SUMMARY

Crohn's disease (CD) is a severe autoimmune disorder with unknown etiology. Up to date, biological therapy is the most effective form of treatment, however it is not free of drawbacks. About 40% of patients are not able to respond to the initial therapy, which is a phenomenon of unknown mechanism, described as primary nonresponse. Recognition of the lack of response mechanism is pivotal for identification of pharmacogenetic markers enabling patients' response prediction which may contribute to the personalized medicine development.

The main goal of the doctoral dissertation was to identify variants of genes affecting patients' response to anti-TNF mAbs in Polish population. Group of 107 CD patients (with 12 primary nonresponders) was investigated. Based on NGS technology, pharmacogenetic panel of 23 genes involved in TNFα action was selected. Patients' nonresponse was associated with 11 *loci* in 5 genes: *FCGR3A, TNFRSF1B, FAS, IL1B* and *IL1R.* These genes code for proteins involved in apoptosis. Different genetic polymorphisms may contribute to the lack of response since one of a potential mechanisms of nonresponse is T cells insensitivity for apoptotic factors. Among identified changes, potentially functional exonic and 3'-UTR variants occurred. Gene expression comparison in intestinal biopsies enabled to identify significant changes in mRNA expression level of genes of interest between nonresponders, responders and healthy individuals. Based on that, assumption that nonresponse is a consequence of a different T cells apoptosis sensitivity triggered by anti-TNF mAbs was raised. However, T cells treatment with anti-TNF did not show any significant differences between nonresponders, responders and healthy individuals, schematic changes in mRNA gene expression level was observed. In two apoptotic genes, *TNFRSF1B* and *FAS*, also in *FCGR3A* gene coding for crucial ADCC receptor, the same pattern of changes occurred. In control group anti-TNF mAbs induced increment of aforementioned genes, in the case of responding patients no significant change was observed and nonresponding patients showed significant downregulation of these three targets when compared to nontreated control cells.

Obtained results did not provide unequivocal answer whether analyzed genes, their activity and its disturbances may contribute to the efficacy of biological treatment in primary nonresponders. However, they indicate valuable direction of studies investigating mechanism of anti-TNF mAbs action and identification of predictive markers, strongly demand in clinical practice and personalized medicine development.