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THE IMPACT OF BIOLOGICAL THERAPY AND TOFACITINIB ON DISEASE´S ACTIVITY AND PATIENT´S DAILY LIFE IN PATIENTS WITH IBD

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Tulehduksellinen suolistosairaus (IBD) on krooninen autoimmuunitauti, joka vaihtelee rauhallisen vaiheen ja pahenemisvaiheiden välillä. IBD sisältää Crohnin taudin sekä haavaisen paksusuolitulehduksen. Nykypäivänä se on maailmanlaajuinen sairaus, jonka ilmaantuvuus on suurin länsimaissa ja ilmaantuvuus kasvaa Suomessa edelleen. Hoidon tavoitteena on saavuttaa endoskooppinen remissio ja ylläpitää sitä. Biologisia lääkkeitä ja tofasitinibiä käytetään kohtalaisessa tai vaikeassa taudinmuodossa ja silloin kun muu lääkehoito ei ole tarpeeksi tehokas tai siitä aiheutuu haittavaikutuksia. IBD-potilailla elämänlaatu on heikompi kuin terveellä väestöllä. Tärkeitä tekijöitä elämänlaadun parantamiseksi ovat taudin aktiivisuus ja pitkäkestoinen rauhallinen vaihe. Tämän tutkimuksen tarkoituksena oli selvittää, vaikuttavatko biologiset lääkkeet IBD:tä sairastavien potilaiden taudin aktiivisuuteen ja jokapäiväiseen elämään, ja siten elämänlaatuun.

Tutkimusaineisto kerättiin Pirkanmaan sairaanhoitopiirin IBD-potilaiden laaturekisteristeristä ja puuttuva informaatio potilasasiakirjoista. Rekisteristä kerättiin dataa esimerkiksi potilaiden lääkityksestä, taudin laajuudesta ja kaprotektiinista. Potilaat olivat pirkanmaalaisia, vähintään 18-vuotiaita ja heidän biologinen lääkitys tai tofasitinibi oli aloitettu syyskuun 2019 ja elokuun 2020 välisenä aikana. Tässä tutkimuksessa biologinen lääkitys tarkoittaa adalimumabia, infliksimabia, ustekinumabia ja vedolitsumabia. Rekisterin itsetäytettävien lomakkeiden avulla arvioitiin aktiviteetti-indeksi ja IBD:n vaikutus potilaiden jokapäiväiseen elämään.

Tutkimusaineisto sisälsi yhteensä 92 potilasta. Aktiviteetti-indeksi pieneni 62 (67 %), pysyi samana 14 (15 %) ja suureni 16 (17 %) potilaalla ($P < 0,05$). IBD:n vaikutus jokapäiväiseen elämään pieneni 60 (65 %), pysyi samana 20 (22 %) ja suureni 12 (13 %) potilaalla ($P < 0,05$). Tutkimus osoitti, että potilaiden aktiviteetti-indeksi ja IBD:n vaikutus jokapäiväiseen elämään väheni tilastollisesti merkitsevästi biologisen lääkityksen tai tofasitinibin myötä vaikuttaen siten positiivisesti potilaiden elämänlaatuun.

Avainsanat: Tulehduksellinen suolistosairaus, biologiset lääkkeet, tofasitinibi, elämänlaatu

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic idiopathic diseases which fluctuate between remission and relapses (1,2). The etiology of IBD is unclear but environment, microbiological flora in gut, genetic and immune defence plays role in the pathogenesis of the disease (3). This disorder consists Crohn´s disease (CD) and ulcerative colitis (UC). Location and extent varies in CD and UC. CD can be located in any part of the gastrointestinal tract and UC extents only from rectum to proximal colon. (4,5) The inflammation in CD is often transmural and in UC inflammation is in mucosa (1,2).

Today IBD is a global disease. The highest prevalence is in the western countries but incidence is also increasing in newly industrialized countries. (6) Finland has been a high-incidence country (7). Recent study by Kontola et al. shows that incidence is still increasing. In Finland between 2000 and 2020 the incidence in UC was 34,7 per 100 000 and in CD 13,4. (8)

The main treatment goal in IBD is to induce and maintain remission. Other goals are to avoid disability, colorectal cancer and surgery. (1,5) Biological therapy is relevant when disease is moderate to severe CD or UC or other medication are inefficient or the use is contraindicated because of the side-effect (2,4). Biological treatment consists anti-TNFα agents such as infliximab and adalimumab, anti-IL-12 and anti-IL-23-blocker ustekinumab and cell migration inhibitor vedolizumab (9). Tofacitinib is a JAK inhibitor used in moderate to severe UC (2).

