ejpmr, 2020,7(12), 170-173

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

PRACTICAL APPROACHES TO THE DIAGNOSIS OF SERUM IL-28 LEVELS IN VIRAL HEPATITIS B IN PREGNANT WOMEN

Zufarova Sh. A., Mirzaabdullahozhieva O. U., *Ismailova A. A., Yuldasheva O. S.

Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan.
*Institute of Immunology and Human Genomics, Tashkent, Uzbekistan.

***Corresponding Author: Ismailova A. A.**

Institute of Immunology and Human Genomics, Tashkent, Uzbekistan.

Article Received on 13/10/2020 **Article Revised on 03/11/2020** **Article Accepted on 23/11/2020**

SUMMARY

According to the results carried out since the discovery of interferons, no one doubts that IFN-λ are polyfunctional. The role of IFN-λ as an interferon that suppresses viral infections on the surfaces of the anatomical barriers of the respiratory tract, gastrointestinal tract, blood-brain barrier and liver has been studied quite extensively and in detail. More recently, studies have appeared on the immunomodulatory role of IFN-λ and its direct and indirect effects on the function of immune cells in various inflammatory conditions, thereby explaining the higher safety profile compared to the undesirable pro-inflammatory effects of IFN-α. Interesting data in the field of infectious diseases, as well as the availability of ready-made pegylated forms of IFN-λ, which have already passed clinical studies and showed a higher safety profile in them than pegylated IFN-α, open scientific and clinical horizons for the study and application of IFN-λ. The studies have shown that the values of IFN-gamma and IL-28, which have pronounced antiviral properties, are significantly suppressed during chronic infection with viral hepatitis B. Research in this area will be continued in order to understand the etiopathogenesis, the characteristics of the course of the infectious process and predict the course of the disease.

KEY WORDS: interferons, immunity, antiviral action, interferon system, antiviral protection of immunity, viral hepatitis B.

Topicality

Viral hepatitis is one of the most significant public health problems worldwide. Of all the known nosological forms, the most relevant are hepatitis B and C.[16,19,23,24] This is due to their widespread occurrence, negative impact on human health and ability to work, as well as the frequent development of adverse outcomes such as chronic hepatitis, liver cirrhosis, hepatocellular carcinoma.[16,19] Hepatitis B is classified as a widespread infectious disease. It is believed that about 2 billion people are infected with the hepatitis B virus, and about 2 million patients die annually from pathology associated with HBV infection.[18]

The increase in the incidence of viral hepatitis B inevitably leads to an increasing involvement in the epidemic process of women of reproductive age, including pregnant women.[12, 16] Hepatitis B remains one of the most common infections in pregnant women, which is why scientific medicine and practical health care face the problem of the influence of the viral process on the course of pregnancy, childbirth and the postpartum period, as well as the effect of pregnancy on the course and outcomes of viral hepatitis.[16,17, 19.22] Today, a unified tactic has not been developed in the clinical and laboratory diagnosis of viral hepatitis in pregnant women. The number of complications in the course of pregnancy in women with parenteral viral hepatitis is almost twice as likely as in women who are not ill, and complications during childbirth are 1.5 times more likely.[21,23]

Despite the fact that 20 years have passed since the discovery of lambda interferons (IFN-λ), it was only in October 2018 that the first ever meeting was held at the US National Institutes of Health entitled "IFN-λ: Effects on Diseases and Therapeutic Potential" dedicated exclusively to IFN-λ.

