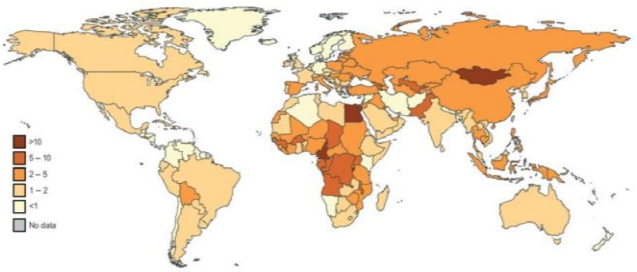

Figure 2: Global prevalence of HCV (12)

Clinical features: Exposure to HCV often causes an asymptomatic infection. In patients with acute hepatitis, there is usually an incubation period of approximately 2 to 12 weeks. Serum HCV RNA can usually be detected after exposure with 1-3 weeks. Unusual liver function tests can be detected after 8 weeks of exposure, with a raised alanine aminotransferase level.

Table 1: Risk factors for HCV infection (12, 13)

Risk factors for HCV infection
Blood transfusions
Haemodialysis
Haemophiliacs
Transplantation patients
Injection drug users
Tattooing
Sex with multiple partners
Birth to an affected mother

The symptoms detected in acute hepatitis are usually nonspecific, mild and less than 25% of patients present with jaundice (see table 2) (8, 14, 15). Patients who present with jaundice have lower rates of progression to chronic HCV infection (16). 20-40% of patients with acute infection will spontaneously clear the virus. For the rest of the patients, the infection will progress to chronic infection. In the patients who spontaneously clear HCV, RNA is cleared within 3 months of onset; so if HCV RNA is detected after the onset with 6 months, then this is usually a sign of progress to a chronic infection (17).

From those patients who develop chronic hepatitis C, 20-30% will go on to develop liver cirrhosis. This usually takes 10-30 years to progress. There are several factors which can speed up this progression such as old age, male gender, race (e.g. African Americans) and excessive alcohol consumption (15, 18). Liver fibrosis occurs as a result of attempts to clear the virus by the body. An effective immune response will clear the virus, while an ineffective immune response will allow the virus to continue replication and recruit immune cells to the hepatocytes, which causes the hepatocellular damage (18). Liver biopsy is the gold standard for detection and staging of liver fibrosis and damage (16). If patients develop compensated liver cirrhosis, then the 5-year survival rate is 90%, while the 5 year risk for progression to hepatocellular carcinoma is 7% and to decompensated liver cirrhosis is 18%. Once patients progress to decompensated liver cirrhosis, the 5 year survival rate drops to 50% (19). Progress to cirrhosis and the deterioration of liver function to decompensated liver cirrhosis often occurs without symptoms, so it is usually recognised at latter stages (see table 2) (20). Approximately 1-2% of patients will develop extra-hepatic manifestations (see table 2) (16).

Screening: The Scottish intercollegiate guidance network (SIGN) has recommended that certain high-risk groups should be screened for HCV . The rationale is that treatment cannot be offered until diagnosis is confirmed and that these individuals are at higher risk of passing on their infection to others. The list of higher risk individuals for screening can be found in table 3 (21)

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Table 2: Signs and symptoms associated with Hepatitis C (8, 14-16)

hepatitis	cirrhosis	
Jaundice	Ascites	Membranoproliferative glomerulonephritis
Fatigue	Oesophageal varices	Porphyria
Anorexia	Hepatorenal syndrome	Vitiligo
Nausea	Hepatic encephalopathy	Hodgkin's and Non-hodgkin's lymphoma
Dyspepsia	Dupuytren's ontracture	Autoimmune thyroiditis
Abdominal pain	Gynaecomastia	Seronegative arthritis
	Spider naevi	Sjogren's syndrome
	Hepatosplenomegaly	Cryoglobulinaemia, found in 50% of patients causing: - Arthralgia - Purpura - Fatigue - Reynaud's phenomenon - Renal disease

Table 3: Screening targets as recommended by SIGN (21)

The following groups should be tested for HCV	The following groups should be offered an HCV test
Blood/tissue donors	People with an unexplained constantly elevated alanine aminotransferase
Patients on haemodialysis	People with a history of injecting drug use
Healthcare workers are involved in a career in a specialty that exposes to high exposure risk procedures	Human immunodeficiency virus (HIV) positive patients
	Patients who received blood clotting factor concentrates before 1987
	Patients who received blood and blood components before September 1991
	Patients who received organ/tissue transplants in the UK before 1992
	Children whose mother is infected with HCV
	Healthcare workers who had percutaneous or mucous membrane exposure to blood which is, or is suspected to be, from a HCV infected source
	People who have received medical or dental treatment in countries where HCV is common
	People with tattoos or piercings obtained in places with questionable infection control
	People who had a sexual partner or contact with a patient with HCV.

The recommended screening tool by SIGN is facilitating the detection of antibodies to HCV using the ELISA method.

The tests have to be sensitive enough to detect a concentration of 50-100 IU/ml and are usually performed using reverse transcription polymerase chain reaction (21). A flowchart showing the diagnostic procedure is shown in figure 3.

