Transitional care, drug withdrawal effects and management of acute pancreatitis in patients with inflammatory bowel disease

Doctoral (Ph.D.) theses

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ABBREVIATIONS

AP	acute pancreatitis
CACHE	patient satisfaction with health care in inflammatory bowel disease questionnaire
CD	Crohn's disease
IBD	inflammatory bowel disease
IBD-SES	inflammatory bowel disease self-efficacy scale for adolescents and young adults,
IS	immunosuppressed
IM	immunomodulator
MARS	medication adherence report scale
NIS	non- immunosuppressed
RCT	randomised controlled trial
STARx	self-management and transition readiness questionnaire
TRAQ	transition readiness assessment questionnaire
UC	ulcerative colitis

1. INTRODUCTION

The incidence of inflammatory bowel disease (IBD) is increasing in both childhood and adulthood. Due to the development of health care and therapeutic modalities, IBD adjusted life years, prevalence, costs of care, and socio-economic burdens are all increasing. The education of patients and amelioration of doctors' professional skills are therefore essential because appropriate expertise, evidence-based care and patient education contribute to the improvement of the quality of care, the quality of life, and the reduction of health care burdens.

1.2. Transition and the effectiveness of joint transition visits

Education and the need for transitional care have recently been emphasized during chronic patient care. Simple transfer or transition are the methods to facilitate adolescents IBD patients to adult health care.

Transition is a complex, well-planned process to increase adolescents' role in the care of their chronic illness, as well as to build their psychological stability for this. Due to ensure high-quality care on an international level and to complete a clinical examination for guideline building, it is essential that the endpoint questionnaires are adapted to the given linguistic and cultural milieu. Adaptation gives the opportunity to use an existing, validated questionnaire in an area with different linguistic and cultural characteristics, since at the end of the process materially equivalent content to the validated questionnaire can be obtained. An adapted tool enables the results to be compared with international studies using the same assessment methodology.

1.3. Investigation of relapse after drug withdrawal in patients with inflammatory bowel disease in remission

Although several rationales for therapy withdrawal during remission exist, e.g.: health burden and cost reduction, side effects, subjective patient factors (compliance, pregnancy, breastfeeding), knowledge of predictors of relapse, drug withdrawal, and potentially expected consequences are still uncertain.

The European Crohn's and Colitis Organization has recently published a recommendation about therapy withdrawal, called "exit strategy". However, there are few and heterogenous data on successful, long-term therapy modification. Several randomized and observational studies with different follow-up periods have already evaluated the relapse rate after therapy withdrawal in Crohn's disease (CD), but there is less data on patients with ulcerative colitis (UC).

1.4. Acute pancreatitis in the courses and therapy of inflammatory bowel disease

The severity of possible pathological changes of the pancreas in patients with IBD range widely. The incidence of acute pancreatitis (AP) is higher in CD than in UC, however, a higher incidence was observed in IBD populations compared to the average. Due to the increasing incidences and the heterogeneous etiological factors of AP, the investigation of the relationship between the two diseases remains a pronounced research topic.

According to our current knowledge, the course and therapy of AP in patients with IBD do not alter from the course of the general population. However, AP may complicate the course of IBD, so prompt clarifying the etiology and starting the adequate therapy are essential to avoid complications in both diseases, as well as to optimize the course of the diseases and reduce the health burden.

2. AIMS

In our scientific work, we aimed to examine the questions that arise during patient care concerning IBD patients. Our work was inspired by our previous studies, questions from everyday practice, and the management of the IBD patient database.

We aimed to adapt the questionnaires measuring transitional endpoints in a multicentre, cross-sectional observational study. The questionnaires will be used in the previously designed TRANS-IBD randomized clinical trial. With the adapted questionnaire, we can perform a higher quality clinical study and create tools for everyday practice.

We also aimed to evaluate the relapse rate in patients with IBD in remission after therapy withdrawal in a systematic review with a meta-analysis.

Further, our aim was to evaluate the course and clinical characteristics of AP as a co-morbidity or as a side effect of medication in patients with IBD in a prospective, multicentric, case-control cohort study.

3. POPULATION AND METHODS

3.1. Adaptation of questionnaires evaluating the effectiveness of joint transition visits

The adaptation was carried out in a *multicentric, cross-sectional observational study*, by filling the validated questionnaires, creating comparable results at international level.

3.1.1. The population of the adaptation

The adaptation was performed with 15-19-year-old adolescents diagnosed with IBD, in nine Hungarian IBD centres. We provided the material conditions for the process. A data sheet was also collected on which several personal and disease-related parameters were recorded.

3.1.2. Characteristics of the adapted questionnaires

The *CACHE („Patient satisfaction with health care in inflammatory bowel disease questionnaire") questionnaire* is a non-transition specific tool for measuring the subjective opinion of patients with IBD about the quality of care. The *MARS („Medication adherence report scale") questionnaire* is a non-disease, non-transition specific tool for assessing medication adherence. The *STARx* („*Self-Management and Transition Readiness Questionnaire")* questionnaire is a transition but not IBD-specific questionnaire measuring self-management and transition readiness of adolescents (STARx-A) and assesses parents' opinions about their children's self-management and adulthood abilities (STARx-P). The *IBD-SES („Inflammatory Bowel Disease Self-Efficacy Scale for adolescents and young adults") questionnaire is a* disease- and transition-specific tool to evaluate the self-efficacy of young adults diagnosed with IBD. The *TRAQ („Transition Readiness Assessment Questionnaire")* questionnaire is a transition but non-disease-specific questionnaire that assesses young people's health and health care self-management skills.

