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Effectiveness of Use of Immunomodulators in the Treatment of Chronic Conjunctivitis in Children and Adolescents with Tuberculosis

Mamatkhujaeva Gulnarakhan Najmidinovna[1,*], Ikramov Azizbek Fozilovich[2], Aleynik Vladimir Alekseevich[2]

[1]PhD, Associate Professor, Andijan State Medical Institute, Andijan, Uzbekistan
[2]DSc., Professor, Andijan State Medical Institute, Andijan, Uzbekistan

Abstract The use of immunomodulators in children and adolescents with tuberculosis and chronic conjunctivitis contributes to changes in the levels of pro- and anti-inflammatory interleukins. The levels of pro-inflammatory interleukin TNF-α in the tear fluid of children suffering from chronic conjunctivitis decreased under the influence of immunomodulators, while the anti-inflammatory interleukins IL-10 and TGF-β1 increased. Significant changes in interleukins were observed in children starting from the age of 7 years. The use of immunomodulators in the treatment of children and adolescents with tuberculosis and chronic conjunctivitis helps to normalize interleukin status and reduces the local inflammatory process in the eyes.

Keywords Children, Adolescents, Chronic conjunctivitis, Tuberculosis, Interleukins, Immunomodulators

1. Introduction

The cause of the development of chronic conjunctivitis in children and adolescents is various infectious and inflammatory diseases [1,2,3]. In children with tuberculosis chronic conjunctivitis is also often observed, which is characterized by a long and persistent course [4,5]. Treatment of chronic conjunctivitis in tuberculosis requires a long time, since there are disorders of the immune system, manifested in the inhibition of intercellular receptor interactions [6]. For effective treatment of chronic conjunctivitis in adolescent children with tuberculosis, it is necessary to use immunomodulators.

Purpose of the study: to study the effect of immunomodulators on the course of chronic conjunctivitis by changing the immunological parameters of tears in children and adolescents with tuberculosis.

2. Material and Methods of the Research

80 children and adolescents with chronic conjunctivitis, suffering from tuberculosis, who were treated at Andijan regional anti-tuberculosis dispensary, were examined. The children ranged in age from 4 to 17 years. All children were divided by age into 4 groups: 4-6 years, 7-9 years, 10-14 years and 15-17 years. There were 10 boys and 10 girls in each age group. As a control group, children of the same age groups and gender ratio with tuberculosis, but without any inflammatory eye diseases, were examined.

To identify the peculiarities of changes in local immunological parameters in the composition of the tear fluid, an ELISA study was carried out for pro-inflammatory interleukin - tumor necrosis factor (TNF-α) and anti-inflammatory - interleukin 10 (IL-10) using test systems from Vector-Best JSC, Russia. Also transforming growth factor-β1 (TGF-β1) using test systems "DRG" Germany. In addition, protease inhibitors α-1-anti-trypsin and α-2-macroglobulin were determined using test systems “Sentinel” Italy.

The day before tear collection, patients did not instill any drops. Before collecting tear fluid, lacrimation was induced (they were given a cut onion to smell). Tear fluid was collected immediately with sterile disposable glass capillaries from the inferior conjunctival fornix into a sterile, labeled Eppendorf. In the same way, tear fluid was collected from the conjunctival cavity and the other eye. The manipulation was carried out until 1.0 ml of tear fluid accumulated in the Eppendorf. The obtained material was stored in a freezer at temperature of -20.0℃ until the stage of laboratory research.

The choice of immunomodulator for treatment was made after determining individual sensitivity to immunomodulators. The study was carried out on lymphocytes isolated from

* Corresponding author:
dr_gulnora@mail.ru (Mamatkhujaeva Gulnarakhan Najmidinovna)
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blood taken from the antecubital vein of patients. To determine the sensitivity of lymphocytes to immunomodulators, the so-called "stress tests" were conducted with the studied drugs, according to the change of the functions of E-rosette formation. Sensitivity was determined to the drugs most often used in pediatric clinical practice: cycloferon, thymalin, immunomodulin, immunal, interferon, polyoxidonium.

Statistical processing was carried out using the method of variation statistics with the calculation of average values and their average errors, as well as relative values and determination of the reliability coefficient of the difference between the compared Student-Fisher values (t). Differences were considered statistically significant at $p<0.05$ or less.

