Original Article

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Assessment and Management of the Dermatological Side Effects of Direct-Acting Antiviral Agent Groups Used in the Treatment of Hepatitis C: A Prospective Study

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Abstract

Aim: As skin disorders may be observed with Hepatitis C, direct-acting antiviral drugs (DAA), dermatological side effects are also reported. The objective is to determine the dermatological side effects of DAA drugs.

Methods: A study was conducted with chronic hepatitis C patients who used Ombistavir/Paritaprevir/Ritonavir + Dasabuvir (Group 1), Sofosbuvir + Ledispavir (Group 2), and sofosbuvir (Group 3) and who supplied the drugs from our hospital. Skin examinations of the patients regarding dermatological side effects were conducted. Patients with dermatological side effects and treatment modalities were followed.

Results: One hundred twelve patients were using Group 1; 69 were using Group 2, 19 were using Group 3. All pruritus patients were in Group 1. It was detected in 56 of 200 patients (28%). Pruritus was more prevalent in patients with diabetes mellitus, hypertension, and heart disease, and the drug could be tolerated in those with no additional systemic comorbidities. Thirty-one patients had renal failure, and 17 of them underwent renal transplantation, and the pruritus rate was high (57%) in the chronic renal disease Group.

Conclusion: Pruritus is the most common side effect observed with DAA drugs used in treating hepatitis C and elderly patients, and patients with comorbidity and renal transplantation are at high risk.

Keywords: Hepatitis C, antiviral agents, pruritus, cutaneous

Introduction

Hepatitis C virus (HCV) is a severe human pathogen with a prevalence of 0.2-4% in different countries. Every year, 3-4 million new hepatitis C cases are detected, and it is thought that 185 million people in total are affected by HCV (1,2). In Turkey, anti-HCV positivity is between 0.6-1.6%, and chronic hepatitis is one of the most important causes of liver cirrhosis and hepatocellular carcinoma (3,4). In Turkey, it is considered that there are 1-1.3 million people infected by HCV (5,6). The objective of chronic hepatitis C treatment is to completely eradicate the virus. The frequent mutation and the availability of multiple genotypes of the virus make it challenging to find a vaccine, affecting treatment success. While peg-interferon and ribavirin are included in the classical treatment of chronic HCV, recently direct-acting antiviral (DAA) regimens for HCV infection has revolutionized its treatment by producing a sustained virologic response of more than 95% in the general population (7-9). Direct-acting antivirals Ombistavir/Paritaprevir/Ritonavir + Dasabuvir are most frequently used in HCV genotype 1b Sofosbuvir + Ledipasvir are used in combination or Sofosbuvir is used alone (10).

There may be underlying dermatological diseases in hepatitis C patients, such as lichen planus, cryoglobulinemic vasculitis, that suggest hepatitis C infection. Such diseases may light the HCV diagnosis, while it is reported that the dermatological disease regresses with HCV treatment (11,12). Pruritus was reported to be 5.1-58.4% in hepatitis C patients (13-15). Pruritus is reported as the side effect of the DAA drugs used in the treatment of HCV (16,17). It is still a matter of discussion whether the pruritus arises from the HCV infection itself or the treatment (18). Direct-

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acting antivirals are safe drugs with a low side effect profile. The reported side effects of this Group of drugs are gastrointestinal side effects and pruritus (19). The safety and efficiency data regarding DAA drugs in chronic kidney disease (CKD) are not sufficient.

In this study, the demographical characteristics of the hepatitis C patients using DAA and the drug side effects, and the dermatological side effects and their management in the patients with CKD and renal transplantation, as well as hepatitis C patients using other DAA, were studied.

Methods

Study Design

This study was approved by the local ethics committee. A prospective study was conducted with adult chronic hepatitis C patients who used ObV/PTV/r + RBV, Sofosbuvir + Ledispavir, and Sofosbuvir and who supplied the drugs from our hospital. In our country, HCV drugs are distributed by certain designated pharmacies appointed by the government. The data of the patients who were diagnosed and had a drug report issued by more than 30 physicians and more than 10 sites, and who agreed to participate in the study was used. The patient data were obtained from the reports required to get the drug, and the study was completed with 200 HCV patients between February 2017 and March 2018.

These patients who were using OBV/PTV/r + RBV (Group 1, n=112), Sofosbuvir + Ledipasvir (Group 2, n=69) and Sofosbuvir (Group 3, n=19) were recorded in 3 separate Groups.

The patients' demographical characteristics, HCV genotype, the pattern of contamination, presence of cirrhosis in the liver, comorbidities, and the drugs used for them were questioned. All skin, hair, and mucosal examinations of the patients with regards to dermatological side effects were conducted before the treatment started and on the 1st month of the treatment. The patients who attended the visits at least three times were included in the study. A patient with any dermatological side effect was followed up throughout the treatment, and treatment was applied for the side effect that developed. The HCV contamination pattern, systemic comorbidities, Ribavirin use, and, if any, the previous treatments, previous dermatological diseases of the patients were questioned and recorded.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. The defining statistics are presented as numbers and percentages for categorical variables, and a mean, standard deviation (SD), and median are included for numeric variables. Comparison of numeric variables in two independent Groups was carried out using Student's t-test for normal distribution and the Mann-Whitney U test for non-normal distribution. The relationships between numeric variables were examined using the Pearson correlation analysis when parametric test conditions were met and the Spearmen correlation analysis when these conditions were not met. Statistical alpha significance level was assumed to be $p<0.05$.

