**Biomarkers of biological therapy inefficiency in children with inflammatory bowel diseases.**

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Background and aim

In the children with inflammatory bowel disease (IBD) who are treated with antibodies blocking TNFα (infliximab – IFX) there is seen a loss of a therapeutic response after a year of treatment in 50% of patients. Our objective is to identify the value of the various biological markers such as residual level of IFX in blood, antibodies to the drug and circulating cytokine levels in the prognosis of the effectiveness of the biological therapy in children with IBD.

Methods

In total 75 children with IBD at the age of 4-18 years who are treated with IFX therapy were included in the study: 31 patients with ulcerative colitis (UC) and 44 patients with Crohn's disease (CD). Clinical response was evaluated using PUCAI (UC) and PCDIA (CD) indices. Blood samples were taken 8 weeks after the last infusion of IFX therapy. Residual levels of IFX (Q-IFX) in serum and IFX antibodies (ATI) were assessed by enzyme immunoassay using Shikari Q-INFLIXI, Q-ATI (Turkey) kits. The levels of cytokines (GM-CSF, CCL20/MIP3a, IL-22, IL-23, IL-27, IL-28A, IL-31, IL-4, IL-17E/IL-25, TNFb, INFγ, IL-10, IL-12, IL-13, IL-15, IL-17A, IL-17F, IL-1b, IL-21, IL-33, IL-5, IL-6, IL-12p70, IL-9, IL-2, TNFα) were measured by multiplex analysis using HumanTh17 MagneticBead Panel (MilliplexMapKit, Germany). Evaluation of the statistical significance was performed using nonparametric Mann-Whitney test and ROC-analysis.

Results

In children with the loss of the effect to IFX (group 1) there was a significant decrease Q-IFX compared to a group of children with persistent positive effect (group 2) in both diseases CD (p=0.002) and UC (p=0.019). We observed increase in the inflammatory processes according to PUCAI and PCDIA indices (p=0.000) in children with the loss of response to IFX. ROC analysis showed that the cut-off level for patients with UC is 2.55 µg/ml (AUC=0.813; sensitivity (Se) 64%, specificity (Sp) 92%), and for children with CD - 2.21 µg/ml (AUC=0.813; Se 79%, Sp 78%). In the examined patients ATI were educed in 17% cases, while the faster the formation of ATI was correlated to the younger age of children (R=0.58). Analysis of cytokine profile revealed significant differences between examined groups in the level of proinflammatory cytokines: IL-23, IL-27, IL-22, INF-γ, TNFα. For group 1 the median values of these cytokines (pg/ml) were: IL-23 – 2.2 [0.7;6.3]; IL-27 – 0.65 [0.51;0.93], IL-22 – 0.07 [0.03;0.58], INFγ –30.3 [10.3;38.6], TNFα –36.1 [5.5;53.6]. ROC analysis revealed good quality of the separation model for TNFα, the cut-off level was 13.4 pg/ml (AUC=0.843; Se 77%, Sp 79%).

Conclusions

We have found that the reduction of the Q-IFX in children with UC below 2.55 µg/ml and in children with CD below 2.21 µg/ml, leads to the loss of the therapy effect and can indirectly cause exacerbation of the disease. These findings correlate with the results obtained in adults (>2 µg/ml, C. Moore at all, 2016). TNFα level (>13.4 pg/ml) can act as a biomarker of loss of effect from IFX. Elevated levels of proinflammatory cytokines correlates with the lower Q-IFX and loss of the therapy effect. Young children require regular control of the residual level of IFX and antibodies for a timely corrective therapy.