3. Results and Its Discussion

To identify the characteristics of changes in local immunological parameters in the composition of the tear fluid, a study of TNF-α and IL-10, TGF-β1 was carried out. Each patient examined, taking into account the maximum indicator of individual sensitivity, was prescribed an appropriate immunomodulator internally for treatment. Oftalmoferon was used topically, daily, by instilling 2 drops into the affected eye 3 times a day for 30 days, until the symptoms of the disease disappeared.

As a result of studies conducted in boys 4-6 years old with tuberculosis with chronic conjunctivitis, it was revealed that after the treatment with immunomodulators, the levels of interleukin TNF-α in the tear fluid relative to the values of the control group were 114%, and were not significantly lower than similar results before the treatment, amounting to 144 % relative to control (Table 1). These changes show a non-significant decrease in TNF-α under the influence of treatment with immunomodulators in boys from 4 to 6 years old with tuberculosis with chronic conjunctivitis. At the same time, in girls of this age group, this indicator after the treatment with immunomodulators, compared with similar results of the same age without chronic conjunctivitis, was equal to 172% and was not significantly higher than the results without treatment, which amounted to 148% relative to patients without chronic conjunctivitis. These results indicate that TNF-α levels decreased more in boys after the treatment than in girls and the effect of immunomodulators on this indicator was not significantly greater. The average TNF-α values in the general group of this age after the treatment were 133% relative to the control, and before the treatment - 162% (Table 1).

When studying IL-10 in boys with chronic conjunctivitis and ill with tuberculosis, the average value of this indicator after the treatment with immunomodulators was not significantly lower and amounted to 81% relative to the control. Whereas before the treatment, in these boys the indicator was not significantly lower than the indicator after the treatment, and in comparison with the control it was significantly lower and their ratio was 66%. These results show that under the influence of immunomodulators in boys aged 4 to 6 years with tuberculosis and chronic conjunctivitis, a slight increase in IL-10 was observed in the tear fluid.

In girls of this age group, the values of this indicator had similar trends with minor differences in the values of the indicators. Thus, the indicators after the treatment were 70% relative to the control group, and before the treatment they were not significantly lower and equaled 59% relative to the control. These data indicate that boys were not significantly more likely to benefit from immunomodulators than girls. The average level of this indicator after the treatment, taking into account both sexes, was 76% relative to the control, which was not significantly higher than the results before the treatment, which was 63% relative to the control (Table 1).

At the same time, when studying TGF-β1 in boys from 4 to 6 years old with tuberculosis and with chronic conjunctivitis, it was found that the indicators before the treatment were significantly lower than the indicators of the control group and their ratio was 62%. After the treatment with immunomodulators, there was a non-significant increase in the average value compared to the value before the treatment, but it was also non-significantly lower than the control group and their ratio was 80%. From these results it is clear that under the influence of immunomodulators there is an unreliable increase in TGF-β1 in boys aged 4 to 6 years with tuberculosis and chronic conjunctivitis.

Meanwhile, in girls of the same age group, this indicator after the treatment was 72% relative to the control group; this result was not significantly greater than the indicator before the treatment, which was 56% relative to the control group. At the same time, the increase in the indicator was slightly less for girls than for boys. When analyzing the average TGF-β1 values in the general group of boys and girls, the value after the treatment was 76%, and before the treatment 59% relatively to the control group (Table 1).

Studies in children aged 7 to 9 years have shown that in boys in this group of patients with tuberculosis and with chronic conjunctivitis at the same time, the value of TNF-α in the tear fluid after the treatment with immunomodulators was not significantly higher, similar results without chronic conjunctivitis. The ratio of the TNF-α indicator after the treatment to that of the control group was 110%. The indicator before the treatment was significantly higher than the control indicator and their ratio was 155%. These changes indicate that in boys 7-9 years old with tuberculosis with chronic conjunctivitis, under the influence of treatment with immunomodulators, a marked decrease in TNF-α was observed. Meanwhile, girls of the same age group showed similar changes; the level of TNF-α after the treatment with immunomodulators decreased insignificantly, but was still higher than the control level. The ratio of indicators to control group was more pronounced than in boys and amounted to 163% before the treatment and 125% after the treatment. These modifications demonstrate that in boys the effects of immunomodulators on TNF-α values are less pronounced. The average TNF-α values in the joint group of boys and girls after the treatment were at the level of 117% and 157% before the treatment relatively to the control group.