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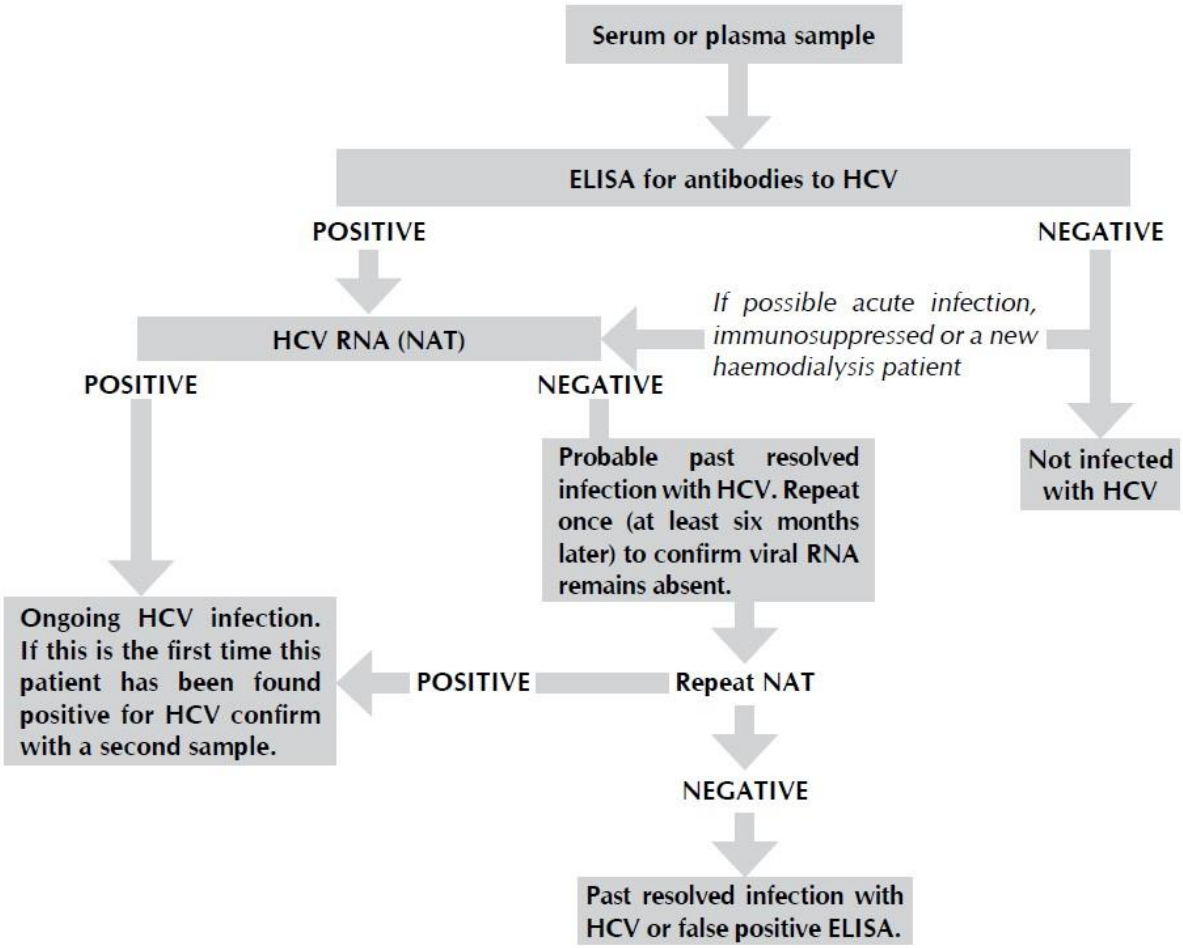

Figure 3: Diagnosis of hepatitis C virus in non-infants. Taken from Management of Hepatitis C: a national clinical guideline: Scottish Intercollegiate Guidelines Network 2006, December 2006

Management: Treatment is for 3 to 6 months after infection if the virus is not cleared . Patients should be monitored and tested regularly for the 1st 3 months. The recommended treatment is the use of Pegylated interferon (PEG-IFN) for 24 weeks .

For patients suffering from chronic infection, the recommended treatment is a combination of PEG-IFN and the nucleoside analogue Ribavirin (RBV). The treatment length depends on the genotype, based on HCV genotyping tests and can last from 12-48 weeks (21). There is currently no vaccine available for the prevention of HCV infection (22).

As of 2011, two direct acting anti-viral agents (DAA) have been approved in the U.S. and Europe. These are Boceprevir and telaprevir, which are protease inhibitors, that inhibit viral replication (23).

Further to the above, the aim of this study is to determinewhich of the direct acting anti-viral agents is the better drug in terms of efficacy, cost and safety - Boceprevir or Telaprevir?

Method: A literature search was conducted using a variety of primary and secondary sources to conduct a general review of HCV. The sources used were textbooks, published guidelines and journals. Three databases were used: Medline, Scopus and web of knowledge. The key words used for the search and the inclusion and exclusion criteria are in table 4 below. In addition, the references of suitable articles were searched.

To select the articles for the structured review, a database search was conducted. Three databases were used: Medline, Scopus and web of knowledge. The broad terms Boceprevir and Telaprevir were used. Other inclusion and exclusion criteria are in table 5 below. The abstracts of the resulting articles were scanned to find suitable articles which address the question. 3 articles in total were chosen.

Table 4: Keywords, inclusion and exclusion criteria for the literature research conducted.

Keywords	Inclusion criteria	Exclusion criteria
Hepatitis C virus	Hepatitis C virus	Original research
History	Review articles	Foreign language articles
Discovery	English language	Paid articles
Virology	Free articles	Veterinary articles
Microbiology	2002-2012	
Replication	Medicine articles	
Epidemiology	Articles on immunology	
Transmission	Articles on microbiology	
Clinical features		
Monitoring HCV		
Management		
Testing		
Vaccines		

Table 5: Keywords, inclusion and exclusion criteria for the literature research conducted to find articles for the structured review.

Keywords	Inclusion criteria	Exclusion criteria
Boceprevir and Telaprevir	Review articles	Articles older than 2011
Cost	Original research articles	Other types of articles not included in the inclusion criteria
Efficacy	Articles with the keywords	Foreign language articles
Safety	Articles in journals	Non-free articles
Clinical trials	Research conducted on humans	Other sources aside from journals
		Research conducted on non-humans

Table 6: Results of keyword searches in the various databases using the inclusion and exclusion criteria.

