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AGNIESZKA SULKA¹, KRZYSZTOF SIMON², PAWEŁ PISZKO²

Effect of a Combination Therapy (Interferon α and Ribavirin) on the Condition of Oral Mucosa in Patients Suffering from Chronic Hepatitis C

Wpływ terapii kombinowanej (interferonem α i ribawiryną)
na stan błony śluzowej jamy ustnej u pacjentów
z przewlekłym zapaleniem wątroby typu C

¹ Department of Oral Surgery, Wrocław Medical University, Poland

² Department and Clinic of Infectious Diseases, Wrocław Medical University, Poland

Abstract

Background. Some of the acknowledged modalities of medical treatment may cause undesired effects in the form of pathological lesions within the oral cavity.

Objectives. The aim of the study was to evaluate the effect of IFN- α + RBV (Ribavirin) therapy on the oral mucosa in patients suffering from chronic hepatitis C.

Material and Methods. The study groups consisted of 15 patients treated with IFN- α + RBV for chronic hepatitis due to HCV infection. The control group comprised 23 untreated patients with chronic hepatitis C. The clinical evaluation of the oral cavity was carried out at 0, 3, 6 and 12 month of the follow-up. Oral mucosa pathology found on clinical examination was confirmed histopathologically.

Results. In patients receiving IFN- α + RBV treatment, labial *herpes* was the most common lesion observed in the 3 month of therapy (4/15), while the control subjects most commonly revealed leukoplakia throughout the whole follow-up period (6/23). The intragroup analysis of all the subjects did not show any statistical difference in the number of lesions during the whole follow up period. Moreover, no statistically significant changes were found in the number of oral mucosa lesions between the groups.

Conclusions. No significant influence of IFN- α + RBV therapy on the incidence of oral mucosa lesions was observed in patients suffering from chronic hepatitis C. Only the incidence of labial *Herpes* was found to be slightly increased in patients treated with IFN- α + RBV, however the difference was statistically insignificant (**Dent. Med. Probl.** 2004, 41, 4, 609–614).

Key words: HCV, oral mucosa diseases, chronic hepatitis C, IFN therapy.

Streszczenie

Wprowadzenie. Działaniem ubocznym niektórych spośród znanych metod leczenia farmakologicznego są zmiany patologiczne w obrębie jamy ustnej.

Cel pracy. Ocena wpływu terapii IFN- α + RBV (ribawiryna) na stan błony śluzowej jamy ustnej pacjentów chorych na przewlekłe zapalenie wątroby typu C.

Materiał i metody. Grupę badaną stanowiło 15 pacjentów leczonych IFN- α + RBV z powodu przewlekłego zapalenia wątroby związanego z zakażeniem HCV. Grupę kontrolną stanowiło 23 nieleczonych pacjentów z przewlekłym zapaleniem wątroby typu C. Badanie kliniczne stanu błony śluzowej jamy ustnej przeprowadzono w 0., 3., 6. i 12. miesiącu obserwacji. Stwierdzoną klinicznie patologię błony śluzowej jamy ustnej potwierdzano badaniem histopatologicznym.

Wyniki. W grupie pacjentów leczonych IFN- α + RBV w 3. miesiącu terapii najczęstszą zmianą była opryszczka wargowa (4/15), w grupie kontrolnej natomiast przez cały czas prowadzonej obserwacji najczęstszą zmianą była leukoplakia (6/23). W analizie wewnątrz każdej z grup badanych nie stwierdzono różnic statystycznych liczby zmian na błonie śluzowej jamy ustnej w czasie prowadzonych obserwacji. Nie wykazano znamiennych statystycznie różnic w liczbie zmian na błonie śluzowej jamy ustnej między grupami.