However, in the study of IL-10 in boys of 7-9 years old with tuberculosis and with chronic conjunctivitis after the treatment with immunomodulators, the ratio of the indicator to the control group was 96%, and the ratio of the indicator before the treatment was 71%. A comparative analysis of average values before the treatment showed that the level in the group of patients with chronic conjunctivitis was significantly lower than in the control group. After the treatment with immunomodulators, IL-10 levels significantly increased, but they were not significantly lower compared to the control group. These changes show that in boys aged 7 to 9 years with tuberculosis and conjunctivitis, there was a significant increase in IL-10 under the influence of immunomodulators.

Table 1. Changes in the indicators of pro-inflammatory (TNF-α), anti-inflammatory (IL-10) interleukins and TGF-β1 in the tears of children of the examined groups

Age groups	Study indicators	Comparison groups	Boys	Girls	Total
4-6 years old	TNF-α pg/ml	1	3,6±0,31	4,6±0,39	4,1 ±0,35
		2	5,2±0,64*	7,9±1,24*	6,6±0,89*
		3	4,1±0,38	6,8±0,57	5,5±0,32
	IL-10 pg/ ml	1	4,4±0,38	4,8±0,44	4,6±0,32
		2	2,9±0,36*	2,8±0,41*	2,9±0,34*
		3	3,6±0,37	3,4±0,31	3,5±0,29
	TGF-β1 ng/ml	1	39,8±3,5	34,7 ±3,1	37,3±2,8
		2	24,7±3,4*	19,4±3,7*	22,1±2,9 *
		3	31,8±3,7	25,0±2,2	28,4±2,1
7-9 years old	TNF-α pg/ml	1	3,8 ±0,35	4,5±0,43	4,2±0,31
		2	5,9±0,55*	7,3±0,66*	6,6±0,49*
		3	4,2±0,38**	5,6±0,49	4,9±0,35**
	IL-10 pg/ml	1	5,1±0,44	4,7±0,42	4,9±0,37
		2	3,6±0,32*	3,0±0,25*	3,3±0,23*
		3	4,9±0,44**	4,0±0,35**	4,5±0,31**
	TGF-β1 ng/ml	1	43,9±3,7	49,4±4,2	46,7±3,1
		2	26,3±2,3*	25,7±2,1*	26,0±1,9*
		3	39,0±3,5**	38,0±3,6**	38,5±3,2**
10-14 years old	TNF-α pg/ml	1	4,5±0,41	5,7±0,53	5,1±3,6
		2	7,6±0,69*	10,6±0,94*	9,1±0,67*
		3	4,9±0,42**	7,5±0,71**	6,2±0,57**
	IL-10 pg/ml	1	5,4±0,49	4,9±0,46	5,2±0,39
		2	2,8±0,24*	2,3±0,19*	2,6±0,21*
		3	5,1±0,44**	4,0±0,39**	4,6±0,37**
	TGF-β1 ng/ml	1	54,1±5,1	47,7±4,3	50,9±3,9
		2	29,2±2,5*	23,4±2,0*	26,3±1,8*
		3	53,0±4,8**	41,0±3,8**	47,0±3,5**
15-17 years old	TNF-α pg/ml	1	4,8±0,39	4,1±0,36	4,5±0,32
		2	7,7±0,69*	7,2±0,62*	7,5±0,54*
		3	5,4±0,51**	5,5±0,43**	5,5±0,47**
	IL-10 pg/ml	1	5,7±0,56	5,1±0,48	5,4±0,43
		2	3,2±0,23*	2,7±0,25*	3,0±0,19*
		3	5,3±0,47**	4,1±0,44**	4,7±0,39**
	TGF-β1 ng/ml	1	58,4±5,3	53,4±4,8	55,9±3,4
		2	33,9±3,1*	29,4±2,5*	31,7±2,1*
		3	53,1±4,7**	46,0±4,7**	50,0±0,42**

Note: 1 – control group; 2 – patients with chronic conjunctivitis before the treatment;
3 – patients with chronic conjunctivitis after the treatment
*- values significantly different from those of the control group.
**- significantly different values before the treatment to values after the treatment.

