Detection of anti-infliximab antibodies in Slovak IBD patients and its costs saving effect

Štefan Raffáč [1,5], Laura Gombošová [2], Juliana Gabzdilová [3], Lucia Novotná [1], Katarína Šajtyová [2], Tímea Pekárová [2], Ivan Kopolovets [4], Štefan Tóth [2]

1 Department of laboratory medicine, Louis Pasteur University Hospital, Košice, Slovakia
2 1st. Department of Internal Medicine, and Louis Pasteur University Hospital, Slovakia
3 Department of hematology and oncohematology, Louis Pasteur University Hospital, Košice, Slovakia
4 Department of Vascular Surgery, East Slovak Institute of Cardiovascular Disease, Košice, Slovakia
5 Institute for Healthcare Disciplines, St. Elizabeth University, Bratislava, Slovakia

Correspondence to:	Štefan Tóth, MD., PhD., MBA
	1st Department of Internal Medicine, and Louis Pasteur University Hospital,
	Trieda SNP 1, 041 90 Košice, Slovakia.
	E-MAIL: stefan.toth@upjs.sk

ORIGINAL ARTICLE

Abstract

OBJECTIVE: Management chronic inflammatory bowel disease (IBD) patients is associated with diagnosis, targeted treatment and and individual approach. There is a group of patients which loss the response to the biologic treatment caused by insufficient levels of biologics or positive antibodies against these drugs. This study was aimed to determine the prevalence of patients with positive antibodies against the biological treatment and the costs saving probabilities of the antibodies detection during the treatment.

STUDY DESIGN: This retrospective study was based on examination of 183 IBD patients' sera (72 with Crohn's disease (CD) and 111 ulcerative colitis (UC)) treated with infiliximab. Methods: Circulating serum infliximab concentrations and anti-infliximab antibodies (ATI) were quantified by ELISA methods. Costs associated with the treatment were analysed from the data of General Health Insurance Company, Slovakia.

RESULTS: The average infliximab concentrations in groups of CD were 2.9 µg/mL, 38.9% of samples had a concentration ≤1 µg/mL. Group with UC had average infliximab levels of 3.19 µg/mL, 32.4% bellow ≤1 µg/mL. Positive ATI levels were detected in 52 patients, in 28 patients with CD (38.8%) and 24 patients with UC (21.6%). The average values of the antibodies were 387.75 U/ml in CD and 391.94 U/ml in UC group. More than 28% IBD patients were positive for ATI. After application of the results to the database of all IBD patients, finishing of the treatment with ATI could lead (after considering the ATI quantification costs) to possible annual savings of more than €2 million in Slovakian health-care system.

CONCLUSION: Monitoring of infliximab and antibodies against infliximab and anti-TNF-α biologics may help optimize treatment strategies and costs for biological treatment.

Štefan Raffáč, Laura Gombošová, Juliana Gabzdilová, Lucia Novotná, Katarína Šajtyová, Tímea Pekárová, Ivan Kopolovets, Štefan Tóth

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) belong to the group of autoimmune-mediated inflammatory diseases, which are known as Inflammatory Bowel Disease (IBD). Patients with the diagnosis of IBD must face a long-term medical therapy and even surgical interventions. CD is associated with a high mortality at the early stages of the disease, in contrast to the UC. Patients can spend a long time in silent, asymptomatic period depending mainly on the severity of the disease, the type of medication and other individual characteristics. Moreover, there is a risk of developing intestinal and extra-intestinal malignancies, extraintestinal arthropathy or other systematic manifestation if IBD (Cohen 2010). For all the above reasons, the direct health care costs of patients with UC and CD put increased demands on the resources of the national health systems. Moreover, there is heavy burden in terms of indirect medical costs, reducing productivity and increasing disability.

Infliximab (IFX) as a monoclonal antibody against TNFα (anti-TNFα) have meant revolution in the treatment for more than half of patients who have not responded to standard treatments. IFX has been introduced into therapeutic regimens for earlier stages in the belief to avoid the side effects of steroids, surgical intervention, and the development of resistant disease. Use of maintenance treatment reduced the need for hospitalization and the need for surgical procedures. Since the biological treatment is highly costly, it appears necessary to monitor their impact on short- and long-term health care costs in these patients (Lennard-Jones 1989; Bernstein et al. 2000).