Results

The female gender was dominant among 200 HCV patients in the study (n=113, 56.5%). The ages of the patients were between 19-92 years. (Avr: 59.2±13.7) While in most patients, the mode of contamination was unknown, dialysis was the second mode of contamination for HCV, followed by childbirth, surgeries, dental treatment, and one of the patients was contaminated by hair transplantation. Most of the patients were HCV genotype 1b (82%), and approximately 70% of the patients were firstly treated by DAA drugs.

Antiviral Treatment and Chronic HCV

One hundred twelve patients were using Group 1. 69 patients were using Group 2. 19 patients were using Group 3. 158 patients were non-cirrhotic, while eight patients were decompensated cirrhotic. 60% of the patients had comorbidities such as diabetes, coronary failure, asthma-COPD. Thirty-one patients had renal failure, and 17 of them underwent renal transplantation. Fourteen CKD patients were under dialysis treatment. Eight of CKD patients had pruritus (Table 1). In this study, 14 CKD patients had hemodialysis n=14, and 57% developed pruritus. While no side effects were observed in 2 patients who had liver transplantation, pruritus developed in 2 of 17 patients with renal transplantation, and others managed to complete the treatment without problems.

The great majority of the patients were using Group 1 drugs, and the most frequent side effect was pruritus. Almost all of the patients who developed pruritus were in this Group. The intensified pruritus in patients who previously had pruritus was recorded as a side effect. The patients whose pruritus was stable were not evaluated as a drug side effect. Pruritus regressed in many of the patients through symptomatic treatment. One of the patients developed nodular prurigo, and the lesions were regressed with topical corticosteroid ointment and antihistaminic tablets. When the patients who previously had xerosis were excluded, two patients had notable xerosis. The other concomitant dermatological diseases were at ratios similar to society. While pruritus was more prevalent in patients with diabetes mellitus (DM), hypertension (HT), and heart disease, the drug could be tolerated in those with no additional systemic comorbidities (Table 2).

Discussion

HCV is a ribonucleic acid virus from the Flaviviridae family with a single positive chain. As the virus is not entirely visualized, its structure is not clearly known, and its classification was made based on its genomic differences. Six genotypes (GT1-6), and each one was typed as several subgroups. The most frequent genotype 1 (GT1) and genotype 1a and genotype 1b subgroups are responsible for most GT1 infections worldwide (6,20). In our study, genotype 1b was the most frequent type, and this was compliant with the studies conducted in the same city and with the literature (4,6,21).

Hepatitis C patients may have some dermatological symptoms (12,15,22). and these are reported in the previous studies (12,23). Mix cryoglobulinemia, porphyria cutanea tarda, lichen planus, pruritus are among the diseases reported (17,24). The association of lichen planus and hepatitis C is being examined. Lichen patients were reported to be treated with DAA (25). In this study, no lichen disease was detected. The dermatological findings such as atopic eczema, psoriasis, acne rosacea, seborrheic dermatitis, and acne observed within the study scope were similar to society.

Pruritus is seen in chronic liver diseases and affects the quality of life (26). Although the cause of the pruritus development in such patients has not been yet determined, studies were conducted regarding the fibrosis in the liver, high enzyme levels, or bilirubin levels. Pruritus is also reported to have developed during the treatment of HCV patients (17,26,27).

DAA is effectively used in the treatment of HCV. In a recent review, the side effects of DAA were reviewed (28). In the studies conducted at advanced ages, it was found to be effective and reliable (29). In the study by Tachi et al. (30) it was reported that 10% of the patients had developed pruritus after DAA use, while some of the patients who had pruritus before treatment reported regression with the treatment. In this study, the pruritus ratio after DAA treatment resulted in 28%. This ratio was higher when compared to the literature. The reason for the

Table 1. Demographic characteristics of the patients, mode of contamination, concomitant systemic diseases, other systemic disease and ribavirin usage

		n%
Gender	Male	87 (43.5)
	Female	113 (56.5)
Age (years)	-	59.2±13.7 (19-92)
Disease time (year)	-	7.0±6.2 (0.5-35)
Diagnosis	Decompensated cirrhotic	8 (4.0)
	Compensated cirrhotic	34 (17.0)
	Cirrhotic	158 79.0
Contamitation type	Unknown	139 (69.5)
	Surgery	7 (3.5)
	Dialysis	41 (20.5)
	Child-birth	11 (5.5)
	Hair transplantation	1 (0.5)
	Drug-abuse	1 (0.5)
HCV Genotype	1a	18 (9.0)
	1b	164 (82.0)
	2	1 (0.5)
	3	5 (2.5)
	3a	11 (5.5)
	3b	1 (0.5)
Concomitant disease	Chronic renal failure	14 (7.0)
	Renal transplantation	17 (8.5)
	Liver transplantation	2 (1.0)
Other systemic disease	-	128 (64.0)
	HT	90 (45.0)
	DM	33 (16.5)
	COPD-ASTHMA	19 (9.5)
	CHF	2 (1)
	CAD	6 (3)
	Other	18 (9)
Ribavirin use	-	58 (29)
Treatment useage before	-	57 (28.5)