At the same time, in girls of the same group, the results of this indicator after the treatment were equal to 86% relative to the control group and significantly higher than the results before the treatment, amounting to 64% relatively to the control group. These modifications demonstrate that the results of exposure to immunomodulators were not significantly higher in boys than in girls. Taking into account the average values of boys and girls, the IL-10 indicator before the treatment was 67%, and after the treatment - 92% relatively to the control group, and the differences were statistically significant.

According to the results of the study of TGF-β1 in boys from 7 to 9 years old with tuberculosis and with chronic conjunctivitis at the same time, after the treatment with immunomodulators, this figure was 89% relative to the control group. Whereas the indicator before the treatment was only 60% relative to the control. The average values for the group of boys with chronic conjunctivitis demonstrate a significant increase under the influence of immunomodulators. At the same time, in girls in this group, the dynamics of TGF-β1 indicators before and after the treatment were similar to the changes in indicators in boys. The rate before the treatment was 52% relative to the control, and after the treatment - 77%. The average value after the treatment was significantly higher than before the treatment with immunomodulators, while the result of the increase was not significantly lower than in boys. According to the results of average TGF-β1 levels in boys and girls, their level after the treatment was 83%, and before the treatment - 56%, relative to the control group (Table 1).

In studies conducted in children aged 10 to 14 years, it was found that in boys of this group of tuberculosis patients with chronic conjunctivitis, TNF-α levels in the tear fluid before the treatment were significantly higher in comparison with boys of the same age without chronic conjunctivitis. After the treatment with immunomodulators, the indicators decreased significantly, but remained statistically insignificantly higher than in boys without chronic conjunctivitis. The ratio of TNF-α after the treatment to that of the control group was 109%. Whereas the ratio of the indicator before the treatment to the control group was 168%. The presented modifications indicate a significant decrease in TNF-α in children aged 10 to 14 years with tuberculosis and chronic conjunctivitis under the influence of treatment with immunomodulators.

At the same time, in girls of the same group, the results of TNF-α after the treatment with immunomodulators in relation to similar data without conjunctivitis were higher and amounted to 131%. The average TNF-α level in the group of patients with conjunctivitis before the treatment was significantly higher than in the control group and their ratio was 186%. These changes show that the TNF-α value increased more significantly in girls compared to boys, and the degree of influence of immunomodulators on this indicator was significantly greater. When taking into account the average values of TNF-α in both sexes, the value after the treatment was 178%, and before the treatment - 122% relatively to the control group.

It was revealed that in boys with chronic conjunctivitis suffering from tuberculosis aged 10-14 years, the level of IL-10 before the treatment was significantly lower than in children without chronic conjunctivitis and their ratio was 52%. After the treatment with immunomodulators, the rate increased almost to the control level and their ratio was 94%. Also, the IL-10 indicator after the treatment became significantly higher than the same indicator before the treatment, their ratio corresponded to 55%. These changes show that under the influence of immunomodulators in boys 10-14 years old with tuberculosis and chronic conjunctivitis, there was a significant increase in IL-10 in the tear fluid.

At the same time, in girls of the same group, the IL-10 values after the treatment were 82% relative to the control group, this was significantly higher than before the treatment, and the ratio of values before and after the treatment was 46%. These data indicate that the effects of immunomodulators were not significantly greater in boys than in girls. The overall indicators for the group of boys and girls together after the treatment were slightly lower than the control group and amounted to 89%, whereas before the treatment the indicator was significantly lower and the ratio was 56% (Table 1).

In children aged 10 to 14 years with tuberculosis and with chronic conjunctivitis, the study of TGF-β1 found out that in boys before the treatment the average rate was 54% compared to boys without chronic conjunctivitis. After the treatment with immunomodulators, this indicator compared to the results before the treatment became significantly higher and amounted to 181%. Its level approached the level of the control group, and the ratio was 98%. These changes show that under the influence of immunomodulators there is a significant increase in TGF-β1 in boys 10-14 years old with tuberculosis and chronic conjunctivitis. Along with this, in girls of this group, the TGF-β1 indicator after the treatment relative to the control group was equal to 86%, which was significantly higher than the level before the treatment, which was 49% relative to the control. It should be noted that the scores for girls were not significantly lower than for boys. According to the results of the average TGF-β1 values of both sexes, the indicator after the treatment was 92% relative to the control group, it was significantly higher than the indicator before the treatment, which was 52% relative to the control (Table 1).