The purpose of this event was to improve interdisciplinary understanding and to promote collaboration in studies of IFN-λ, which, in the opinion of the meeting participants, have significant diagnostic and prognostic potential in the field of infectious, oncological and autoimmune diseases.[4,9] The first publications devoted to IFN-λ appeared in 2002–2003.[2,8,13,25], and they showed that IFN-λ (also known as IFN type III) have significant similarity with IFN-α / β (IFN type I) in that they induce the expression of antiviral and host antiproliferative genes by signaling through the JAK / STAT pathway. At the same time, it was found that, in contrast to the expression of the IFN-α

/ β receptor, which occurs in almost all nuclear cells, the expression of the IFN-λ receptor is determined mainly in human blood, lungs, pancreas, epithelial cells of the mucous membranes, placenta, ovaries, prostate, testicular tissue and keratinocytes of the skin and is tissue-specific.[2,3,6,12] At the same time, the kinetics of STAT activation of IFN-α and IFN-λ and the potential of the genes induced by them differ: the effector functions of the IFN-α genes increase and decrease rapidly, peak-like, and the IFN-λ genes - increase gradually and steadily.[1,5,6,10 ,11]

The influence of IFN-λ on the immune system since their discovery has been the object of close attention, and at present the existence of such an effect is indisputable, however, the mechanism by which IFN-λ regulates the adaptive immune response is still not fully understood.[5,8, 12.14] IFN-λ has been detected in a wide range of animals, while its antitumor, anti-inflammatory and antiviral effects have been recorded.[19,21] It has been shown that IFN-λ plays a role in the pathogenesis of infectious diseases, in particular in viral hepatitis.[9,15]

In connection with the above, we studied the serum concentration of IL-28 in a group of pregnant women with chronic viral hepatitis B. For this purpose, 42 pregnant women with viral hepatitis B were examined, who were examined on an outpatient basis.

MATERIAL AND RESEARCH METHODS

42 pregnant women were examined at 4-2 weeks of gestation, with a history of chronic viral hepatitis B. The women were between 19 and 32 years old.

Interleukin-28A / Interferon lambda-2. The reagent kit for the determination of interleukin-28A / interferon lambda-2 by the enzyme immunoassay is intended for the quantitative determination of human interleukin-28A / interferon lambda-2 in blood serum samples. Interleukin-28 (IL-28) is a cytokine that has 2 isoforms, IL-28A and IL-28B, and plays an important role in immune defense against viruses, including the induction of "antiviral status" by activating Mx proteins, 2 ', 5 '-oligoadenylate synthetase and ISGF3G (factor 3 interferon-stimulated gene). IL-28A and IL-28B belong to the type III interferon cytokine family and are very similar (in amino acid sequence) to IL-29. Interleukin-28A is a new cytokine discovered in recent years. It has been shown to have antiviral activity. IL-28A, IL-28B and IL-29 are a family of class II cytokines that stimulate an antiviral response through a heterodimeric receptor different from the type I interferon receptor. Measurement range: 5.6-1000 pg / ml. Analytical sensitivity: 5.6 pg / ml. The serum concentrations of IFN-alpha and IFN-gamma were also studied by the enzyme immunoassay using the test systems "Human", Germany, 2020. Statistical processing of the results was carried out by calculating M ± m.

THE RESULTS OF THE STUDY

As you know, different interferons differ in their cellular origin. Thus, IFN-is produced by monocytes, macrophages, neutrophils and B-lymphocytes.[16] The inducers of the formation of IFN-основном are mainly viruses (RNA- and DNA-containing).[12,17] As you know, the antiviral effect of interferons is associated with their ability to suppress the processes of transcription and translation of the viral genome. The effect of IFN-α on the immune response is manifested in the induction of the production of some cytokines (in particular, proinflammatory).[17,22] Again, it is important to note that in sufficiently high doses, interferons suppress both humoral and cellular immune responses, but at more moderate concentrations they have an immunoregulatory effect.[6,17]

Analysis of IFN-gamma in the group of pregnant women with hepatitis B revealed that the level of serum IFN-gamma was suppressed with the value of the control group. Thus, it was revealed that in the group of pregnant women with hepatitis B the value of IFN-gamma was 4.82 ± 1.4 pg / ml, while the norm for practically healthy pregnant women was 14.2 ± 0.9 pg / ml, which is significantly different. It has been established that activated T-lymphocytes and NK are the source of IFN-γ (antigens and mitogens act as activators first of all). Among T-lymphocytes, IFN-γ producers are primarily cytotoxic CD8 + and helper CD4 + cells, however, when the latter differentiate into TX1 and TX2, only TX1 cells retain the ability to produce IFN-γ.[14,17,20,23] Consequently, IFN-gamma in the group of pregnant women with viral hepatitis B was significantly reduced, which indicates the formation of an immunodeficiency state. As you know, the activation of TX1 lymphocytes promotes the production of IFN-g, therefore, suppression of IFN-gamma affects the suppression of cellular immunity against the background of a chronic viral process.