Recent studies have shown that the costs of patients with CD were significantly influenced by the genotype and phenotype. In a cohort of 418 patients with CD and 10-year follow-up, overall health care costs according to the Montreal classification, taking into account the progress and behaviour disorders, were € 1,690 for illness without strictures and without penetration, € 2,081 for stage with formation of strictures, € 3,133 for penetrating disease and € 3,356 for penetrating form with the formation of perianal fistulas. All values are expressed as the mean price / phenotype of the patient / year. Expenses of surgical procedures of above listed phenotypes were € 215; € 751; € 1,293 and € 1,275 / phenotype of the patient / year (Riis et al. 2007; Economou et al. 2004).

Overall, 2–40% of patients lost the response to treatment, it is about 13% of patients each year (Arseneau et al. 2001; Lindsay et al. 2008). There are non-immunological and immunological factors associated with loss of the response. The non-immunological factors include a complication of diseases such as intercurrent infection, smoking in Crohn's disease, stress, drug interaction with other drugs. Immunological factors are: high activity of the disease with a massive production of TNF-α antibody to biologics, paradox exacerbation of autoimmune disease during the biological treatment, the shift of TNF-α on the other mediators of inflammation (cytokines) under chronic inflammatory disease, autoantibody formation and aggregation of the rheumatoid factor (Saro et al. 2007; Steenholdt et al. 2011). Monitoring of anti-TNFα agents, and antibodies directed against them (antibodies to infliximab – ATI) may help to explain the loss of response to treatment, reduce redundant health-care costs and help in the further management of the patient.

The aim of this study was to determine the average circulating levels of anti-TNFα agents, and antibodies directed against in patients with IBD and calculate the healthcare costs associated with the loss of response to the treatment.

METHODS

Study design

This study was designed as a retrospective study aimed to determine the mean levels of IFX and antibodies to IFX (ATI) in 183 IBD patients receiving a biological anti-TNFα therapy. The group consisted of 72 patients with CD and 111 patients with UC. All patients had initial induction regimen of 5 mg/kg administered on week 0 – 2 – 6 and continued to maintenance regimen of 5 mg/kg every 8 weeks. Blood samples were collected up to the end of the induction treatment, it means before the first maintenance therapy and later.

Preanalytical phase

Blood samples were collected on departments and in outpatient clinics of Louis Pasteur University Hospital. Blood was withdrawn from the antecubital vein under standard conditions, after at least 12 hours of starvation, early in the morning until 8 a.m. For detection of ATI, blood samples were taken into the test tubes containing heparin. Strongly lipemic, icteric and haemolytic samples were excluded. The samples were kept in cold during the transfer and processing. Serum samples were stored at –20° C until the analysis (for not longer than 1 month). It is necessary to realize sampling plan prior to infusion or another option is taking it at least two weeks after the IFX application. All patients, which were included in this study, agreed by their own free will with the standard examination of blood samples and signed an informed consent. Samples were taken as a standard blood examination; no redundant samples were taken from the patients.

Measure the plasma levels of IFX and ATI

Blood samples were processed and analysed at the Department of laboratory medicine, Louis Pasteur University Hospital. ATI and IFX levels were examined by standardized ELISA kit infliximab-Q and Q-ATI (Matriks Biotek ELISA). Samples were analysed by automatic analyser Dayton (company RANDOX) by

spectrophotometric method at a wavelength of 450 nm. The concentrations of antibodies to infliximab (ATI) in the samples were read directly from the standard curve established using special software REVELATION. Samples that reached a higher concentration than the concentration of ATI in highest standards were diluted and re-tested repeatedly.

Investigation of cost-effectiveness of IBD treatment

We used data from the General Health Insurance Company (General Health Insurance Company, VšZP) from year 2011. The amount of all IBD patients and the costs of the treatment was based on this database. Cost associated with quitting the treatment after detection of positive ATI were calculated based on their treatment expenses. Additionally, we evaluated the cost associated with the quantification of ATI (standard market price of ATI ELISA kits and costs of the examination).

RESULTS

Circulating levels of IFX and ATI

In the CD group, the average age was 34 years and the average number of infliximab applications was 8. In the UC group, the mean age was 42 years and the average number of applications was 8 (Table 1).