Wnioski. Nie wykazano istotnego wpływu terapii IFN- α + RBV na częstość pojawiania się zmian na błonie śluzowej jamy ustnej u pacjentów z przewlekłym zapaleniem wątroby typu C. Zaobserwowano jedynie większą częstość opryszczki wargowej u pacjentów leczonych IFN- α + RBV, ale nie była istotna statystycznie (**Dent. Med. Probl.** 2004, 41, 4, 609–614).

Słowa kluczowe: HCV, choroby błony śluzowej jamy ustnej, przewlekłe zapalenie wątroby typu C, terapia IFN.

The results of epidemiological studies indicate that about 170 to 300 mln people all over the world are infected with HCV [1, 2]. In Europe the estimated number of HCV infected people is well over 5 mln. However, the incidence of the infection in the European population reveals significant geographical diversity reaching 0.5% in the countries of Northern Europe, 2% in Central Europe and as much as 11% in South Italy [3]. According to Juszczak et al. [4], in Poland, the incidence ranges from 0.2 to 1.4%

In view of possible serious consequences of HCV infection, in 1986, in the United States trials were undertaken to treat chronic non-A and non-B viral hepatitis with immunomodulator such as alpha interferon (IFN- α) [5]. The use of IFN- α is associated with a number of undesired effects such as influenza-like complaints, hypertension, insomnia, tachycardia, anorexia, depression, thrombocytopenia, as well as other symptoms of bone marrow damage [6]. Some authors point at the possibility of developing lesions of the type of oral lichen planus (OLP) or at the exacerbation of previously occurring OLP, what may necessitate cessation of treatment [7, 8].

Apart from immunomodulatory treatment, the therapy for chronic HCV infections may include antiviral agents such as Ribavirin (RBV). This agent is used exclusively in combination therapy with IFN. RBV is a nucleoside analogue which exhibits activity for RNA and DNA viruses resulting in the inhibition of viral polymerases. RBV is contraindicated in cases complicated with anaemia or renal insufficiency. Moreover, it has a teratogenic effect [9]. In case of viral hepatitis C, the efficacy of treatment is determined on the basis of HCV-RNA disappearance from serum, what is observed in 49–70% of treated patients [10, 11].

In patients with chronic HCV infection, the clinical picture of oral mucosa lesions as well as their association with the therapy have not been recognized. The aim of the study was to evaluate the effect of IFN- α + RBV therapy on the condition of oral mucosa in patients suffering from chronic hepatitis C.

Table 1. Demographic data of the study groups

Tabela 1. Charakterystyka grup badanych

	HCV n = 38	
	Group I (Grupa I) n = 15	Group II (Grupa II) n = 23
n ₁ (%)	15 (100)	17 (73,9)
Age (Wiek)	35.4 \pm 14.1	44.7 \pm 9.3
Gender-M/F Płeć (M/K)	11/4	15/8

n₁ – number of patients who completed 12-month follow-up.

n₁ – liczba pacjentów, którzy ukończyli 12-miesięczną obserwację.

Material and Methods

The investigations involved 38 patients hospitalized at the Department and Clinic of Infectious Diseases, Wrocław Medical University for chronic hepatitis due to HCV infection (Tab. 1). All the patients gave their informed consent for participation in the study. All other infectious, immunological, toxic and metabolic reasons of liver pathology were excluded serologically, immunologically and biochemically in all the patients. The patients were divided into two study groups:

Group I – 15 patients treated with IFN- α + RBV,
Group II – 23 patients awaiting treatment.

The patients were followed up for 12 months and in that time they were 4 times examined (at 0, 3, 6 and 12 months). The assessment included condition of the oral mucosa, its moisture (0 – normal, 1 – dry), moreover, permanent or transient pathological lesions of the oral mucosa were recorded. Histopathological examinations of the pathological lesions were performed in patients who gave their consent.

The findings of the study were analyzed statistically. The incidence of variables determined for the study groups (at 0, 3, 6 and 12 months) and between the groups was assessed using χ^2 test with Yates' modification assuming $p \leq 0.05$ as statistically significant.