Database	Keywords used				
Medline	Boceprevir, Telaprevir	Boceprevir, Telaprevir and efficacy	Boceprevir, Telaprevir and efficacy	Boceprevir, Telaprevir and safety	Boceprevir, Telaprevir and clinical trials
Scopus	73	5	11	7	28
Web of knowledge	115	21	89	61	115
	67	8	28	14	31

Table 7: Articles chosen for the structured review

Article	Author	Title	Journal
1	Shiffman ML, Esteban R.	Triple therapy for HCV genotype 1 infection: Telaprevir or boceprevir?	Liver International. 2012;32(SUPPL. 1):54-60.
2	Liu S, Cipriano LE, Holodniy M, Owens DK, GoldhaberFiebert JD.	New protease inhibitors for the treatment of chronic hepatitis C: A cost-effectiveness analysis.	Annals of Internal Medicine. 2012;156(4):279 - 90.
3	Cooper CL, Druyts E, Thorlund K, Nachega JB, El Khoury AC, O'Regan C, et al.	Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis.	Therapeutics and clinical risk management. 2012;8:105-30.

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Discussion

Shiffman and Esteban: Triple therapy for HCV genotype 1 infection: telaprevir or boceprevir? (24)

The first article reviewed is the review article by Shiffman and Esteban, looking at whether Telaprevir or Boceprevir should be used. The article mentions that both drugs are very effective, with similar outcomes. The article suggests that choosing between these 2 drugs should depend on several factors, to guide the decision process. These factors include, duration of therapy, adverse event profile and cost effectiveness (24).

Evaluation: Even though the author acknowledges the fact that there are no studies showing superiority of one drug over the other, it was still possible to achieve the study's aim, since the study looks at the best choice of the 2 drugs using several criteria, not just using drug efficacy. The study's relevance is still affected by this limitation. The clinical trials used to look at the efficacy of these drugs and at the adverse effect profiles, were well chosen, since these were the studies that led the food and drug administration to approve these drugs. However, the conclusions from these trials were related to the proposed duration of treatment of these new drugs. It would have been more useful to use studies, which look more directly at efficacy. Clearly this is a required area of research before the authors can evaluate the efficacy of the 2 drugs.

The conclusion that Telaprevir has a more streamlined treatment regimen is a very subjective rather than objective criterion. In addition, the simplicity of the regimen was not one of the factors stated in the initial aims set out by the authors. To investigate the relevance of this judgment, more objective evidence in the form of trials should be carried out to see if simplicity of regimen improves adherence and quality of life. Simpler regimens have been shown to do that in other conditions such as HIV, where sparing of protease inhibitors improved the adherence and quality of life (25).

The treatment duration for Boceprevir, is longer than the treatment duration of Telaprevir and can be close to 3 times as long as the treatment duration of Telaprevir. This is one of the factors mentioned in the aims of the study, to affect the choice of therapy. In this aspect, the authors are justified in preferring Telaprevir as the drug with the better treatment duration.

The authors commented about the cost of treatment, mentioning that the costs are similar for Telaprevir to the patients on Boceprevir, in patients on 32 and 44 weeks treatment, with only the patients on the 24 weeks treatment duration experiencing the reduced costs compared with Telaprevir. There are a few problems with this conclusion. The author does not mention whether the value of PEG-IFN + RBV treatment is taken into account since treatment with these agents could potentially last for longer in patients on Telaprevir, potentially incurring more costs. In addition, the difference in price between 32 weeks of Boceprevir and 12 weeks of Telaprevir

is approximately $14,000 according to the cost-effectiveness analysis conducted by Liu et al (2012) (26). This accounts for over 28% reduction in the cost of treatment with Telaprevir, which is quite significant, so both costs should not be considered as similar.

It should also be taken into account the conflict of interest that the authors have declared, where they have declared ties with Merck and Vertex who produce Boceprevir and Telaprevir respectively (24, 26).

Liu et al: New Protease Inhibitors for the Treatment of Chronic Hepatitis C. A Cost-Effectiveness Analysis (26)

The 2nd article reviewed is an original research article by Liu et al, where a cost effectiveness analysis of Boceprevir and Telaprevir is performed. The article looks at the use of standard therapy, universal triple therapy and IL-28B guided triple therapy, where CC genotype patients will receive standard therapy and non-CC genotype patients will receive triple therapy. The study concludes that the triple therapy, whether universal or IL-28B guided, is cost effective (26).

Evaluation: The aims of this study were clear and the results were well presented in terms of money per quality adjusted life years (QALY). The use of QALYs should enable service providers to make appropriate decisions regarding these new drugs.

A huge drawback was that the study relied on research carried out by others, rather than own research on effectiveness and cost. As a result there were some downsides, such as the fact that the researchers considered a protease inhibitor similar to Boceprevir and Telaprevir rather than test these drugs themselves. In addition the researchers could not estimate adherence effectively and had to make assumptions about the adherence rate. The researchers also were not able to compare the use of triple therapy directly with the use of standard therapy in terms of effectiveness and cost.

The study to a great extent, considered the possible costs incurred in use of services and treatment. The study used previous research to consider patient's own spending, research in medical expenditure related to HCV, data from medical claims data and other areas which could affect the overall cost of treatment, for example adherence. The authors have also importantly considered cost of treating fibrosis and of treating adverse events. In addition, the costs were adjusted to include inflation. However, the authors did not consider the wider social costs potentially saved. For example reducing amount of hours of work lost due to the illness and reduced transmission rates which can influence others in the society.