Our findings showed that the average level of the IFX in group with CD was 2.91 µg/ml. The average levels of the IFX was 3.19 µg/ml in UC group. In the CD group, 38.9% of all patients had a concentration ≤1 µg/mL, in UC group 32.4%. Positive ATI levels were detected in 52 patients, in 28 patients with CD and 24 patients with UC. Their average values of the antibodies were 387.75 U/ml in the group with CD and 391.94 U/ml in the UC groups (Table 2, Figure 1). ATI positivity was proved in 28.42% of all patients with IBD. The prevalence of ATI positivity was significantly higher in patients with CD *vs.* UC (38.8% *vs.* 21.6%).

Investigation of IFX and ATI levels in terms of cost-effectiveness of IBD treatment

In terms of cost-effectiveness of the treatment, data from the General Health Insurance Company (General Health Insurance Company, VšZP) in 2011 on the costs for biological treatment of anti-TNF α in patients with IBD were used. The cost reached in that year level of €7,676,469. In 2011, the proportion of policyholders in VšZP was 65.80% it means 3,572,784 insured persons. According statistical analysis Crohn's disease was presented in 1,688 patients and ulcerative colitis and 3,189 patients, making a total of 4,877 policyholders of VšZP. It follows that the expected cost per patient with IBD treated with infliximab in year 2011 could represent €1,574. According to the information of the General Health Insurance Company and the results of our study group, the cost of 1 year of biological treatment in patients with positive antibody to infliximab (ATI) – 28.42% of patients – is 2181; €652.4.

**Tab. 1.** Characteristic of analyzed group of patients.

	Crohn's disease	Ulcerative colitis
Number of patients	72	111
Average age (years)	34	42
Average infliximab applications	8	8

Tab. 2. Average level of the infliximab (IFX) and the ATI (antibody to infliximab) in group of patients with Crohn's disease (CD) and ulcerative colitis (UC).

	Crohn's disease (*n=72*)	Ulcerative colitis (*n=111*)
The level of IFX (µg/ml)	2.91	3.19
	(0.00–31.5)	(0.00–52.28)
Negativity of the ATI	44 patients	87 patients
	61.11%	78.38%
Positivity of the ATI	28 patients **38.8%**	24 patients **21.6%.**
The level of the ATI (U/ml)	387.75	391.94
	(33.5–1 930.4)	(27.4–1 968.0)

Tab. 3. Possible economic impact of the ATI and IFX quantification (our data together with free data of VšZP – General Health Insurance Company).

Number of policyholders in the General Health Insurance Company (VšZP) with IBD (CD and UC)	4 877
Costs of infliximab in year 2011	7 676 469,00 €
-costs per 1patient	1 574.00 €
Positivity of ATI	1 386 pat.
Saving of finishing of treatment, when ATI are positive / year	2 181 564.00 €
Cost of one examination of IFX and ATI	24.60 €
Total costs of examinations for all palicyholders of (4 877 patients) of VšZP	119 974.20 €
Total saving per one year	2 061 589.80 €
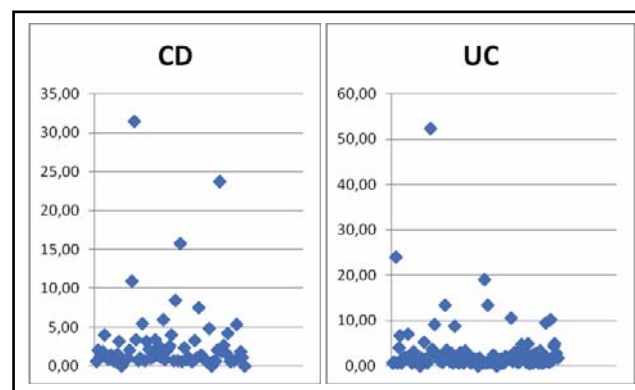
Fig. 1. Distribution of the infliximab levels in patient with Crohn's disease (CD) and ulcerative colitis (UC).

After application of the results of our different groups, should be presence of positive antibodies to infliximab in 1386 patients. At an estimated annual average cost for biological treatment – €1574/patient/year, finishing of the treatment with ATI could lead to possible annual savings of more than €2 million.

Costs associated with the examinations of IFX levels and ATI by ELISA amounted to €5,596.8. Cost of 1 Kit for detection of IFX and ATI is €932.80. We consumed a total of 6 kits. The total cost of testing one sample for IFX and ATI is €12.30, which is negligible amount, from the perspective of potential savings with the effective administration of biological therapy (Table 3).