3.1.3. Steps of adaptation

The procedure was led by the guideline of Beaton *et* al. (**Figure 1.**)

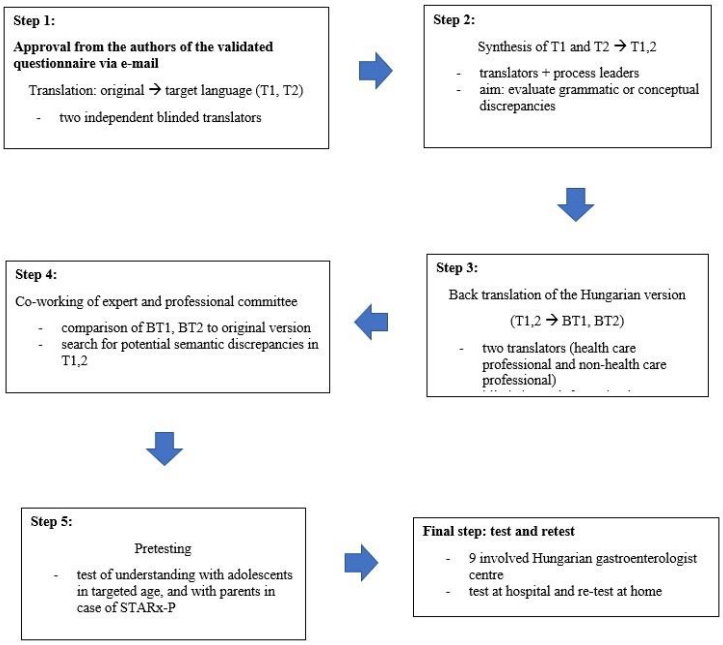

Figure 1. Steps of adaptation
T: translation; BT: back-translation; IBD: inflammatory bowel disease

3.1.4. Statistical analyses in the adaptation process

Demographic data were summarized using descriptive statistics. The floor and ceiling effect was determined when more than 15% of the patients marked extreme values. Confirmatory factor analysis was conducted to assess the fit of the original model, root means square error of approximation (accepted if <0.08), comparative fit index, Tucker-Lewis index, and scaled Chi-Square were used. A cut-off criterion ≥ 0.90 has been recommended for CFI and TLI. The internal consistency was determined using Cronbach's alpha coefficients. Statistically, α=0.70 is the minimum acceptable value, while ≥0.9 can be interpreted as excellent internal consistency. The test-retest reliability was evaluated by Spearman's rank correlation of the total scores of the questionnaire, which is statistically acceptable ≥0.7. The relationship between demographic variables and questionnaire totals or subscores was tested by Spearman's rank correlation for continuous variables, Mann-Whitney U-test or Kruskal-Wallis rank sum test for categorical variables.

The results were considered significant if $p < 0.05$. All statistical analysis were conducted using the R programming language and the lavaan R package.

3.2 Evaluation of relapse rate after therapy withdrawal in patients in remission with inflammatory bowel disease

The protocol of the *systematic review and meta-analysis* assessing the efficacy and safety of immunosuppressive drug withdrawal used in the treatment of IBD patients in remission was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42020155848). Our results were presented in accordance with evidence-based guidelines for systematic review and meta-analyses publications.

3.2.1. Search strategy, study eligibility in the systematic review and meta-analyses

Our research was conducted in the following five electronic databases: MEDLINE, the Central Cochrane Register of Controlled Trials, Web of Science and Scopus. Manual search was also performed in the reference lists of the included studies to identify additional eligible studies.

Randomised controlled trials (RCT), cohort studies, and conference abstracts dealing with patients with IBD in remission after de-escalation or withdrawal of effective therapy were enrolled. Based on the acquired therapy, four intervention groups were made: withdrawal of immunomodulator (IM) monotherapy, withdrawal of an IM from the combination therapy, withdrawal of biologic monotherapy, and withdrawal of a biologics from the combination therapy. The comparators were patients with IBD on ongoing medication. The primary outcome was the evaluation of relapse rate, and the secondary outcome consisted of the identification of the predictive factors of relapse, and the evaluation of side-effects and consequences of therapy withdrawal.

After the set-up of the questions and aims, we worked with predetermined search query, and the search was last updated on September 5, 2020.

3.2.2. Study selection and data extraction

After the systematic search and import of all references into a reference management software (EndNote X8, Clarivate Analytics). After removing duplicates, the further selection and screen based on title, abstract and full text. Data extraction was carried out with predefined criterions.

3.2.3. Risk of bias assessment

The potential risk of bias was evaluated in the included studies by two independent investigators, any disagreement was resolved by a third party. The revised Cochrane risk-of-bias tool for randomised trials (RoB2) was used for the risk of bias assessment of the included

RCTs. The Risk of Bias In Non-Randomized Studies–of Interventions (ROBINS-I) tool was used to assess the risk of bias of the included observational studies.

3.2.4. GRADE method – quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used for estimating the quality of evidence for the primary outcome of the meta-analysis.