IBD-patients have more anxiety and depression than healthy population. This disorder causes painful and stigmatic symptoms, fatigue, social isolation and fear of cancer or surgery. (10) Quality of Life (QoL) and health-related quality of life (HRQoL) have been decreased in IBD-patients (10,11). Important factors in HRQoL are activity of the disease

and a longterm remission. Biological medication improves significantly HRQoL in patients with IBD. There is disparity between different biologic medication. (11)

The aim of this study is to investigate how biological medications and tofacitinib affects in IBD-patient´s activity of the disease and influence of the IBD in the daily life. The hypothesis is that biological therapy and tofacitinib decrease activity of the disease and the effect in daily life and thus increase the quality of life in patients with IBD.

MATERIALS AND METHODS

Data collection

The study population consist of IBD-patients of Pirkanmaa Hospital district in Finland. In 2020 the background population was 518 703 inhabitants in Pirkanmaa which is about 9 % of the hole Finnish population. Material was collected from BCB IBD registry. There are 4 075 IBD-patients in the registry, which has information of patients and their IBD-treatment e.g. date of diagnosis, extent of the disease, endoscopic finding and medication. Medical records were used to gather missing information.

Patients included to this study were 18 years or older, biological therapy or tofacitinib started between September 2019 and August 2020. In this research biological therapy consists adalimumab, infliximab, ustekinumab and vedolizumab. Response to tofacitinib was also evaluated. There were no patients starting golimumab during study period. Based by the study of Puolanne et al. the symptom index and the patient-reported influence of the IBD in the daily life, measured by VAS, were assessed less than three months before therapy and three to six months after the beginning of the treatment.

Symptom index measures noninvasively activity of the disease. (12) Patient-reported influence of the IBD in daily life is measured by the severity and activity of symptoms. Scale of the symptom index is 0 to 15 and scale of the patient-reported influence of the IBD in the daily life is 0 to 7. The patient fills the questionnaires before medical infusions, nurse´s or doctor´s appointment. The correlation with symptom index and patient-reported influence of the IBD in daily life with other factors was also estimated. Other factors were medication, diagnosis, disease extent, smoking history, previous biological therapy or tofacitinib, year of diagnosis, year when symptoms started, extraintestinal manifestation, IBD in first-degree relative, gender and age. Feacal calprotectin value was evaluated no more than six months before and after the biological therapy or tofacitinib. Research frame is a cohort study.

Statistical analysis

Analysis were executed with SPSS statistic version 27. Wilcoxon signed-ranks test were used to estimate the benefit of biological therapy and tofacitinib. Chi-Square test, T-test and Mann-Whitney test evaluated correlation with other factors.

RESULTS

In total 92 patients started biological therapy or tofacitinib between September 2019 and August 2020. Demographic data is shown in table 1. In 62 (67 %) patients the symptom index was lower than before receiving the medication. In 16 (17 %) patients there were no change in symptom index and in 14 (15 %) patients the symptom index was higher than before the therapy ($P < 0,005$) (figure 1). In 60 (65 %) patients the patient-reported influence of the IBD in the daily life was lower than before the treatment, in 20 (22 %)

patients there were no change in patient-reported influence of the IBD in the daily life and in 12 (13 %) patients the patient-reported influence of the IBD in the daily life was higher after the medication (P < 0,005) (figure 2). Median of the symptom index before the medication was 5,00 (95 % CI 4,10–5,40) and after the medication it was 1,00 (95 % CI 1,54–2,49). Median of the patient-reported influence of the IBD in the daily life was 4,00 (95 % CI 3,34–4,21) before the medication and 1,00 (95 % CI 1,81–2,61) after the medication.

Statistically significant correlation was found in estimating correlation of each medication with symptom index. There was observed that 20 (71%) got benefit from using infliximab, 31 (78 %) from vedolizumab, ustekinumab or tofacitinib and 11 (46 %) from adalimumab (P < 0,05) (figure 3). No benefit from medication got 8 (27 %) patients from using infliximab, 9 (33 %) from vedolizumab, ustekinumab or tofacitinib and 13 (54 %) from adalimumab. Figure 4 shows the change of the symptom index after the treatment in each medication (P > 0,05).