DISCUSSION

Biological therapy represents a significant advance in the treatment of non-specific chronic intestinal inflammation. A key cytokine in the inflammation cascade of IBD is TNF-α, which is also the target of biological treatment. The most experiences are available with anti-TNFα drug – infliximab, which is in clinical use since 1999. The benefits of keeping patients in remission include a significant decline in the number of hospitalizations and surgical treatment and consequent reduction in healthcare costs in patients with UC and CD (Steenholdt et al. 2011). Development of new biological therapies for CD and UC, as these drugs have significantly improved the treatment of these diseases, but increased also the costs of treatment. Monitoring of biological therapy and antibodies could be reflected in the optimization of the cost of health insurance for biological treatment. These endpoints are interesting in economic terms, especially due to the large number of patients treated with monoclonal antibodies, that are widely used not only in gastroenterology but also in other medical fields. This study was aimed to determine the prevalence of IBD patients, which produce ATI or have decreased circulating IFX and because of these conditions they do not achieve proper clinical results.

Possibility of monitoring the levels of IFX and ATI, in recent years contributes to the individualisation of access to the patient. In monitoring levels of IFX, pharmacokinetics and pharmacodynamics are still many uncertainties. When assessing the levels of IFX and ATI is necessary to consider the large inter- as well as intra-individual variations, false positive and false negativity results. By measuring the levels of IFX or the presence of ATI shows the possibility to adjust the treatment in terms of dose escalation and shortening the interval of IFX, changing one anti-TNF α modality to another and thus justified to continue the treatment or it eventually stopped. If a patient has during treatment with biological severe allergic reaction, it is possible to support further decisions to continue the treatment by the results of monitoring IFX and ATI (Kaplan et al. 2007).

Scandinavian research results present the lowest level of IFX in which is anti-TNF α treatment effective. The findings show that the levels of IFX 0.5 g/ml and the levels of antibodies to infliximab (ATI) to 10 U/ml are effective (sensitivity 81%, specificity 94%). IFX levels> 0.5 mg / ml as compared to the undetectable are associated with a significantly higher clinical remission (69 vs. 28%, $p<0.01$). The effectiveness of the drug decreases significantly with decrease the level of the IFX under 1μg/ ml (Economou et al. 2004). The prevalence in our study of these patients was 38.9% in CD group and 32.4% in UC. These groups of patients could benefit from increase of the applied IFX dosage. These results also show the need to make further studies and information that would specify the role of monitoring the levels of anti-TNF α drugs and their antibodies in the management of patients with IBD (Afif et al. 2010).

In the Slovak Republic, the prevalence of Crohn's disease is 47.24/100,000 inhabitants, the prevalence of ulcerative colitis is 89.26/100,000 inhabitants (Gregus 2014). When the number of inhabitants of the Slovak Republic is 5,429,763 in the last census in the 2010, it can be assumed approximate number of patients with these diseases: Crohn's disease: 2,565 inhabitants and Ulcerative colitis: 4,847 inhabitants.

Based on our results and in accordance with literature data analysed detection of level of IFX and positivity ATI, we can assume impact of positive antibody to infliximab on insufficient efficacy of the biological treatment. In the analysed group of 183 patients with IBD treated with IFX, the presence of positive ATI was confirmed in 52 patients (28.42%). From economic point of view ATI presence appears to be an interesting factor in the group of patients with IBD treated with expensive biological therapies. Because, as mentioned above, ATI positivity and level of infliximab correlate with inflammatory activity of the underlying disease and are reflected in the lack of efficacy of treatment. Based on the available information of infliximab costs given by the General Health Insurance Company, investigation of IFX levels and the presence of ATI represents an important economical and cost-saving strategy. This strategy could lead to the allocation of a group of patients where it is necessary to change the treatment strategy of underlying disease. These findings are confirmed the results of the recently published study of Roblin et al. (2015), which assesses the 5-year follow-up of patients with IBD, who have lost response to biological treatment with anti-TNF preparation. Study compares two large cohorts of patients with CD. Patients were either managed by strategy of following the level of anti-TNF α drugs (adalimumab –ADA, IFX) and setting the monoclonal antibody anti-TNF α or by empirical escalation by therapeutic protocols for CD. The main objective was to compare the costs of anti-TNFα treatment in these two groups. This study confirmed the savings and a cost-effectiveness of the model based on results of diagnostic methods (monitoring levels of antibodies against anti TNF-α preparation). These costs amounted to savings of €131,300,293

an average of €13,130/patient and saving 24.5% of the total cost over five years. Direct costs for testing levels of anti-TNFα drugs and their antibodies did not affect significantly the results, because the price of laboratory tests did not exceed €2,000 (Roblin et al. 2015). These observations could also confirm our results, in which we could highlight significant savings in Slovak health care system by the personalized approach in the treatment of IBD.