3.2.5 Statistical analyses

Data analysis was based on the intention-to-treat principle. Risk ratios (RRs) were calculated for dichotomous outcomes with 95% confidence intervals. The random-effects model was used for all analyses with DerSimonian-Laird estimation. Statistical heterogeneity was assessed using Cochrane's Q, the I^2 statistics and chi^2. We planned to investigate the predictive factors of relapse by pooling RRs or hazard ratios; however, data were seldom and not truly comparable. We planned to evaluate publication bias by Egger's test and visual inspection of the funnel plot. We also performed Trial Sequential Analysis for the primary outcomes to determine whether further randomised trials with similar design are needed. Subgroup analyses were performed to analyse if the application of placebo (placebo and placebo-free studies after therapy withdrawal in the intervention arm) and disease type (CD and UC) affect the relapse rate. A leave-one-out sensitivity analysis was performed to test if the removal of any study changes the association.

Statistical analyses were performed with Stata 16 (StataCorp LLC, College Station, Texas, USA) and Trial Sequential Analysis Program version 0.9 beta.

3.3. Acute pancreatitis during the course of inflammatory bowel disease

After the diagnosis of AP, all patients provided written informed consent to be anonymously analysed in the Hungarian Acute Pancreatitis Registry. Our cohort study follows the STROBE statement for observational cohort studies.

3.3.1. Design, settings, and participants

Adult patients (over 18 years of age) with AP were consecutively involved in this international, multicentre Hungarian Acute Pancreatitis Registry operated by the Hungarian Pancreatic Study Group from 2012. In 2020 registry-based, exact gender and age matched cohort analyses were performed from a database of 2,459 patients at a 1:3 match ratio. The IBD subjects were patients with both AP and IBD, and the non-IBD ones were patients with AP without IBD. The nationality of patients in both groups was Hungarian to receive more accurate details of the diseases.

3.3.2. Data sources and outcomes

Patients were followed daily during their hospitalization for AP, and their detailed data were collected into an electronic database. Additional information on IBD was collected from the hospitals' electronic medical records. Based on the pharmacological treatment of IBD used during the AP episode, patients were classified as immunosuppressed (IS) and non-immunosuppressed (NIS) patients. The severity of AP, local complications, and organ failure were categorized according to the modified Atlanta criteria.

Our aims were the examination of prognostic parameters of AP in the IBD and non-IBD patient groups, severity indicators, and applied therapy during hospital stay.

3.3.3. Study population and statistical analyses

Between 2012-2020 2,459 patients with AP were enrolled in the prospective registry, and the daily follow-up ended at the day of discharge. 2170 final reports were checked to avoid

information bias, to control comorbidities, and to search for missing information about IBD. 289 patients with AP were excluded due to missing final reports.

Representativity analyses was performed to control selection bias, then descriptive statistics of the cohort group was carried out. Due to the non-normal distribution of data median and IQR were calculated for continuous variables, whereas incidence was determined for categorical ones. The control subjects were precisely matched by gender and age in a 1:3 ratio. Firstly, all statistical analyses comparing IBD and non-IBD populations were performed with the controls randomly selected in a 1:1 ratio to obtain detailed results with p values. In case of missing data, the participant was excluded from that specific analysis. Secondly, subgroups of IBD were compared as well, based on disease type (CD vs. UC), immunosuppression therapy (IS vs. NIS), and disease activity (clinical relapse vs. clinical remission).

Depending on the data distribution, Wilcoxon-Mann-Whitney was used for the continuous variables and Fisher's exact test or the chi-square test for the categorical ones. A p-value less than 0.05 (<0.05) was defined as statistical significance. All calculations were performed with R statistical language.

4. RESULTS

4.1. Adaptation of questionnaires evaluating the effectiveness of joint transition visits

4.1.1. Main characteristics of adolescents involved in the adaptation process

Table 1. Main characteristics of adolescents involved

	population of CACHE, MARS (n=122)	***population of STARx-A, STARx-P, IBD-SES, TRAQ (n=112)***
male/female	58/64	51/61
ethnicity: Hungarian/other	115/6	105/7
age (mean±SD; years)	17.00±1.00	17.00±1.98
disease duration time (mean±SD; yrs)	10.00±8.00	3.61±2.90
Crohn's disease/ ulcerative colitis	80/42	71/41
previous intestinal surgery (%)	16.66	13,39
comorbidities (%)	15.00	21.42
biological therapy (%)	44.16	41.96
steroid (%)	25.00	24.10
*azathiopri*ne *(%)*	37.50	36.66
5-ASA (%)	59.16	58.92

n: number; SD: standard deviation; CD: Crohn's disease; UC: ulcerative colitis; 5-ASA: 5-aminosalicylic acid

4.1.2. First steps and results of the questionnaire adaptation

During the pre-test process of the *CACHE questionnaire* minimal changes in the phrases were needed. The *MARS questionnaire* was well understood during the pre-test process, no additional changes to the phrases were required. The *STARx-A* questionnaire was filled by the adolescents, while the *STARx-P questionnaire* was answered by their parents. After the cognitive check, minimal changes were performed in parallel to the questionnaires to preserve the original uniformity. Q4 and 15 have been deleted as they cannot be properly interpreted in our cultural environment and daily habits. During the adaptation minimal modification was performed in the *IBD-SES questionnaire*. Q13 had to be excluded from the adaptation due to extremely oblique distribution and error in further analyses. During the pore-test process, the questions related to the local insurance system had to be changed in *TRAQ questionnaire.*