Results

Analysis of the incidence of the subjective sensation of dryness of the oral mucosa in the observation period revealed that statistically significantly more patients from group I reported the sensation of dryness after 6 and 12 months in comparison to the initial data ($p \leq 0.05$). Group II patients did not demonstrate any statistically significant differences in the subjective sensation of dryness on subsequent visits (Tab. 2). Comparative analysis of group I and II patients did not indicate any significant differences in the number of patients reporting the subjective sensation of dryness on 4 successive examinations.

The incidence of pathological lesions of the oral mucosa did not differ significantly throughout the observation period in both study groups (Tab. 3). Comparison of group I and group II patients did not reveal any statistically significant differences in the number and distribution of lesions appearing on the oral mucosa. The incidence of pathological lesions in the study groups in the observation period is presented in Table 4.

Discussion

Infections with hepatotropic viruses, including HCV, are a worldwide epidemiological, clinical and social problem, the more that the course of HCV infection may be asymptomatic or may progress with very few symptoms both in acute as well as in chronic stage of the disease. The clinical diagnosis may be complicated with various pathological conditions being both, the extrahepatic manifestations of HCV infection, or the consequence of the side effects of the applied drugs.

The findings of own observations point to the lesions occurring in the oral cavity of patients suffering from chronic HCV infection [12]. The mechanisms of hepatocyte damage inflicted by HCV have not been understood. It is known that the elimination of infected cells is affected by the immunological response of cellular type as well as HCV induced autoimmunity [13]. That is why a number of authors associate the incidence of extrahepatic manifestations with autoimmunological processes induced by the virus [14, 15].

Patients with chronic HCV infection also develop disturbances in salivation resembling clinically Sjögren's syndrome [15–17]. This disturbance affects 0.04–4.8% of the human population [18, 19], but it is more commonly observed in the course of other diseases, like e.g. in 25% of patients suffering from rheumatoid arthritis [20].

Analysis carried out in the study groups seems

Table 2. Dryness of the oral mucosa

Tabela 2. Suchość błony śluzowej jamy ustnej

Examination – month (Badanie – miesiąc)	Dryness (Suchość*)	Group I (Grupa I)	Group II (Grupa II)
		n (%)	n (%)
0	0 1	15 (100) 0	19 (82.6) 4 (17.4)
3	0 1	12 (80.0) 3 (20.0)	13 (72.2) 5 (27.8)
6	0 1	8 (53.3) 7 (46.7)	12 (70.6) 5 (29.4)
12	0 1	10 (66.7) 5 (33.3)	12 (70.6) 5 (29.4)

n – number of patients in the groups changed in time.

* 0 – lack of dryness, 1 – dryness.

n – liczba pacjentów w grupie zmienna w czasie

* 0 – brak suchości, 1 – suchość.

Table 3. The incidence of oral mucosa pathology in the study groups

Tabela 3. Występowanie zmian patologicznych na błonie śluzowej jamy ustnej w grupach badanych

Examination – month (Badanie – miesiąc)	Lesion (Zmiana)	Group I (Grupa I) n = 15	Group II (Grupa II) n = 17
		no of lesions (liczba zmian)	no of lesions (liczba zmian)
0	0 1	10 5	7 10
3	0 1	5 10	5 13
6	0 1	6 9	3 14
12	0 1	8 7	3 14

n – number of patients in the group who attended all 4 examinations.

* 0 – no lesions, 1 – lesions.

n – liczba pacjentów w grupie, którzy przeszli wszystkie badania.