DISCUSSION

Main goal of this study is to asses does therapy and tofacitinib improve the clinical outcome and impact of IBD in patients´ lives. This study showed that biological therapy and tofacitinib statistically improve symptom index and patient-reported influence of the IBD in daily life and that way quality of life in patients with IBD. Compared to study by Vogelaar et al. we found differences in symptom index in various biological therapies and tofacitinb. Vogelaar L et al. found that both adalimumab and infliximab improved HRQoF, but adalimumab was better than infliximab. (11) Un like the study by Vogelaar et al. we observed that adalimumab had the weakest response in our study. In our study only 46 % patients benefit from using adalimumab. Burisch J et al. discovered that HRQoL was better using biological treatment in patients with CD than UC. They found that HRQoL in patients

with UC did not significantly get better after the treatment. (13) We did not find statistically significant differences between CD and UC.

The strenght of this study was that material of this research was a real-life data. BCB medical registry consists all IBD-patients in Pirkanmaa hospital district. This is population-based cohort.

Often patients use glucocorticoid treatment to treat relapsies which may have impact on the results. There was also variation how often questionnaire was filled. Some patients had many filled questionnaires and some had only two necessary ones.

Limitations of the study was small material size. We had all information of the symptom index and patient-reported influence of the IBD in daily life but some part of the other information such as diagnosis, extent and smoking habits were insufficient. That could have been affecting the results and may explain why we did not find statistically significant correlation with other factors. Frame of the study was retrospective and it was single-center trial.

This study showed that the biological therapy and tofacitinib improve life in patients with IBD. This study also suggest that adalimumab may be inefficient compared to other biological medication and tofacitinib.

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Table 1. Demographic information of the patients.

Diagnosis		
	UC no. (%)	52 (57)
	CD no. (%)	37 (40)
	IBDU no. (%)	3 (3)
Montreal classification of extent		
	E2 no. (%)	9 (17)
	E3 no. (%)	44 (83)
	L1 no. (%)	8 (24)
	L2 no. (%)	7 (21)
	L3 no. (%)	19 (56)
Biological treatment		
	Adalimumab no. (%)	24 (26)
	Infliximab no. (%)	28 (30)
	Ustekinumab no. (%)	9 (10)
	Vedolizumab no. (%)	17 (18)
	Tofacitinib no. (%)	14 (15)
	The first biological therapy or tofacitinib no. (%)	52 (57)
	The second biological therapy or tofacitinib no. (%)	26 (28)
Calprotectin		
	Before treatment	2367±1731,7
	After treatment	699±1006,0
Smoking		
	UC no smoking no. (%)	39 (80)
	UC smoking no. (%)	1 (2)
	CD no smoking no. (%)	17 (49)
	CD smoking no. (%)	8 (23)
Other		
	Male sex no. (%)	55 (60)
	Age yr.	40±14,2
	Extraintestinal manifestation no. (%)	25 (27)
	IBD in first-degree relative no. (%)	14 (19)
	IBD diagnose year	2011±8,5
	Year when the symptoms started	2011±8,3