As shown above, the role of IL-28 is quite large, especially during the infectious process. Thus, the concentration of IL-28 in the blood serum of pregnant women was significantly suppressed in comparison with the value of pregnant women without viral damage. Thus, a significant decrease in IL-28 was revealed in the group of women with viral hepatitis B compared with the value of healthy women of reproductive age. It has been proven that normal IL-28 values contribute to a pronounced antiviral attack, which is much reduced against the background of a chronic viral process. We have revealed a twofold suppression of serum IL-28 in women with hepatitis B compared with the data of practically healthy pregnant women. Thus, it was revealed that in the group of pregnant women with hepatitis B the IL-28 value was 3.74 ± 0.92 pg / ml, while the norm for practically healthy pregnant women was 12.8 ± 0.75 pg / ml, which was significantly different. According to the literature, the antiviral activity of IFN-λ in vitro was investigated in various cell

cultures against a variety of both RNA and DNA-containing viruses.[13, 16] It has been proven that the antiviral activity of IFN-λ in in vivo studies is the ability to stimulate the body's immune system as a whole in response to the invasion of a foreign agent. However, against the background of a chronic process, the depletion of the IL-28 potential is observed, which will lead to the suppression of production and the formation of an immunodeficiency state. There are indications in the literature that the prophylactic administration of IFN-λ, like IFN-α, suppressed the initial replication of the virus, then suppression of IL-28 was observed. Therefore, IL-28 performs a decisive and non-redundant function in the body, which significantly limits the replication of the virus.[26,27]

Thus, according to the results of studies carried out since the discovery of IFN-λ, no one doubts that IFN-λ are polyfunctional. The role of IFN-λ as an interferon that suppresses viral infections on the surfaces of the anatomical barriers of the respiratory tract, gastrointestinal tract, blood-brain barrier and liver has been studied quite extensively and in detail. More recently, studies have appeared on the immunomodulatory role of IFN-λ and its direct and indirect effects on the function of immune cells in various inflammatory conditions, thereby explaining the higher safety profile compared to the undesirable pro-inflammatory effects of IFN-α. Interesting data in the field of infectious diseases, as well as the availability of ready-made pegylated forms of IFN-λ, which have already passed clinical studies and showed a higher safety profile in them than pegylated IFN-α, open scientific and clinical horizons for the study and application of IFN-λ. Thus, our studies have shown that the values of interferon gamma and IL-28, which are expressed antiviral proteins, are significantly suppressed against the background of chronic viral hepatitis B in pregnant women in the early stages of pregnancy, which can lead to a pronounced suppression of cellular immunity and activation of viral replication. Research in this area will be continued in order to understand the etiopathogenesis, features of the course of the infectious process and predict the course of the disease.