The study presented the results in a simple enough format to enable analysis of the cost-effectiveness of these drugs. The article also made recommendations regarding the use of these drugs as first or as second line treatment choices. However, the article did not present clearly the difference in QALYs achieved using the different treatment strategies.

The conclusions of this study are hard to justify since the figures achieved were described as reasonable, which is a subjective measure rather than an objective measure. These values should be compared with other treatments to explore

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their true cost-effectiveness. The authors mentioned the better value of Boceprevir, however a direct comparison with Telaprevir will be vital before healthcare providers commit to the use of either of these drugs. The study's conclusions about adherence and cost should still be useful to healthcare providers hoping to use one of these drugs.

The lack of evidence regarding the use of these drugs in real life decreases the usefulness of the results obtained from this research. This is due to the unpredictability of the use of these drugs. For example, the author mentioned that adherence tends to be higher in trials, so if the authors overestimated adherence then this would reduce the cost effectiveness of the drugs investigated.

Application of this study will also be difficult due to the fact that the patients used are monoinfected, treatment naive patients. Therefore, one cannot generalise these results with confidence to the general population.

One last problem with the application of this study is that the actual increases in QALYs, may not be significant enough to warrant extra treatment using the universal triple therapy, in the opinion of the different healthcare providers. Therefore the cost effectiveness will be heavily dependent on the judgement and the financial position of healthcare providers (26).

Cooper et al: Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis (27)

The third article reviewed is a meta-analysis conducted by Cooper et al. The meta-analysis looked at the efficacy and safety of both Boceprevir and Telaprevir in combination with PEG-IFN and RBV using an indirect comparison method. The articles used were phase 2 and 3 randomised placebo controlled trials. The author concluded that there are no significant differences between the 2 drugs clinically, however changes in the adverse effects profile could influence choice (27).

Evaluation: The article had clear aims, with clear population characteristics, measurable and suitable outcomes. SVR for example has been recommended by the SIGN guidelines as an accepted objective of treatment (21).

In general terms, the authors have included appropriate papers. The papers are all of random controlled trials, with a placebo for control, which is the highest level of evidence one can get in this scenario. There have been a few problems with trial selection, with the fact that the Telaprevir has only ever been compared with PEG-2a, while Boceprevir has only been compared with PEG-2b. This could be due to simply the availability of the trials, rather than poor study design of the meta-analysis. In addition it is a drawback of the study that none of the trials used compared Boceprevir and Telaprevir directly. However, the authors did carry out analysis to investigate the effects of carrying out indirect comparisons, which showed encouraging results.

The authors in this study seem to have carried out an extensive literature search. The authors looked at the references of published reviews, obtained help from the industry in finding relevant clinical trials, searched through non-English articles and included 2 publications, which are still in press. It is also good methodology to have 2 independent investigators carrying out the literature research and analysing the inter-observer agreement.

The trials used have shown some inter-differences in the results. For example the results for discontinuation of treatment in treatment naive patients on Boceprevir, showed a difference of 28 percentage points between the results of the 2 trials. This is possibly due to the differences in the numbers of participants used in the different trials, with some trials using over twice the number of participants as others. The authors have stated that they accounted for variation in populations and methodology by carrying out meta-regression and subgroup analysis.

In general the results of these studies should be applicable to the general population due to the fairly large cumulative number of participants involved. However, due to the problem of indirect comparisons rather than direct one, that study will never be quite as useful as a direct comparison between the 2 drugs. In terms of the adverse effects, which the authors say will be a key variable in choosing between one of the 2 agents, neutropenia was only shown to be significantly more likely in Boceprevir, in response guided therapy in treatment naive patients. With this being quite a specific finding, it is not very easy to apply this to the general population from this finding. However, for rash and pruritis, the study did find an increased risk for Telaprevir in most of the patient groups, so one can confidently derive this conclusion from the study.

It is worth mentioning, that despite the authors claiming no conflict of interest, 2 of the authors are linked to Merck, the producers of Boceprevir which is a possible undeclared conflict of interest (27).

Conclusion

In terms of efficacy, both drugs seem to be very effective but neither drug has been shown to be superior so far, as can be clearly seen from the study by Cooper et al.

In terms of cost, it seems that despite Shiffman and Esteban's claim that both costs are the same, according to the more accurate cost analysis carried out by Liu et al, Boceprevir probably has better value simply due to its lower price. However, both drugs are fairly cost-effective.

In terms of safety both drugs have a differing adverse effects profile. Still, as can be seen from the results of the meta-analysis by Cooper et al and looking at the study by Shiffman and Esteban, Boceprevir may have a lightly more tolerable adverse effects profile.

However, it is obvious from the critical analysis of these studies that further research comparing both of these agents is needed to fully answer the question of whether one of these drugs is superior to the other.

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Author's Contributions: **MA:** Research the literature preparation of the article.

Ethical issues: All Authors declare, originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities.

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Strain index values in the ultrasonographic evaluation of psoriasis

Mehmet Sait Menzilcioğlu[1]*, Serdal Çitil[2] , Yasemin Akman[3], Fatih Tüten[2]

Abstract

Objective: Psoriasis is a widespread, chronic, recurrent, inflammatory disease of the skin which affects men and women equally. Elastography is a novel technique which uses elasticity of the lesion. The aim of this study is to determine the elastographic findings of dermal psoriasis. This is the first study to evaluate SI in psoriasis patients and SI is helpful to evaluate psoriasis patients. We suggest that determining cut-off SI values for normal and dermal psoriasis can be helpful in the early diagnosis and follow-up of psoriasis patients.

