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

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

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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 goal of the study was to evaluate the condition of oral mucosa in patients suffering from chronic hepatitis B treated with IFN- α (6 months) + lamivudin (12 months).

Material and Methods. The study groups consisted of 18 patients treated with IFN- α + lamivudin for chronic hepatitis due to HBV infection. The control group comprised 20 untreated patients with chronic hepatitis B. 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 the group of patients treated with IFN- α + lamivudin, the most common lesion found on initial examination was leukoplakia (5/18), while on the final examination it was labial *herpes* (6/18). The only finding in the control group was the increased incidence of labial *herpes* (5/20) in the 3 month observation. The intragroup analysis of all the subjects did not show any statistical difference in the number of lesions within the oral mucosa on follow-up. Comparison between groups showed a statistically significant difference in the number of oral mucosa lesions which was observed in the 12 month follow up. The lesions were significantly more frequent in the group of patients on IFN- α + lamivudin therapy ($p \leq 0.05$).

Conclusions. IFN- α + lamivudin therapy seems to increase of the number of oral mucosa lesions in patients suffering from HBV (*Dent. Med. Probl.* 2004, 41, 4, 603–607).

Key words: HBV, oral mucosa diseases, chronic hepatitis B, IFN therapy.

Streszczenie

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

Cel pracy. Ocena wpływu terapii interferonem alfa IFN- α i lamiwudyną na stan błony śluzowej jamy ustnej pacjentów chorych na przewlekłe zapalenie wątroby typu B.

Materiał i metody. Grupę badaną stanowiło 18 pacjentów leczonych IFN- α + lamiwudyną z powodu przewlekłego zapalenia wątroby związanego z zakażeniem HBV. Grupę kontrolną stanowiło 20 nieleczonych pacjentów z przewlekłym zapaleniem wątroby typu B. 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 + lamiwudyną w badaniu wyjściowym najczęstszą zmianą była leukoplakia (5/18), a w badaniu końcowym opryszczka wargowa (6/18). W grupie kontrolnej jedynie w 3. miesiącu obserwacji odnotowano wzrost liczby opryszczki wargowej (5/20). W analizie wewnątrz każdej z grup badanych nie stwierdzono różnic statystycznych liczby zmian na błonie śluzowej jamy ustnej w czasie prowadzonych obser-

wacji. W analizie wewnątrzgrupowej znamiennej statystycznie różnicę liczby zmian na błonie śluzowej jamy ustnej zaobserwowano w 12. miesiącu obserwacji. Zmiany te były znamienne częstsze w grupie pacjentów leczonych IFN- α + lamiwudyną ($p \leq 0,05$).

Wnioski. Terapia IFN- α + lamiwudyną wydaje się mieć wpływ na wzrost liczby zmian na błonie śluzowej jamy ustnej u pacjentów przewlekle zakażonych HBV (**Dent. Med. Probl.** 2004, 41, 4, 603–607).

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

Estimated epidemiological data suggest that over 2 billion people all over the world have been infected with HBV. The largest infected population are the Asians (about 75% of all the infections), in Western Europe the problem concerns about 2% of the population. In Poland, the incidence of HBV infections is 1–1.5%, what means that about 380 000 Poles replicate HBV on permanent or temporary basis [1, 2].

It is estimated that about 25–40% of patients with chronic hepatitis B who have not received specialist medical care and appropriate treatment 5–10 years after the infection develop cirrhosis of the liver that may progress to primary carcinoma of the liver [3]. Hence the therapeutic effectiveness attributed to immunomodulators such as interferon alpha (IFN- α) in the treatment of viral hepatitis B has become so important [4]. However, IFN- α is associated with numerous undesired effects which include influenza-like symptoms, hypertension, insomnia, tachycardia, anorexia, depression, thrombocytopenia as well as other symptoms of bone marrow injury [4]. Apart from the immunomodulating therapy, the treatment of chronic HBV infections relies on antiviral drugs, such as Lamivudin (3TC). 3TC is a new generation nucleoside analogue which blocks replication of the virus (it is HBV polymerase inhibitor) and is generally well tolerated by the patients [5]. The effectiveness of therapy in viral hepatitis B determined on the basis of seroconversion in HBe/antiHBe system and elimination of HBV-DNA from blood sera is assessed as 9.1–45.6%, although HBs/antiHBs seroconversion has been observed only in 1.7–7.7% of the treated patients [6, 7].

In patients with chronic HBV infection, the clinical picture of oral mucosa lesions as well as their possible association with the administered therapy are unknown. The aim of the study was to evaluate the effect of a combined IFN- α + lamivudin therapy on the condition of oral mucosa in patients suffering from chronic hepatitis B.