HT: Hypertension, DM: Diabetes mellitus COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CAD: Coronary artery disease, HCV: Hepatitis C virus

Table 2. DAA usage Groups and skin side effects. Skin disease accompany to HCV patients

		n%
DAA	Group 1	112 (56)
	Group 2	69 (34.5)
	Group 3	19 (9.5)
Treated cures	-	2.7±1.2 (1-7)
Skin side effects	Pruritus	56 (28)
	Xerosis	2 (1)
	Conjunctivitis	1 (0.5)
Concomitant skin disease	Xerosis	11 (5.5)
	Dermatitis	13 (5.5)
	Psoriasis	6 (3.0)
	Pruritus	1 (0.5)
	Acne	1 (0.5)
	Atopic dermatitis	1 (0.5)
	Acne rosacea	1 (0.5)
	Vitiligo	1 (0.5)
	Seborrheic dermatitis	1 (0.5)

Group 1: Ombistavir/Paritaprevir/Ritonavir + Dasabuvir. Group 2: Sofosbuvir and ledispavir. Group 3: Sofosbuvir, DAA: Direct-acting antiviral drugs, HCV: Hepatitis C virus

different side effects reporting may be the patients failed to report due to mild progress or due to the humudity. The majority of the patients had comorbidities and the inclusion of CKD patients in the group, and the majority of the patients were 65 years or above. Most of the patients within the Group were 65 years or above. The ratio of pruritus development in patients who were under 65 years was 18.1%. Villani et al. (31) reported that pruritus, rash, and photosensitivity were slightly high in patients over 65 years of age. No examinations were made on the patients in our study. Therefore, no comments were made regarding the liver functions and bilirubin levels. There was no statistically significant difference between cirrhotic and non-cirrhotic groups.

Sofosbuvir was used alone in 19 patients and combination in 69 patients. Those who used this group of the drug did not develop pruritus (32).

In hemodialysis patients, the most frequent cause of the liver disease is HCV infection, and the anti-HCV ratio varies between 21.3 and 41.5. DAA was safely used in renal transplantation patients, and no side effects were observed in the patients (7,33). Although it was possible to observe systemic gastrointestinal side effects in CKD and renal transplantation patients, all patients managed to complete the DAA treatment (34). The authors reported that it is safe and relatively well tolerated in advanced renal failure and that no of-related specific toxicity was detected. The high ratio may be due to the absence of continuity in drug elimination in CKD patients. The side effects of renal transplantation patients matched the literature. The persistent pruritus following the skin moisturizing for xerosis in patients with renal failure and the pruritus regressed after discontinuing DAA were considered drug side effects.

Ribavirin was used as a supplement to the treatment (35). In the previous studies, it was reported that ribavirin might be a factor, and it has dermatological side effects by 10%, such as xerosis, alopecia, eczema, psoriasis (16,36). No difference was detected in terms of pruritus between the use of ribavirin or not.

Intravenous narcotic use is an essential mode of contamination for the virus infection. In our study, the use of narcotics was made through patient declaration. One patient continued using narcotics, and that he did not have dermatological side effects. No differences in dermatological side effects were detected between the patients experienced in terms of treatment and those using for the first time.

When asked about the drug's positive effect, almost all patients using DAA stated that they did not have flu. Since there is no pandemic during the study, and it is not included in planning at the beginning of the study, no clear data can be given. Data on the course of Coronavirus disease-2019 (COVID-19) patients in HCV patients using DAA may contribute to these drugs' COVID-19 effect. Currently, remdesivir has received fluorescein diacetate approval for COVID-19.

In dermatological side effects developed with DAA, the symptoms were minimized with good skincare, and the treatment was accomplished. Emollient creams, pomades with corticosteroid for short term use in patients with severe pruritus, and antihistamines were added to the treatment.

Study Limitations

The deficits of this study were the absence of liver function tests of the patients, and the viral charge at the beginning and the post-treatment efficiency were not evaluated. The correlation between treatment success and side effects was not evaluated.

Conclusions

Pruritus and skin rash are common with DAA drugs used in HCV treatment. Elderly patients with comorbidities such as DM and HT may be under at more risk, and pruritus complaints may be controlled with efficient skincare in such patients. The detailed examinations to be conducted in patients with pruritus and dermatological side effects may contribute to the explanation of the etiology.

Authorship Contributions

Concept: S.A., M.A., Design: S.A., M.A., Data Collection or Processing: S.A., M.A., Analysis or Interpretation: S.A., M.A., Literature Search: S.A., M.A., Writing: S.A., M.A.,

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