Materials and Methods: This prospective study included a total of 21 (10 females, 11 males) healthy volunteers and 32 (17 females, 15 males) psoriasis patients between 2015 and 2016. An Aplio 500 ultrasound device (Toshiba Medical Systems Corp., Otawara, Japan) and a 5-13 MHz linear transducer were used for ultrasonographic and ultrasound elastographic examinations. The measurements were made from the flexor sides of upper and lower extremities. At least three measurements were performed for each lesion and strain index (SI) values were recorded

Results: The median SI values of healthy volunteers and psoriasis were 1.25 (0.16-8.00) (interquartile range (IR) 1.50) and 2.73 (0.43-13.32) (IR 3.39), respectively, indicating a significant difference between the groups (p: 0.001).

Conclusion: Our study results showed that the SI values of dermis in psoriasis patients were significantly higher than those of healthy volunteers. We suggest that determining cut-off SI values for normal and dermal psoriasis can be helpful in the early diagnosis and follow-up of psoriasis patients. Due to literature search, this is the first study to evaluate SI in psoriasis patients and SI is helpful to evaluate psoriasis patients.

Keywords: Elastography, Strain Index, Psoriasis.

Introduction

Psoriasis is a widespread, chronic, recurrent, inflammatory disease of the skin affecting men and women equally (1,2)(1,2). Its etiology is still unknown. Most psoriasis manifest with patches of thick, red skin with silvery scales. These patches usually involve the elbows, knees, scalp, lower back, face, palms, and soles of the feet (3). The differential diagnosis is made based on clinical findings and skin biopsy results (4).

Elastography is a novel technique which uses elasticity of the lesion (5). The principle of this technique is to acquire data about the stiffness of the tissue to assist the differential diagnosis. There are various types of ultrasound elastography. These methods can be divided as dynamic and quasi-static according to the type of force, while shear-wave and strain according to method. Shear-wave elastography is a dynamic method using shear-waves to obtain the data and presents quantitative value (6).

Acoustic Radiation Force Impulse (ARFI) elastography, transient elastography, and shear-wave elastography use shear-waves. In addition, strain elastography is divided into two types as qualitative real-time elastography and semi-quantitative strain elastography. Real-time elastography presents color scale according to the stiffness of the related tissue, and the operator classifies the stiffness according to the colors. Semi-quantitative strain elastography presents strain ratio or strain index (SI) using region of interests (ROI). Furthermore, strain elastography is operator-dependent due to the probe compressions and decompressions, while shear-wave does not need operator compressions with the aid of generating electro-mechanical waves (6- 8).

In the present study, we aimed to reveal the effectiveness of elastographic findings on dermal psoriasis.

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1 Gaziantep University, Faculty of Medicine, Dept of Radiology, Gaziantep, TR
2 Kahramanmaras Necip Fazıl City Hospital, Clinic of Radiology, Kahramanmaras, TR
3 Kahramanmaras Necip Fazıl City Hospital, Clinic of Dermatology, Kahramanmaras, TR
*** Corresponding Author:** Mehmet Sait Menzilcioğlu **E-mail:** dr.m.sait@hotmail.com **Phone:** +90 342 3606060

Material and Methods

Informed consent form was obtained from all patients and the study was performed in accordance with the ethical guidelines of the Helsinki Declaration and approved by the committee of Sütçü İmam University approved in this study . No financial support was received for the present study. This prospective study included a total of 21 (10 females, 11 males) healthy volunteers and 32 (17 females, 15 males) psoriasis patients between 2015 and 2016. The inclusion criteria were as follows: previous psoriasis diagnosis, absence of any coexistent skin lesions except psoriasis, and not using drugs affecting the skin, except drugs for psoriasis. Patients with non-psoriatic skin lesions were excluded.

An Aplio 500 ultrasound device (Toshiba Medical Systems Corp., Otawara, Japan) and a 5-13 MHz linear transducer were used for ultrasonography (USG) and ultrasound elastography examinations. The USG examinations were performed by a single radiologist who had more than 10 years of experience on the use of USG. All measurements were made particularly from the flexor sides of upper and lower extremities. At least three measurements were performed for each lesion and SI values were recorded

Elastography examination was made following routine USG imaging, applying mild compression and decompression to the affected skin surface of the extremity. The screen was divided into three parts, while elastography was active, as left, right, and bottom. The color coded left side indicated elastography mode, while the right side indicated the routine B mode, and the bottom side indicated the sinusoidal wave, which assists the user to follow regular compression and decompressions. The symmetrical sinusoidal wave means regular compression and decompression. The measurements were applied, adjusting the ROI to the psoriasis lesions and adjacent muscles (Figure 1).

Statistical Analysis

Statistical analysis was performed using SPSS version 21 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic data. One-sample Kolmogorov-Smirnov test was used to analyze for normality. The Mann-Whitney U test was used to analyze significant differences between SI of healthy controls and psoriasis group. The receiver operating characteristic (ROC) curve was used to define the cut-off value for SI. A value of the mean SI of normal healthy individuals and patients with respectively, p: 0.001 was considered statistically significant.

Results

A total of 21 (10 females, 11 males) healthy volunteers and 32 (17 females, 15 males) psoriasis patients were included. The mean ages of healthy volunteers and psoriasis patients were 33.62±11.76 (range: 17 to 61) years 40.59±15.24 (range: 15 to 74) years. There was no significant difference in the mean age between the groups (p: 0.094).

The median SI values of healthy volunteers and psoriasis patients were 1.25 (range: 0.16 to 8.00; interquartile range (IR) 1.50) and 2.73 (range: 0.43 to 13.32; (IR 3.39), indicating a significant difference between the groups (Mann-Whitney U test, p: 0.001).

The ROC curve revealed a cut-off value of 1.91 to differentiate the psoriasis patients from healthy volunteers (the maximum value of sensitivity+specificity) (Figure 2).