4.1.3. Questionnaire's adequacy (confirmatory factor analyses) and reliability

Table 2. Indices of the statistical analyses

Indices	*CACHE questionnaire*	*MARS questionnaire*	*STARx-A questionnaire*	*STARx-P questionnaire*	*IBD-SES questionnaire*	*TRAQ questionnaire*
number of filled questionnaires (n)	122	117	112	102	112	111
total score, mean (SD)	76 (12.369)	23 (2.907)	60 (±5.5)	56 (±16.8)	44 (±6.4)	3.4 (±0.7)
CFI	0.937	0.987	0.865	0.878	0.961	0.977
TLI	0.930	0.973	0.818	0.836	0.948	0.972
RMSEA (CI)	0.071 (0.060-0.081)	0.174 (0.105-0.250)	0.123 (0.104-0.143)	0.154 (0.134-0.173)	0.101 (0.071-0.130)	0.084 (0.068-0.101)
Cronbach's α	0.906	0.864	0.415	0.693	0.729	0.865
number of re-tests (n)	52	51	70	69	69	71
re-test total score, mean (SD)	70 (16.76)	24 (2.880)	59 (±7.5)	58 (±8.9)	42 (±9.7)	3.3 (±0.7)
test- re-test: ρ (p)	0.892 (0.001)	0.814 (0.001)	0.787 (<0.001)	0.778 (<0.001)	0.819 (<0.001)	0.034 (0.779)

n n: number; SD: standard deviation; CFI: comparative fit index, TLI: Tucker-Lewis index, RMSEA: root mean square error of approximation CI: confidence interval

4.2. Evaluation of relapse rate after therapy withdrawal in patients in remission with inflammatory bowel disease

4.2.1. Literature search, study selection

After the literature search and selection in five databases 46,673 records were identified. At the end of the selection process, 10 RCTs were eligible for inclusion in meta-analysis, and in systematic review, an additional RCT and 8 cohort studies were discussed.

4.2.2. Characteristics of the studies included

The 19 included study was published between 1978 and 2020. Patients with CD were analysed in 13 studies and patients with UC in 4 studies, and 2 studies recruited both CD and UC population. The mostly used IM was azathioprine in 12 studies, followed by mercaptopurine in and methotrexate in 3 studies. Infliximab was examined as a biologic in 6 withdrawal studies, adalimumab was used only in 1 study.

Sixteen of 19 studies compared drug discontinuation to ongoing therapy, while 3 of 19 studies, where IM was withdrawn, compared placebo in the intervention group to ongoing medication in the control group. A dose reduction or an increase in the therapeutic interval of the drug was found in only 1 study, so that we were unable to create a 'de-escalation' subgroup in meta-analysis. The difference in stable remission before therapy withdrawal was remarkably different.

4.2.3. Result for withdrawal of immunomodulator monotherapy

Seven of 10 RCTs, including a total of 334 and 67 patients with CD and UC, respectively, assessed the rate of relapse after therapy withdrawal compared to continued therapy. The follow-up time ranged from 10 to 24 months across the studies.

There was a significantly higher relapse rate within two years, after stopping IM monotherapy compared to ongoing therapy (RR=1.85, 95% CI: 1.44-2.38, p <0.001). (**Figure 2**) Subgroup analyses for CD and UC revealed a significantly higher relapse rate in CD but not in the single study of UC (RR=2.06, 95% CI: 1.53–2.77, p <0.001 and RR=1.39, 95% CI: 0.85–2.26 p=0.189). (**Figure 2**) In a subgroup analysis, the relapse rates were significantly higher after discontinuation of the IM therapy in studies with or without placebo control. (RR=1.95, 95% CI: 1.29-2.97, p=0.002; and RR=1.79, 95% CI: 1.31–2.46, p<0.001). (**Figure 3**)

In the three observational studies analysed, increased disease activity and relapse rates were found after withdrawal of IM.

4.2.4. Results for withdrawal of an immunomodulator from combination therapy

Only 3 including a total of 186 patients with IBD in stable remission on IM in combination with infliximab or adalimumab, analysed the relapse rate after the withdrawal of an IM from combination therapy. No statistically significant difference was observed between the groups (RR=1.30, 95% CI: 0.81—2.08, p= 0.269). (**Figure 4**)

In two retrospective cohort studies, no significant differences were found between the groups after IM withdrawal from combination regimen.

4.2.5. Results for withdrawal of biologics from mono- or combo-therapy

Although our primary aim was to include withdrawal of biologic monotherapy and a biologic from IM combination treatment in meta-analysis, we were unable to create this group due to insufficient data.

One retrospective cohort study, published in abstract form, compared 111 UC patients who discontinued infliximab monotherapy to 82 patients with scheduled IFX therapy. Patients who stopped infliximab showed a higher risk of relapse after therapy withdrawal (hazard ratio=3.41, 95% CI: 1.88-6.20, p<0.001). One RCT the relapse rates at week 48 were 19.6 and 45.7% in the groups in which infliximab was continued and discontinued respectively.

Two retrospective studies analysed the withdrawal of a biologic from the IM combination regimen: children with CD in long-standing clinical remission discontinuing infliximab treatment experienced relapse within 1 year in 75%, while in the other study, no significant difference was observed after infliximab withdrawal in CD (hazard ratio=0.73, 95% CI: 0.41-1.30), p=0.29).

4.2.6. Safety analysis

Of the 19 studies analysed, 10 reported the rate of adverse events. In most of the articles, the exact number of events in the different groups was not reported, therefore, no meta-analysis could be performed.