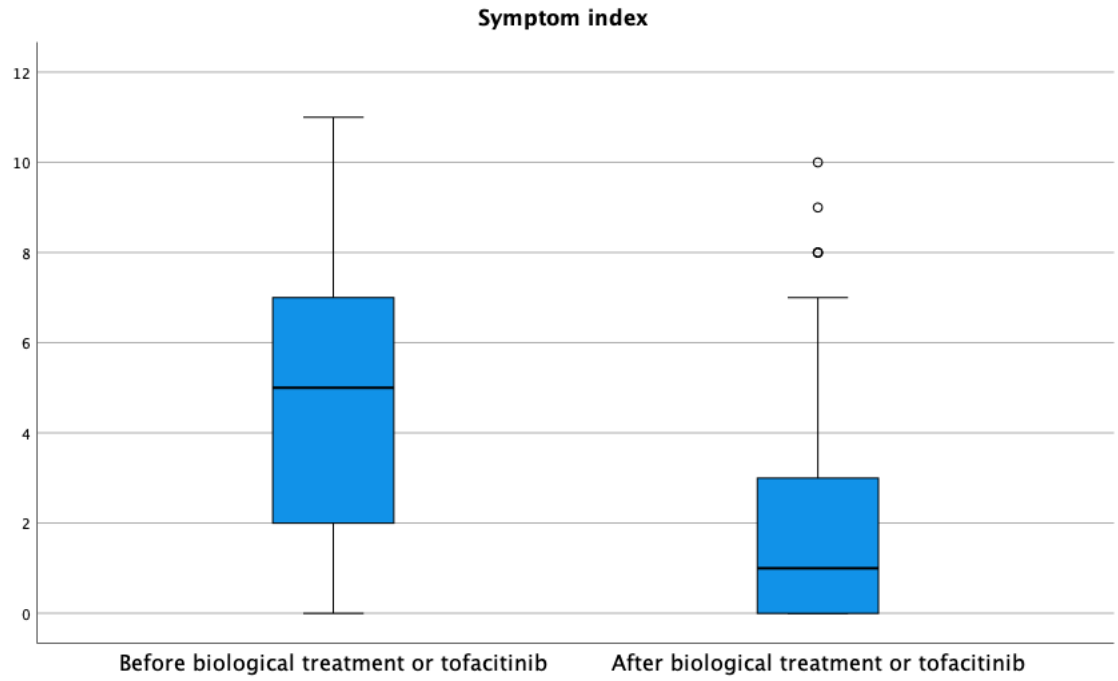

Figure 1. Symptom index before and after biological treatment or tofacitinib.

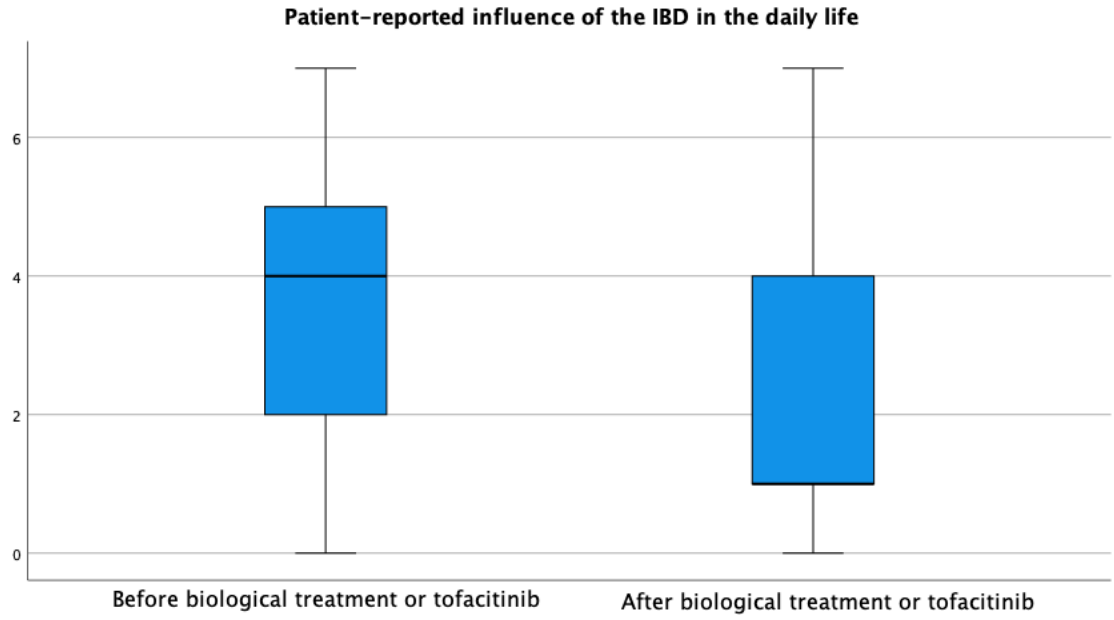

Figure 2. Patient-reported influence of the IBD in the daily life.