The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and power were 62.5%, 81%, 83.3%, 58.6%, 3.28 (range: 1.31 to 8.25), 0.46 (range: 0.28 to 0.76), and 70%, respectively.

Table 1: Demographic Data of the Participants. There was no significant difference in the mean age between the groups.

Parameters	Healthy Volunteers n=32 (17 to 61)	Psoriasis Patients n=21 (15 to 74)	P Value
Age	33.62±11.76	40.59±15.24	0.094

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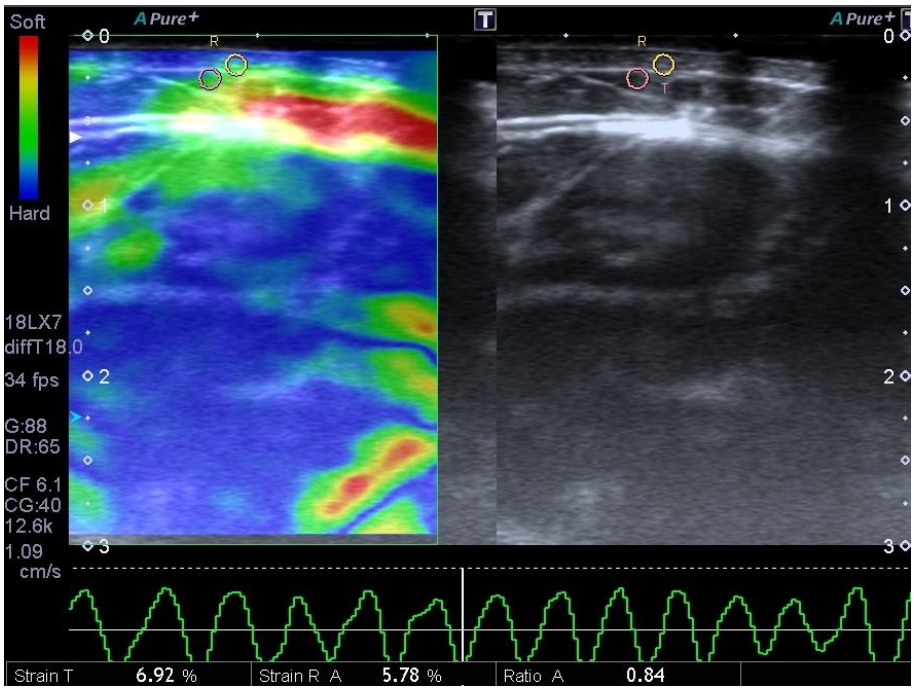

Figure 1: An ultrasound elastography image showing dermal psoriasis. The screen is divided into three parts: right side is gray scale USG image, left side is color coded USG elastography image, and the bottom side is the sinusoidal wave of compression and decompression. The circles indicate the ROIs. Measurements were applied adjusting the ROI to the psoriasis lesions and adjacent muscles.

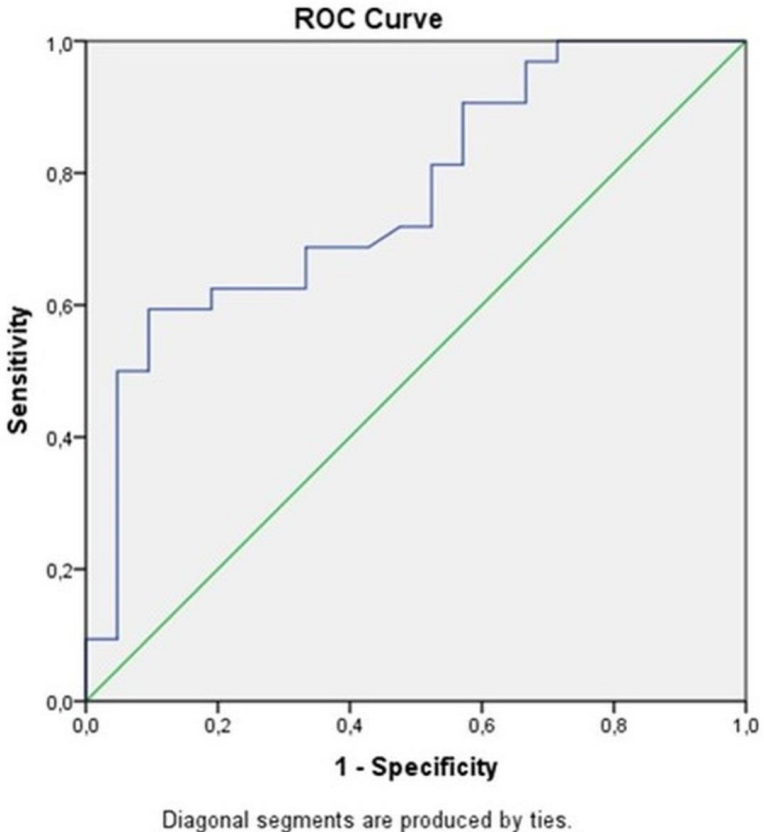

Figure 2: The ROC curve of healthy volunteers and psoriasis. The cut-off value was 1.91 and the AUC was 0.764 with a standard error of 0.067 and confidence interval of 95% (0.634-0.895).

Discussion

Elastography is a novel technique which uses the stiffness of the lesions to diagnose. In the literature, there is no published study about elastography about psoriasis, although more studies exist about ultrasound elastography. In this study, we aimed to determine the elastography measurements of psoriasis lesions. The diagnosis of psoriasis is based on history, clinically and sometimes skin biopsy results. Biopsy is required in the differential diagnosis of similar lesions, such as seborrheic dermatitis, mycosis fungoides fungoides, and lichen planus (9,10).