4.2.8. Trial Sequential Analysis

According to the TSA, further studies with similar design are unlikely to change the significant results on relapse rates after withdrawing IM monotherapy in CD. TSA proved to be inconclusive in the analysis in the UC subgroup on IM monotherapy withdrawal (Figure S2C), in that on IM withdrawal from combination treatment (Figure S2D) and in that on biologic monotherapy withdrawal (Figure S2E) due to insufficient data.

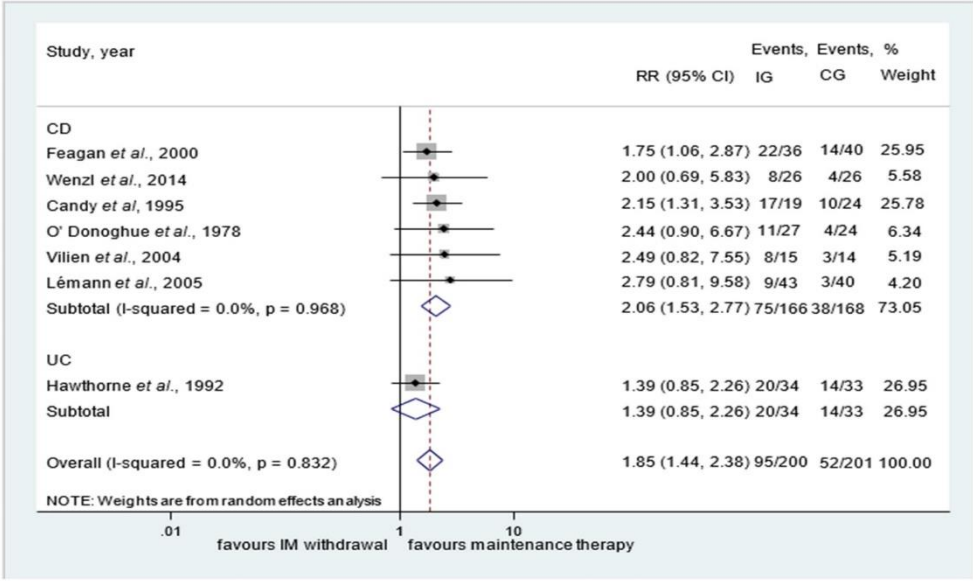

Figure 2 Results for withdrawal of immunomodulator monotherapy within 24 months of follow-up subgroup analysis of studies with Crohn's disease and ulcerative colitis

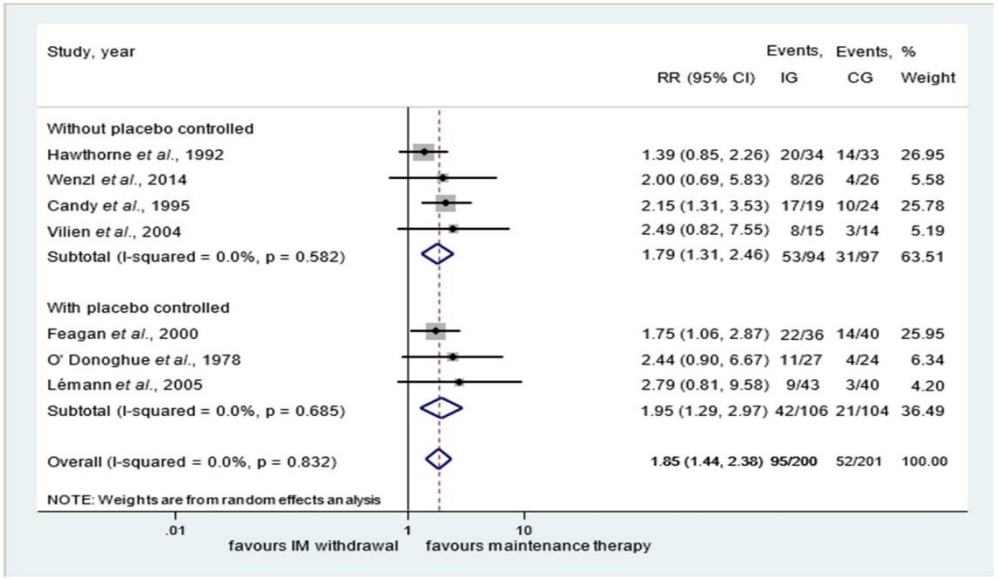

Figure 3 Results for withdrawal of immunomodulator monotherapy within 24 months of follow-up, subgroup analysis of studies with placebo and without placebo control