REFERENCES

1. Artamonov A.V., Bekarev A.A., Dygai A.M., Zhdanov V.V., Kinsht D.N., Madonov P.G., Sherstoboev E Yu. Pegylated interferon lambda for oral administration, and method for producing same. Patent 2678332 RF; Publ. 28.01.2019. [In Russian].
2. Maldov D.G., Andronova V.L., Grigoryan S.S., Isaeva E.I., Balakina A.A., Terentev A.A., Ilichev A.V., Galegov G.A. The mechanism of stimforte action on herpesvirus infection. Voprosy virusologii = Problems of Virology. 2018; 63(5): 218–222. [In Russian]. doi: 10.18821/0507-4088-2018-63-5-218-223
3. Ank N., West H., Bartholdy C., Eriksson K., Thomsen A.R., Paludan S.R. Lambda interferon (IFNlambda), a type III IFN, is induced by viruses and IFNs and displays potent antiviral activity against select virus infections in vivo. J. Virol. 2006; 80(9): 4501–4509. doi: 10.1128/JVI.80.9.4501-4509.2006
4. Bandi P., Pagliaccetti N.E., Robek M.D. Inhibition of type III interferon activity by orthopoxvirus immunomodulatory proteins. J. Interferon Cytokine Res. 2010; 30(3): 123–134. doi: 10.1089/jir.2009.0049
5. Baños-Lara Mdel R., Harvey L., Mendoza A., Simms D., Chouljenko V.N., Wakamatsu N., Kousoulas K.G., Guerrero-Plata A. Impact and regulation of lambda interferon response in human metapneumovirus infection. J. Virol. 2015; 89 (1): 730–742. doi: 10.1128/ JVI.02897-14
6. Bartlett N.W., Buttigieg K., Kotenko S.V., Smith G.L. Murine interferon lambdas (type III interferons) exhibit potent antiviral activity in vivo in a poxvirus infection model. J. Gen. Virol. 2005; 86 (6): 1589–1596. doi: 10.1099/vir.0.80904-0
7. Blazek K., Eames H.L., Weiss M., Byrne A.J., Perocheau D., Pease J.E., Doyle S., McCann F., Williams R.O., Udalova I.A. IFN-l resolves inflammation via suppression of neutrophil infiltration and IL1b production. J. Exp. Med. 2015; 212: 845–853. doi: 10.1084/jem.20140995
8. Caine E.A., Scheaffer S.M., Arora N., Zaitsev K., Artyomov M.N., Coyne C.B., Moley K.H., Diamond M.S. Interferon lambda protects the female reproductive tract against Zika virus infection. Nat. Commun. 2019;
9. Carrick D.M. Interferon lambda: an immune system factor that cancer epidemiologists should consider. J. Interferon. Cytokine Res. 2019; 39(10). 592– 593. doi: 10.1089/jir.2019.0033 [Epub ahead of print]
10. Castillo-Martínez D., Juarez M., Patlán M., PáezA., Massó F., Amezcua-Guerra L.M. Type-III interferons and rheumatoid arthritis: Correlation between interferon lambda 1 (interleukin 29) and antimutated citrullinated vimentin antibody levels. Autoimmunity. 2017; 50(2): 82–85. doi: 10.1080/08916934.2017.1289181
11. Chan H.L.Y., Ahn S.H., Chang T.T., Peng C.Y., Wong D., Coffin C.S., Lim S.G., Chen P.J., Janssen H.L.A., Marcellin P., Serfaty L., Zeuzem S., Cohen D., Critelli L., Xu D., Wind-Rotolo M., Cooney E.; LIRA-B Study Team. Peginterferon lambda for the treatment of HBeAg-positive chronic hepatitis B: A randomized phase 2b study (LIRA-B). J. Hepatol. 2016; 64(5): 1011–1019. doi: 10.1016/j.jhep.2015.12.018
12. Cui L., Yu F., Ma J., Pei H., Zuo L. Effects of DENV-2 infection on the expression of IL-29 in primary HUVECs cultured on hydrogel substrates. Chinese Journal of Microbiology and Immunology (China). 2015; 35(1): 7–13. doi: 10.3760/cma.j.issn.0254-5101.2015.01.002
13. Dantas A.T., Gonçalves S.M., Pereira M.C., de Almeida A.R., Marques C.D., Rego M.J., Pitta Ida

R., Duarte A.L., Pitta M.G. Interferons and systemic sclerosis: correlation between interferon gamma and interferon-lambda 1 (IL-29). Autoimmunity. 2015; 48(7): 429–433. doi: 10.3109/08916934.2015.1054028