A study of TNF-α indicators in boys with tuberculosis with chronic conjunctivitis aged 15-17 years found out that the indicators after the treatment with immunomodulators were not significantly higher than the same indicators in boys without chronic conjunctivitis. Before the treatment, the level of TNF-α was significantly higher than the level of the control group, their ratio was 160%. After the treatment with immunomodulators, the average indicator for the group decreased significantly, the ratio between indicators before and after the treatment was 70%. These results demonstrate a significant decrease in TNF-α in boys 15-17 years old with tuberculosis and chronic conjunctivitis under the influence of immunomodulators.

In girls of the same age group with chronic conjunctivitis, TNF-α values before the treatment were significantly higher compared to girls without chronic conjunctivitis, their ratio was 176%. The average indicator after the treatment with immunomodulators in relation to similar indicators for girls without chronic conjunctivitis was not significantly higher, their ratio was 134%. Compared with the indicator before the treatment, the level of TNF-α significantly decreased and their ratio was 76%. These changes show that in boys the level of TNF-α decreased more significantly compared to girls and therefore the effect of immunomodulators on this indicator was not significantly greater. Taking into account the average TNF-α values of both sexes, the ratio of the result before the treatment to the result of the control group was equal to 166%; after the treatment, the level decreased significantly relative to the level before the treatment, their ratio was 73% (Table 1).

Along with this, the results of IL-10 in boys from 15 to 17 years old with chronic conjunctivitis ill with tuberculosis, the results after the treatment with immunomodulators were at the level of 93% relative to boys without chronic conjunctivitis. This indicator was significantly higher than the same indicator before the treatment, their ratio was 166%. These changes demonstrate that the effect of immunomodulators in boys aged 15 to 17 years with tuberculosis and chronic conjunctivitis was expressed in the significant increase in IL-10 in the tear fluid.

At the same time, in girls of the same group, the value of IL-10 after the treatment was 81% relatively to the control group, and before the treatment - 53%. Judging by these results, it is clear that boys, as a result of the use of immunomodulators, had significantly higher rates than girls. When calculating the average IL-10 values for both sexes, it was found that after the treatment the levels increased to 87% relative to the control group, while before the treatment the ratio was 55%.

In boys with tuberculosis with chronic conjunctivitis aged 15-17 years who were treated with immunomodulators, TGF-β1 was 91% relative to the control group and was significantly higher compared to the results before the treatment, the ratio of which to the control group was 58%. These results show that under the influence of immunomodulators there is a significant increase in TGF-β1 in boys aged 15-17 years with tuberculosis and chronic conjunctivitis. Meanwhile, in girls of this group, the ratio of the TGF-β1 indicator after the treatment to that of the control group was equal to 86%, and in relation to the results before the treatment, the ratio of which to the control was 55%, was significantly higher, and the result of the increase was not significantly lower than boys. When taking into account the average values of TGF-β1 in both sexes, the ratio of the level after the treatment to the control level was 89%, this was significantly higher than before the treatment, the ratio of which to the control was 57% (Table 1).

4. Conclusion

The presented data allow us to conclude that the use of immunomodulators in children with tuberculosis and chronic conjunctivitis contributes to changes in the levels of pro- and anti-inflammatory interleukins. The levels of pro-inflammatory interleukin TNF-α in the tear fluid of children suffering from chronic conjunctivitis decreased under the influence of immunomodulators, while the anti-inflammatory interleukins IL-10 and TGF-β1 increased. It should be noted that significant changes in interleukins were observed in children starting from the age of 7 years. It is noteworthy that higher indicators, as well as pronounced changes in indicators, were observed in boys compared to girls.

The use of immunomodulators in children and adolescents with tuberculosis and chronic conjunctivitis helps to normalize interleukin status, which reduces the local inflammatory process in the eyes. Accordingly, it helps to improve the clinical condition and speedy cure of chronic conjunctivitis.

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