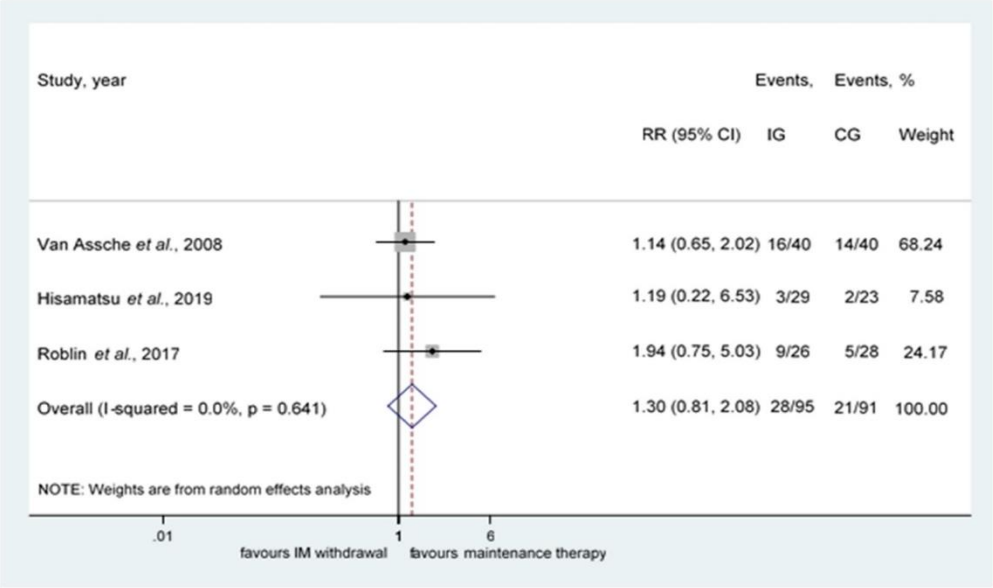

Figure 4 Results for withdrawal of an immunomodulator from combination therapy

IG: intervention group; CG: control group; CD: Crohn's disease, UC: ulcerative colitis, RR (95% CI): Relative Risk (95%) Confidence Interval

4.3. Acute pancreatitis during the course of inflammatory bowel disease

4.3.1. Study population

Of the 2,459 enrolled patients with AP, 289 were excluded due to missing final reports. The representativeness analysis demonstrated that our cohort (2170 patients) presents the same epidemiological (age, gender, body mass index, aetiology) and major outcome distribution (severity, mortality, LOH) as the total cohort (2459 patients). Thus, our cohort population describes a general AP population.

The detailed review of 2,170 final medical AP records confirmed 27 cases of IBD as an IBD population, the non-IBD population without the diagnosis of IBD was precisely matched by age and sex from the Hungarian Acute Pancreatitis Registry (n=81).

Twenty-nine AP episodes were diagnosed in 27 patients with IBD, including 14 patients with CD and 13 with UC. Twelve of the 27 patients were in relapse, while 15 patients were in remission during the AP episode. Nine patients were identified with IS and 17 with NIS treatment. The patients involved may have had other comorbidities; they were not involved in the description and analysis due to their significant variances.

4.3.2. Main results of prognostic parameters

Eight parameters were examined to investigate any difference between AP patients with or without IBD and between subgroups of the IBD population. Due to the high proportion of missing data, procalcitonin levels could not be examined. Of the 27 patients with IBD, procalcitonin was measured in only nine patients on admission, with a mean of 0.107 ng/ml (min-max: 0.02-0.29).

None of the laboratory parameters of prognostic factors showed significant differences between IBD and non-IBD cases (C-reactive protein: p=0.297; white blood cells [WBC]: p=0.538; serum creatinine: p=0.794). No differences were observed between the two groups in Bedside index of severity in acute pancreatitis scores (p=0.832), pancreatic structure, or the presence of ascites (pancreas structure: p=1.000; ascites p=0.203). The rate of current alcohol consumption and smoking showed no differences either (33.3% vs. 48.1%; p=0.263, and 33.3% vs. 29.6%; p=0.810).

On admission, WBC levels in NIS patients were significantly lower than IS patients (p=0.007). (**Figure 5.A**) Further prognostic parameters analysed did not show significant differences between subgroups of patients with IBD.

4.3.3. Main results of the severity indicators

Six parameters (LOH, peak level of CRP and WBC, severity, local and systemic complications) were analysed to reveal differences between groups. None of the patients with IBD and AP died during follow-up, and none of the IBD patients were treated in the intensive care unit for AP.

The length of hospitalisation (p=0.677), the peak levels of WBC and C-reactive protein (p=0.239 and p=0.432) did not show significant differences between the IBD and non-IBD populations. There was no significant change in the severity of AP (p=0.384). However, the rate of moderate and severe cases was higher in the non-IBD group (mild: 89% vs. 74%, moderate: 11% vs. 24.7%, severe: 0% vs. 1.2%). None of the local or systemic complications of AP showed a significant alteration between the groups examined (p=0.790, and p=0.328).

The three different IBD subgroup analyses demonstrated no significant alteration in the severity indicators.

4.3.4. Inpatient treatment

Of the 27 cases in the IBD group, eight drug-induced AP were registered, the putative aetiological factors, azathioprine in three, and 5-aminosalicylic acids in five AP episodes, were stopped immediately.

Antibiotic treatment showed no significant differences between IBD and non-IBD groups (46.2% vs. 40.0%; *p*=0.642). Significantly more patients from the non-IBD group required analgesics than patients in the IBD group (55.6% vs. 80.6%; *p*=0.020). (**Figure 5.B)**

Antibiotic use was significantly higher in the IS group compared to the NIS group (*p*=0,017), although a clear indication (e.g., fistula or abscess) was not present. (**Figure 5.C**) No significant differences were found in antibiotics or analgesics use between patients with CD or UC and patients with active or inactive disease.