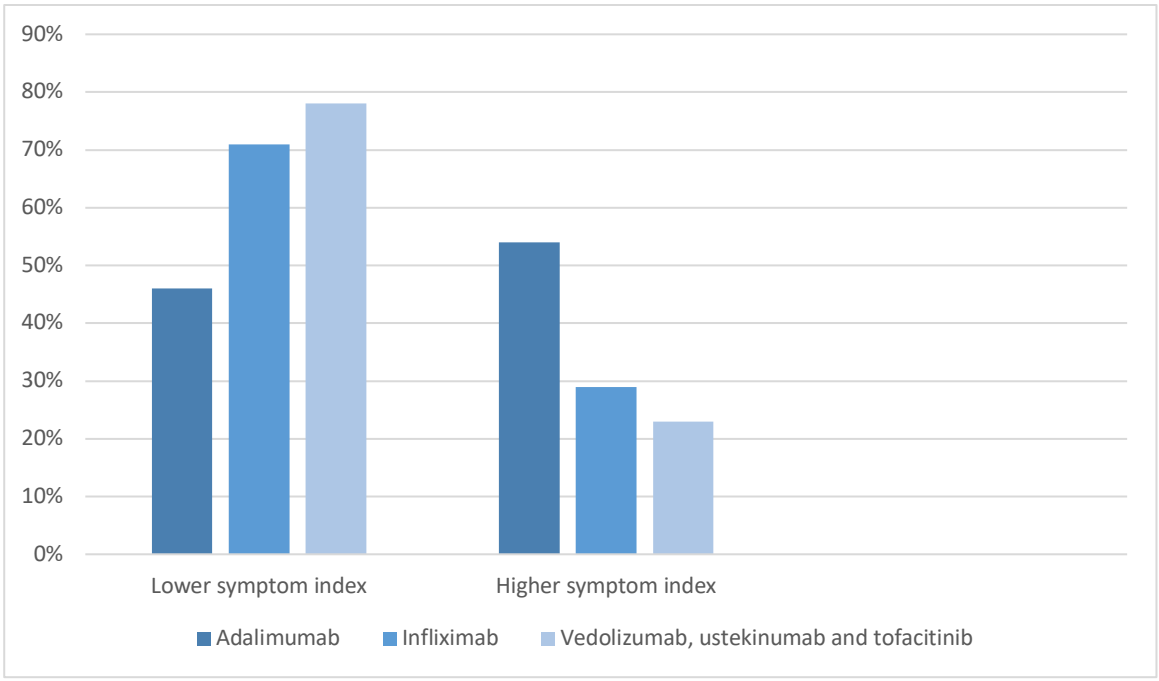

Figure 3. Change of the symptom index after the biological medication or tofacitinib in each medication.

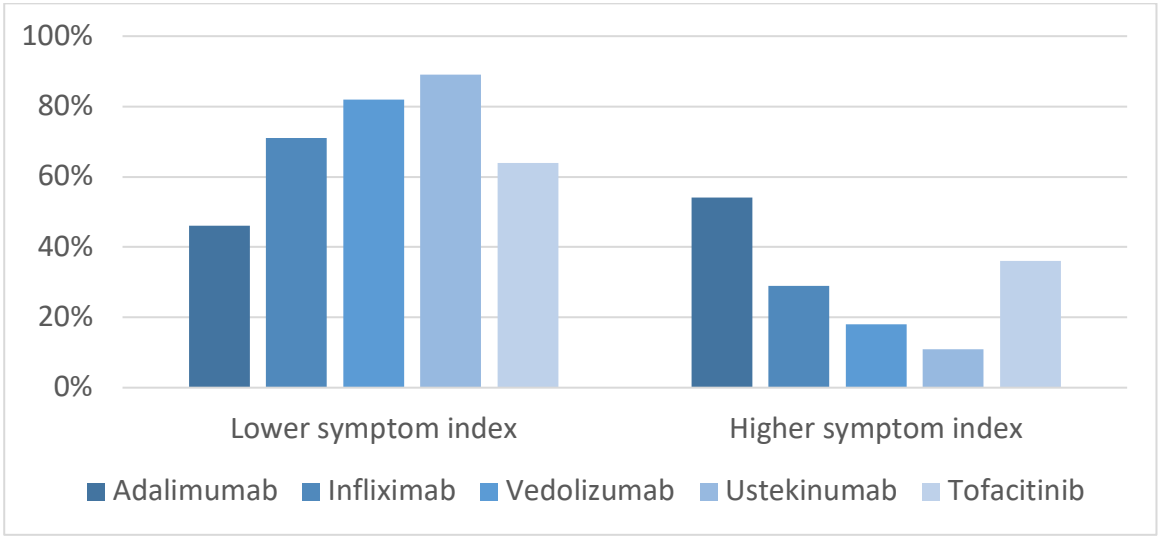

Figure 4. Change of the symptom index after the biological medication or tofacitinib.