14. Davidson S., McCabe T.M., Crotta S., Gad H.H., Hessel E.M., Beinke S., Hartmann R., Wack A. IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of IFNα treatment. EMBO Mol. Med. 2016; 8(9): 1099–112. doi: 10.15252/ emmm.201606413
15. Douam F., Soto Albrecht Y.E., Hrebikova G., Sadimin E., Davidson C., Kotenko S.V., Ploss A. Type III interferon-mediated signaling is critical for controlling live attenuated yellow fever virus infection in vivo. MBio. 2017; 8(4): e00819-17. doi: 10.1128/ mBio.00819-17
16. Espinosa V., Dutta O., McElrath C., Du P., Chang Y.J., Cicciarelli B., Pitler A., Whitehead I., Obar J.J., Durbin J.E., Kotenko S.V., Rivera A. Type III interferon is a critical regulator of innate antifungal immunity. Sci. Immunol. 2017; 2(16): eaan5357. doi: 10.1126/sciimmunol.aan53
17. Flisiak R., Shiffman M., Arenas J., Cheinquer H., Nikitin I., Dong Y., Rana K., Srinivasan S. A randomized study of peginterferon lambda-1a compared to peginterferon alfa-2a in combination with ribavirin and telaprevir in patients with genotype-1 chronic hepatitis C. PLoS One. 2016; 11(10): e0164563. doi: 10.1371/journal.pone.0164563
18. Ha Y.J., Choi Y.S., Kang E.H., Chung J.H., Cha S., Song Y.W., Lee Y.J. Increased expression of interferon-λ in minor salivary glands of patients with primary Sjögren's syndrome and its synergic effect with interferon-α on salivary gland epithelial cells. Clin. Exp. Rheumatol. 2018; 36(Suppl. 112, 3): 31–40.
19. Hausman D.F., Dodds M.G. Use of pegylated type III interferons for the treatment of hepatitis C. Patent WO2009149377A1; Publ. 10.12.2009.
20. Hermant P., Michiels T. Interferon-λ in the context of viral infections: production, response and therapeutic implications. J. Innate Immun. 2014; 6: 563–574. doi: 10.1159/000360084
21. Ilyushina N.A., Lugovtsev V.Y., Samsonova A.P., Sheikh F.G., Bovin N.V., Donnelly R.P. Generation and characterization of interferon-lambda 1-resistant H1N1 influenza A viruses. PLoS One. 2017; 12(7): e0181999. doi: 10.1371/journal.pone.0181999 Kikhtenko N.A. et al. Interferons lambda – therapeutic application SIBERIAN SCIENTIFIC MEDICAL JOURNAL 2020; 40(2): 15–23 21.
22. Jounai K., Sugimura T., Ohshio K., Fujiwara D. Oral administration of Lactococcus lactis subsp. lactis JCM5805 enhances lung immune response resulting in protection from murine parainfluenza virus infection. PLoS One. 2015; 10(3): e0119055. doi: 10.1371/journal.pone.0119055
23. Kim H.J., Jo A., Jeon Y.J., An S., Lee K.M., Yoon S.S., Choi J.Y. Nasal commensal Staphylococcus epidermidis enhances interferon-λ-dependent immunity against influenza virus. Microbiome. 2019; 7(1): 80. doi: 10.1186/s40168-019-0691-9
24. Koch S., Finotto S. Role of interferon-l in allergic asthma. J. Innate Immun. 2015; 7: 224–230. doi: 10.1159/000369459
25. Kotenko S.V., Gallagher G., Baurin V.V., LewisAntes A., Shen M., Shah N.K., Langer J.A., Sheikh F., Dickensheets H., Donnelly R.P. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. Nat. Immunol. 2003; 4(1): 69–77. doi: 10.1038/ni875
26. Lasfar A., Zloza A., Silk A.W., Lee L.Y., Cohen-Solal K.A. Interferon lambda: toward a dual role in cancer. J. Interferon Cytokine Res. 2019; 39(1): 22–29. doi: 10.1089/jir.2018.0046
27. Nice T.J., Baldridge M.T., McCune B.T., Norman J.M., Lazear H.M., Artyomov M., Diamond M.S., Virgin H.W. Interferon-λ cures persistent murine norovirus infection in the absence of adaptive immunity. Science. 2015; 347: 269–273. doi: 10.1126/science.