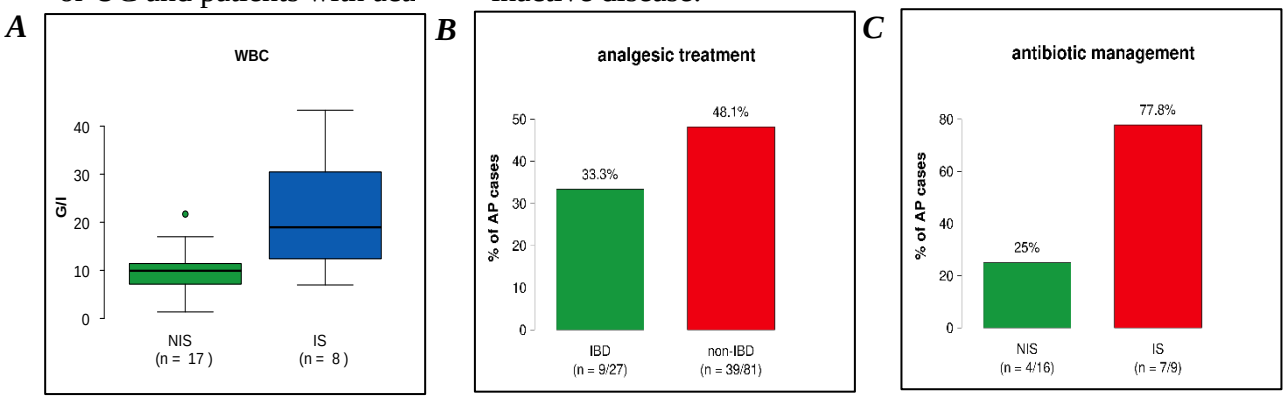

Figure 5. White blood cells, as a prognostic factor in the IS-NIS subgroup analyses (A); analyses of analgesic treatment in the IBD and non-IBD groups (B), and the analyses of antibiotic use in the IS-NUS subgroups (C)

wbc: white blood cells; n: represent the total number of the groups

5. DISCUSSION AND COCNLUSION

A *multicentre, cross-sectional observational study* was carried out to adapt five questionnaires measuring disease knowledge and self-efficacy.

A successful cross-cultural, age- and disease-specific adaptation of MARS and TRAQ questionnaires and as well as a cross-cultural, and age-specific adaptation of CACHE and IBD-SES was performed. According to our results, the Hungarian questionnaires are appropriate, trustworthy, reproducible, and comparable to the validated versions. Unfortunately, the adaption of the STARx tools was not successful, thus, future evaluations with Hungarian STARx tools cannot be compared with international results.

Evaluating our adaptations, several limitations should be considered: due to the pandemic situation the number of participants was lower than expected, the administration was done centrally, separate deadline of the re-test was not possible. The rate of incomplete participation was low, but in these cases the unanswered items were filled with median values to avoid exclusion.

The strength of our study, that it was guided by a strict methodology, and different Hungarian IBD centres participated, so the conclusions can be generalized.

Quality of life, and the consideration of the advantages and disadvantages of long-term medication use are critical points of chronic patient care. We summarize the results of therapy withdrawal in a *systematic review with a meta-analysis*. Several rationales for stopping treatment exist, such as toxicity, health care burden, national regulations. However, before published consensus on stopping treatment, called “exit strategy” by the European Crohn's and Colitis Organisation in 2018, there were not any rational guideline. The importance of the topic is indicated by the fact that numerous studies have already been published in this topic. So far, a meta-analysis summarized the results of anti-tumor necrosis factor-alpha therapy withdrawal.

Our present study confirms that the withdrawal of IM monotherapy increases the risk of relapse in patients with quiescent CD. According to the GRADE approach, the certainty of evidence is low, so that further studies may change the results. However, in TSA, the statistical power reached the required level, meaning that future studies with similar design will be unlikely to change the results.

The strength of our study is the evaluation of evidence levels of the study results with GRADE method, and the analyses degree of risk of bias. With TSA we proved that the studies investigating IM monotherapy withdrawal in CD patients have adequate strength, so further studies with a similar structure do not change the result.

Our meta-analysis has several limitations suggesting caution in interpreting the results: we were unable to create more homogenous groups for meta-analysis in terms of remission duration, the number of studies analysing patients with UC was low, most of the studies dealt with clinical remission. The number of studies dealing with dose reduction was low, thus analyses could not be performed with these data. Our pre-defined secondary outcomes could not be met due to the lack of studies. Due to lack of published data, we could not evaluate other biologics than infliximab. The number of studies with low evidence level analysing patients with UC patients and combined treatments was low, confirming the need for further controlled verification studies in this area.

Further research is expected to shed light on the exact timing and optimal group of patients to discontinue treatment. This topic has still high relevance and unanswered questions, further research is expected to shed light on the exact timing and optimal group of patients to discontinue treatment, and to choose the optimal therapeutic regimen. Besides the suggestions of the guidelines, it is recommended to make individual decisions; predictive factors of relapse,

evidence of mucosal healing, personal aspects, and toxicity should be included in the risk/benefit analysis prior to therapy withdrawal.

To ensure the quality and cost of care, as well as the patients' adequate quality of life, it is essential to take acute situations during chronic patient care in accordance with guidelines and protocols. It is essential that the treatment of the underlying chronic disease is not compromised, so that an excessively protective form of care does not develop. The care and clinical characteristics of AP as a potential acute deteriorating disease was analysed n a *prospective, multicentre, case-control cohort study*.