Elastography measures the stiffness of the tissue. Accordingly, several studies were carried out made using elastography to differentiate malignant lesions from the benign ones (7). In addition, ultrasound elastography is reliable in differentiating benign and malignant breast lesions (11-13).

In the present study, there was a significant difference in the SI values of psoriatic and normal skin lesions. The difference can be attributed to the local tissue inflammation which makes the tissue stiffer.

Nonetheless, there are some limitations to our study. First, the thin skin surface did not allow adjusting the ROI; therefore, only thick lesions were selected for the measurement. Second, we only compared the psoriatic and normal skin lesions; however, further studies are required to examine more skin disorders such as psoriasis. As a result, our results did not allow differentiating psoriasis from the psoriasis-like lesions.

Conclusion

Our study results showed that the SI values of dermis in psoriasis patients were significantly higher than those of healthy volunteers. We suggest that determining cut-off SI values for normal and dermal psoriasis can be helpful in the early diagnosis and follow-up of psoriasis patients. Also, to the best of our knowledge, this is the first study to evaluate SI in psoriasis patients, and SI is helpful to evaluate psoriasis patients. However, further large-scale studies are required to establish a definite conclusion.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Sudden hearing loss due to bee sting: A rare case

Erkan Yıldız[1]*, Orhan Kemal Kahveci[2]

Abstract

Sudden hearing loss (SHl); Define as, at least 30 dB sensorineural hearing loss in 3 consecutive frequencies. In general, idiopathic, viral and vascular causes are at the forefront. Local or systemic hypersensitivity reactions due to insect bites such as bee sting may occur. Sudden hearing loss is a more unknown finding in the literature due to bee sting. The first choice in treatment is systemic or local corticosteroid uses.

In this case report, the patient who had bilateral sudden hearing loss following bee sting and treatment approaches have been presented.

Keywords: Bee sting, sudden hearing loss, steroids

Introduction

Sudden hearing loss (SHL) or sudden sensorineural hearing loss (SHL) defined as; Hearing thresholds in 3 days consecutively in 3 frequencies more than 30 dB loss of hearing level. The incidence of SHL was reported avarage 5-20 / 100,000 in the literature. The average age for SHL is close to 50-60 ages between men and women. Due to etiology, viral infections, vascular occlusion, autoimmune diseases, metabolic diseases, neoplastic, toxic and neurological diseases may play role in SHL (1). In the diagnosis, high level noise exposure, history of infection, trauma and systemic diseases should be questioned. In this case, diagnosis is made by the audiometric test by showing the hearing loss. Autoacoustic emission and Bera tests also be used in patients who cannot perform audiometry. A significant number of patients have complaints of tinnitus. Blood tests performed in most patients have no effect on etiology and treatment. The only imaging that can help with the diagnosis is MRI and should be asked to all patients. Cerebellopontin corner tumors and other neoplastic changes, vascular-ischemic causes, labyrinthitis due to infection can be seen very clearly in MRI. Vestibular tests can be performed for patients with dizziness (2). Sudden hearing loss is an otologic emergency situation. The treatment should be started as soon as possible. The most important solution for the treatment is systemic corticosteroids. Because, they are idiopathic and do not require the treatment for the cause. Intratympanic steroids can also be given to those with systemic disease. Alcohol, smoking should be prohibited. In addition, vitamins, antiviral treatments, hyperbaric oxygen therapy, vasodilators and autoimmune treatments may planned (1,2,3).

In patients with sudden hearing loss, the 32-65% of patients may improve without any treatment. The presence of vertigo, involvement of low frequencies, advanced hearing loss and increased sedimentation are the criteria of poor prognosis (4,5). Reactions related to bee stings may occur depending on Ig E dependent or independent. Localized reactions can also lead to fatal general reactions such as anaphylactic shock.Gullian-Barre-like myelitis, hemolytic anemia, interstitial nephritis, encephalomyelitis and peripheral neuropathy have been detected in the literature for some patients. Earlier hearing loss due to bee sting was reported in one case. Venom immunotherapy and systemic steroids, as well as antihistamines, can be used to reduce the severity of symptoms in the treatment of bee stings.

Case

A 38-year-old female was admitted to the emergency department, one day after stinging of bees from the left auricle. Intramuscular phenyiramine maleate 45.5 mg / 2 ml + Dexamethasone 2 ml / Mg 1 * 1 was administered in the emergency department. In the otoscopic examination, bilateral tympanic membrane was intact. Hemogram and biochemistry tests were normal. Bilateral total sensorineural hearing loss was present in the pure voice audiometry. The oacoustic emission test was negative in both ears. In bilateral tympanogram, while bilateral Type A tympanogram was obtained, reflexes could not be bilateral. Cranial and acoustic MRI have been reported as normal. The 1 mg / kg prednisolone treatment and proton pump inhibitor (esomeprezol 1 * 1 p.o) were started. Audiometry and otoacoustic emissions of patient were normal.

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1 Afyonkarahisar Şuhut Government Hospital, Dept. of ENT, Afyon, TR
2 Afyon Kocatepe University, Faculty of Medicine, Dept. of ENT, Afyon, TR
*** Corresponding Author:** Erkan Yıldız **E-mail:** dr.erkanyildiz@hotmail.com **Phone:** +90 530 8950416