Material and Methods

The investigations involved 38 patients hospitalized at the Department and Clinic of Infectious Diseases, Wrocław Medical University for chronic

Table 1. Demographic data of the study groups

Tabela 1. Charakterystyka grup badanych

	HBV n = 38	
	Group I (Grupa I) n = 18	Group II (Grupa II) n = 20
n ₁ (%)	17 (94.4)	15 (75.0)
Age (Wiek)	35.3 \pm 19.4	29.0 \pm 16.4
Gender-M/F (Płeć (M/K))	12/6	14/6

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

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

hepatitis due to HBV infection (Tab. 1). All the patients signed an informed consent for participation in the study. Other known infectious, immunological, toxic and metabolic liver diseases were excluded on the basis of serological examinations in all the patients. The patients were divided into two study groups:

Group I – 18 patients treated with IFN- α + 3TC (interferon- α and lamivudin),

Group II – 20 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 did not indicate any statistical-

ly significant differences (Tab. 2). Comparative analysis of groups I and II 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). However, comparative analysis of the incidence of pathological lesions within the oral

mucosa between the groups revealed increased incidence in group I in comparison to group II after 6 months of observation ($p \leq 0,05$) (Tab. 4).

Discussion

Infections with hepatotropic viruses, including HBV, are a worldwide epidemiological, clinical and social problem, the more that cirrhosis of the liver and primary tumour of the liver induced by chronic HBV infection result in hundred thousands deaths a year all over the world [1, 3]. The clinical diagnosis may be complicated with various pathological conditions being both, the extrahepatic manifestations of HBV 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 HBV infection [8]. Patients from the study groups did not report any functional disorders of the salivary glands manifested by sensation of dryness of the oral mucosa, thus IFN therapy did not cause decreased salivation. No periodic observations of disturbed salivation were carried out in available literature.

Among diseases of the oral mucosa, only oral lichen planus (OLP) has been associated with chronic liver pathology and IFN therapy by some authors [9, 10].

Own observations were carried out in the period of 12 months, what was not done by the above authors. OLP was diagnosed in 1 (1/18) patient from Group I receiving IFN- α + 3TC. The lesion appeared in the 6th month of the observation (Tab. 4). Group II patients, awaiting the treatment did not report any changes of OLP type. At present, the question concerning a direct cause of OLP in patients with chronic liver pathology remains unanswered. The relationship reveals a geographical diversity. The findings of authors' observations point to the necessity of monitoring the patients treated with IFN for OLP. Although some authors suggest the necessity if discontinuation of IFN therapy due to exacerbation of OLP [11], this did not occur in authors' patient and all the subjects completed the treatment according to the protocol.

The patients occasionally developed other diseases of the oral mucosa (Tab. 4). The incidence of labial herpes in Group I patients on IFN- α + 3TC therapy increased to 6/17 (35.29%) and was higher than in untreated Group II patients. This seems to be associated with non-physiological dose of IFN. High doses of this immunomodulator may block natural immunological response, what facilitates reactivation of *Herpes* virus infections. Although the results of experimental studies indi-

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	17 (94.4)	15 (75.0)
	1	1 (5.6)	5 (25.0)
3	0	13 (72.2)	13 (86.7)
	1	4 (27.8)	2 (13.3)
6	0	12 (70.6)	13 (86.7)
	1	5 (29.4)	2 (13.3)
12	0	12 (70.6)	12 (80.0)
	1	5 (29.4)	3 (20.0)

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 = 17	Group II (Grupa II) n = 15
		no of lesions (liczba zmian)	no of lesions (liczba zmian)
0	0	10	13
	1	7	2
3	0	8	10
	1	9	5
6	0	7	12
	1	10	3
12	0	4	9
	1	13	5

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.

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 = 18	Group II (Grupa) n = 20	p
		No of lesions (Liczba zmian)	Number of lesions (Liczba zmian)	
0	lack leukoplakia delbanco disease melanoplakia petechiae	12/18 5 1	17/20 1 1 1	ns
3	lack leukoplakia delbanco disease labial herpes melanoplakia petechiae	9/17 4 3 2	10/15 1 5 1 1	ns
6	lack leukoplakia lichen planus delbanco disease labial herpes melanoplakia petechiae aphthae atrophy of filiform papillae	7/17 4 1 2 2 2 1 1	12/15 1 1 1	≤ 0.05
12	lack leukoplakia lichen planus delbanco disease labial herpes melanoplakia petechiae	4/17 4 1 3 6	9/15 1 2 1 2	ns

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

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

Conclusions

cate 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 [12, 13]. 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 HBV infections as well as the effects of IFN- α + 3TC therapy.

1. No significant effect of IFN- α + 3TC therapy on the incidence of oral mucosa lesions was observed in patients suffering from chronic hepatitis B.

2. Patients treated with IFN- α + 3TC developed more often labial *Herpes*, however, the increase was statistically insignificant

3. IFN- α + 3TC therapy may contribute to the occurrence of pathological lesions on the oral mucosa.

4. The incidence of OLP may be suggestive of IFN- α + 3TC effect.

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