* 0 – brak zmiany, 1 – występowanie zmiany.

to confirm the causative effect of chronic HCV infections on the dysfunction of salivary glands (Tab. 2). Throughout the whole observation period, the number of patients reporting the sensation of dryness in the mouth in both study groups ranged from 0 to 46.7%. It should be stressed that in group I treated with IFN- α + RBV, the incidence of reported complaints due to diminished

Table 4. Oral mucosa pathology in the study groups**Tabela 4.** Zmiany patologiczne na błonie śluzowej jamy ustnej w grupach badanych

Examination – month (Badanie – miesiąc)	Lesion (Zmiana)	Group I (Grupa) n = 15	Group II (Grupa) n = 23	p
		number of lesions (liczba zmian)	number of lesions (liczba zmian)	
0	lack leukoplakia oral lichen planus delbanco disease labial herpes melanoplakia petechiae	10/15 2 2 1	12/23 6 1 2 1 1	ns
3	lack leukoplakia oral lichen planus delbanco disease labial herpes melanoplakia petechiae angular stomatitis	5/15 2 2 4 3	5/18 5 1 2 1 1 2	ns
6	lack leukoplakia lichen planus delbanco disease labial herpes melanoplakia petechiae angular stomatitis aphthae atrophy of filiform papillae	6/15 1 1 2 2 1 2 1 1	3/17 4 1 3 1 1 2 1	ns
12	lack leukoplakia lichen planus delbanco disease labial herpes melanoplakia petechiae angular stomatitis	8/15 1 2 2 3	3/17 4 1 4 1 1 1	ns

n – number of patients in the group, ns – non-significant.

n – liczba pacjentów w grupie, ns – brak istotności statystycznej.

salivation increased with time. It seems that the increasing dryness may be additionally associated with immunomodulatory and antiviral therapy.

Among oral mucosa diseases, only oral lichen planus (OLP) has been associated by the Italian and Japanese authors with chronic HCV infection [21–23]. The reports from Scotland, Germany and Poland are contradictory [24–26].

Present studies lasted 12 months, what has not been done by the above authors. OLP was found in 1 (1/23) patient from group II including untreated patients and the lesion sustained throughout the whole follow up period (Tab. 4). Two lesions (2/15) of OLP type were observed during therapy in patients from group I receiving IFN- α + RBV

(Tab. 4). At present the question concerning a direct cause of OLP in patients with chronic liver pathology remains unanswered. The relationship reveals a geographical diversity, what may be associated with various virus C genotypes prevailing in a given area. The findings of authors' observation suggest the necessity of monitoring patients treated with IFN in view of OLP exacerbation. Although the necessity of cessation of IFN therapy due to OLP exacerbation has been suggested by some authors [7, 8], this was not necessary in described patients and all of them completed the study according to the protocol.

Described patients also developed other oral mucosa diseases (Tab. 4). Group I patients, receiving

IFN- α + RBV, revealed an increased incidence of labial *Herpes* – 4/15 (26.67%) and this incidence was higher than in untreated patients from group II. This seems to be associated with “non-physiological” dose of IFN. Higher doses of this immunomodulator may block natural immunological response, what favours reactivation of *Herpes* virus infections. Although the results of experimental studies indicate that IFN- α inhibits transmission of labial *Herpes* virus (HSV-1) from nerve axons to the epidermal cells, they do not exclude the possibility of inducing lesions resembling clinically those of a typical herpes during IFN therapy [27, 28]. Other oral mucosa diseases observed in patients from the study groups are presented in Table 4. Available literature does not contain more comprehensive studies concerning the oral mucosa

pathology in patients with chronic HCV infections as well as the effects of IFN- α + RBV therapy.

Conclusions

1. No significant effect of IFN- α + RBV therapy on the incidence of oral mucosa lesions was observed in patients suffering from chronic hepatitis C.

2. Patients treated with IFN- α + RBV developed more often labial herpes, however the increase was statistically insignificant

3. During IFN- α + RBV therapy, the majority of patients reported the sensation of dryness in the mouth.

4. The incidence of OLP may be suggestive of IFN- α + RBV effect.

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Address for correspondence:

Agnieszka Sulka
Department of Oral Surgery, Wrocław Medical University
Krakowska 26
50-425 Wrocław
Poland
tel.: +48 71 484 02 51

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