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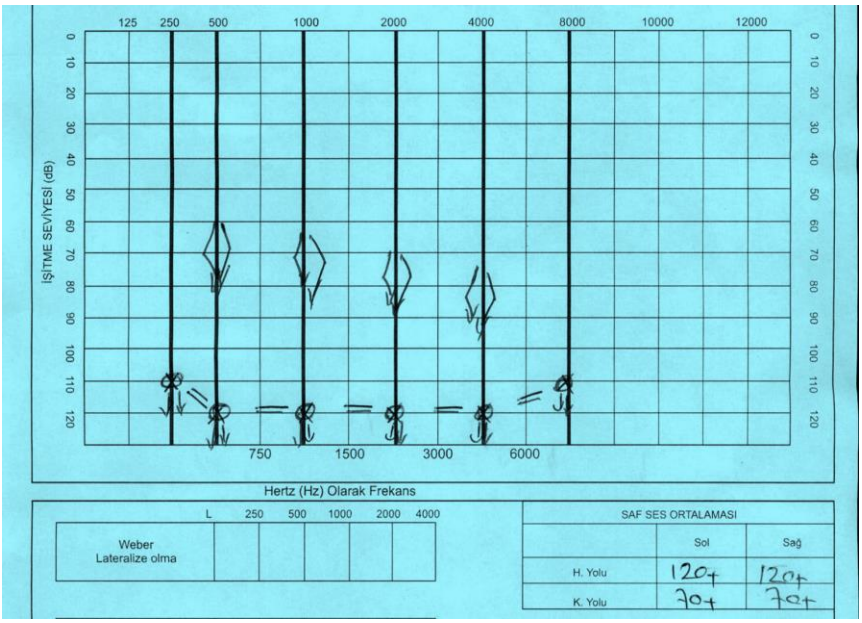

Figure 1: Audiometry measurement of Patient after bee sting

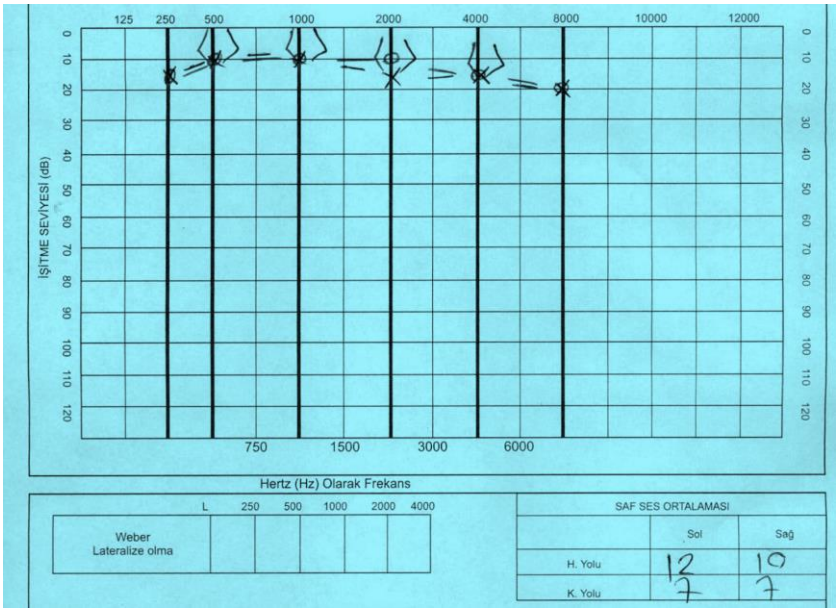

Figure 2: Audiometry measurement of patient was performed after 1 week of treatment

Discussion

After the bee sting, toxic, immunological and allergic reactions, anaphylaxis and shock may change the patient situation. Hypertension, myocardial infarction and multiorgan insufficiency may develop after Type 1 anaphylactic shock caused by bee sting from head and neck. Although insect bites have common effects, serious effects are rare. Optic neuritis, convulsion, lesions similar to Henoch Schonlein purpura, neuropathies similar to Guillain Barre syndrome, intravascular coagulation, compartment syndrome have been reported in the literature. But so far, no toxic effects have been reported on the cochlea. We could not detect any cause of sudden hearing loss because of bee sting in the literature.

Sudden sensorineural hearing loss is defined as sensorineural hearing loss of at least 30 dB at 3 consecutive frequencies occurring within 3 days (1,2). It is usually accompanied by tinnitus and vertigo (3,4). Sudden hearing loss, which usually occurs unilaterally, is usually seen in 65% of patients and symptoms return back with or without treatment. Losses at low frequency have a better prognosis than at high frequencies (4,5). In our patient, there was total hearing loss affecting all frequencies in both ears. etiopathogenetic factors such as autoimmune diseases, infectious diseases, trauma, circulatory microvascular disorders, ototoxicity, neoplasms, transient obstructive membrane rupture and viral infections can be cause of SHL. The other 90% is called idiopathic sudden sensorineural hearing loss (1,2,3).

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Apart from viral and vascular causes, etiology is the main cause of etiology. (4) None of the reasons described in our patient were present, only one case was reported in the literature (7).

Cause of sudden hearing loss cannot be found for most patients. Therefore, the treatment should be planned comprehensively such that it responds to all causes. In sudden hearing loss, vasodilators, volume expanders, antivirals and anticoagulants, together with steroids, constitute the most important part of the treatment (4,5). Treatment approaches and molecular mechanism is still not fully clear. Due to literature, the full recovery rate of SHL is 25%, the probability of partial recovery is 25% and the probability of not recovering is 50%.

The fact that our patient responded faster than the other sudden hearing loss cases suggested that the steroid was related to both the sudden hearing loss treatment and its use in general for anaphylaxis. In our patient, a complete improvement in the audiometry was achieved. Also, oral prednisolone therapy may use in the treatment of hearing loss due to bee sting.

Conclusion

Systemic examination of patients with bee sting, as well as systematic otolaryngological examination is inevitable treatment plan for the benefit of patient. For better response for SHL treatment due to insect stings, treatment should be immediately started. Regression of symptoms depends on the time of initiation of treatment.

Consent

All images are entirely anonymized and the individual cannot be identified. No personal information of the individual was included.

Ethical statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Funding statement The authors received no funding for this work.

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