CONCLUSION

Biological treatment represents a significant advance in the treatment of inflammatory bowel diseases. It is currently affected by the economic aspect of the possible termination or de-escalation of biological treatment. Linked to this is the need to include monitoring of serum level of IFX respectively antibody to infliximab ATI. This appear to be beneficial in view of the next therapeutic approach. De-escalation strategy, the termination or continuation, or changing of the biological treatment appears economically interesting and can lead to saving of costs associated with treatment of IBD. In this context, the need to stand out even more precise criteria and guidelines to determine the de-escalation of biological treatment, as in the case of inadequate interrupting of biological treatment occurs multiple overpriced of treatment of IBD patients due to increased costs for re-hospitalization and surgical interventions in relapsed patients. There is an emerging need for larger studies designed specifically to be able to proceed conclusions based on evidence and national recommendations.

REFERENCES

1 Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, Sandborn WJ (2010). Clinical Utility of Measuring Infliximab and Human Anti-Chimeric Antibody Concentrations in patients With Inflammatory Bowel Disease. Am J Gastroenterol. **105**: 1133–1139.
2 Arseneau KO, Cohn SM, Cominelli F, Connors AF Jr. (2001) Cost-utility of initial medical management for Chrohn`s disease perianal fistulae. Gastroenterology. **120**: 1640–1656.
3 Bernstein CN, Papineau N, Zajaczkowski J, Rawsthorne P, Okrusko G, Blanchard JF (2000). Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. Am. J. Gastroenterol. **95**: 677–683.
4 Cohen RD (2010). The pharmacoeconomics of biologic therapy for IBD. Nat Rev Gastroenterol Hepatol. **7**: 103–109.
5 Economou M, Trikalinos TA, Loizou KT, Tsianos EV, Ioannidis JP (2004). Differential effects of NOD2 variants on Crohn`s disease risk and phenotype in diverse populations: A metaanalysis. Am. J. Gastroenterol. **99**: 2393–2404.
6 Gregus M (2014). The incidence and prevalence of IBD in Slovakia. Oral presentation. Czech and Slovak IBD conference. Prague.
7 Kaplan GG, Hur C, Korzenik J, Sands BE (2007). Infliximab dose escalation vs. initiation of adalimumab for loss of response in Chrohn`s disease: A cost-effectiveness analysis. Aliment. Pharmacol. **26**: 1509–1520.
8 Lennard-Jones J (1989). Classification of Inflammatory bowel disease. In Scand. J. Gastroenterol. Suppl. **170**: 2–6.
9 Lindsay J, Punekar YS, Morris J, Chung-Faye G (2008). Health-economic analysis: Cost-effectiveness of schedule maintenance treatment with Infliximab for Crohn`s disease - modeling outcomes in active luminal and fistulisins disease in adults. Aliment. Pharmacol. Ther. **28**: 76–87.
10 Riis L, Vind I, Vermeire S, et al. (2007). The prevalence of genetic and serologic markers in an unselected european population-based cohort of IBD patients. Inflamm. Bowel Dis. **13**: 24–32.
11 Roblin X, Attar A, Lamure M, Savarieau B, Brunel P, Duru G, Peyrin-Biroulet L (2015). Cost savings of anti-TNF therapy using a test-based strategy versus an empirical dose escalation in Crohn's disease patients who lose response to infliximab. J Mark Access Health Policy. doi: 10.3402/jmahp.v3.29229. eCollection 2015.
12 Saro C, da la Coba C, Casado MA, Morales JM, Otero B (2007). Resource use in patients with Crohn`s disease treated with infliximab. Aliment Pharmacol Ther. **26**: 1313–1323.
13 Steenholdt C, Bendtzen K, Brynskov J, Thomsen OØ, Ainsworth MA (2011). Cut-off levels and diagnostic accuracy of infliximab trough levels and, anti-infliximab antibodies in Crohn`s disease. Scand J Gastroenterol. **43**: 310–318.