Based on the results of our cohort study and the literature data, it can be concluded that regardless of the type (CD vs. UC) and activity of IBD, our results did not confirm any difference in the prognosis and severity of AP between IBD patients and the general AP population. Overuse of antibiotics was observed in patients on immunosuppressive therapy, probably due to elevated levels of on admission WBC, platelet, and peak WBC counts. Based on our previous cohort analysis, in agreement with the F17-18 recommendations in the IAP/APA guidelines, overuse of antibiotics in the treatment of AP should be avoided as there is no benefit. Due to the same severity and prognostic results observed in the IBD population, antibiotics are not required in IS patients. Our findings should be analysed in more extensive prospective cohort studies with high evidence level.

Our present study has several strengths. This prospective cohort study collected daily clinical data with standardized question forms, thus minimizing information bias. We analysed the cohort's main epidemiological and outcome parameters compared to the whole cohort to minimize selection bias. Exactly matched control selection was used to compensate for the possible biases resulting from the small number of IBD cases.

Our cohort analysis has several limitations that suggest a careful interpretation of the results. our clinical research question was defined post hoc, so not all aspects of AP-IBD could be investigated. The validity of our evaluation and results may be impaired by the small sample size of IBD patients. Patients excluded due to missing final reports may contribute to selection bias. Furthermore, the analyses of the IBD subgroups were not feasible in the case-control design due to the low number of cases. There was a considerable variation in the etiology of AP, so subgroup analyses were not feasible in the present study.

We hope that our extensive, multi-topical scientific work has highlighted the important and critical elements of IBD care and will contribute to the launch of successful transition programs/patient educations; to consider discontinuation of therapy; and to develop uniform and optimal patient care guidelines.

6. THESIS

- With the participation of 9 centres in Hungary, our working group was the first to adapt questionnaires assessing the knowledge, awareness, medication adherence and subjective opinion of adolescents with inflammatory bowel disease facing the transition (CACHE, IBD-SES, MARS, TRAQ).
- In the case of all questionnaires, we carried out cross-cultural, linguistic, and age adaptation, as well as disease-specific adaptation in the case of the MARS and TRAQ questionnaires, so the Hungarian results can be compared with international values of these questionnaires.
- In our meta-analysis and systematic review, we found a higher relapse rate in inflammatory bowel patients in remission after withdrawing immunomodulatory monotherapy. Based on the trial sequence analysis of the results concerning the relapse rate, it can be concluded that there are enough studies dealing with immunomodulatory monotherapy withdrawal in patients with Crohn's disease, and further studies with a similar structure would be unlikely to modify the conclusion.
- We did not observe any significant difference in the relapse rate of patients with inflammatory bowel after the immunomodulator withdrawal from combined therapy, however, using the GRADE method, the quality of the evidence is very low, and according to the trial sequence analysis, there are currently not enough studies for this group of patients.
- Our research group was the first to evaluate patients with acute pancreatitis in order to investigate the severity, treatment, and outcome of acute pancreatitis in patients with inflammatory bowel disease who were hospitalized for acute pancreatitis.
- The prognosis of acute pancreatitis in patients with inflammatory bowel did not alter compared to the average, non-inflammatory bowel patient population. The evaluated severity indicators did not show significant differences between patients with inflammatory bowel disease and the average population treated for acute pancreatitis. Based on the Atlanta criteria, the proportion of moderate and severe acute pancreatitis cases was lower in the group of patients with inflammatory bowel disease.
- During hospital care, patients with inflammatory bowel disease who were currently hospitalized due to acute pancreatitis, required significantly fewer pain relievers, and there was no significant difference in antibiotic use compared to the group of patients without inflammatory bowel disease.
- Among patients with inflammatory bowel disease, the immunosuppressed patients received unreasonably more often medication during the treatment of acute pancreatitis than the non-immunosuppressed patients with inflammatory bowel disease.

7. PUBLICATIONS

7.1. Publications supporting the dissertation

Dóra Dohos, Alex Váradi, Nelli Farkas, Adrienn Erős, Katalin Eszter Müller, Anna Karoliny, Eszter Gombos, Éva Nemes, Noémi Vass, András Tárnok, Péter Hegyi, Patrícia Sarlós. Hungarian Linguistic, Cross-Cultural and Age Adaptation of Transition Specific Questionnaires in Patients with Inflammatory Bowel Disease. Children (Basel). 2023; 10(4):711. **Q2 IF: 2,835 (2021)**

Dóra Dohos, Alex Váradi, Nelli Farkas, Adrienn Erős, Andrea Párniczky, Eszter Schäfer, Éva Kosaras, Judit Czelecz, Péter Hegyi, Patrícia Sarlós. Hungarian Linguistic, Cross-Cultural, and Age Adaptation of the Patient Satisfaction with Health Care in Inflammatory Bowel Disease Questionnaire (CACHE) and the Medication Adherence Report Scale (MARS). Children (Basel). 2022; 29;9(8):1143. **Q2 IF: 2,835 (2021)**

Dóra Dohos, Lilla Hanák, Zsolt Szakács, Szabolcs Kiss, Andrea Párniczky, Bálint Erőss, Piroska Pázmány, Péter Hegyi, Patrícia Sarlós. Systematic review with meta-analysis: the effects of immunomodulator or biological withdrawal from mono- or combination therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2021; 53(2):220-233. **Q1/D1 IF: 9,524**

Dóra Dohos, Nelli Farkas, Alex Váradi, Bálint Erőss, Andrea Párniczky, Andrea Szentesi, Péter Hegyi, Patrícia Sarlós, Hungarian Pancreatic Study Group. Inflammatory bowel disease does not alter the clinical features and the management of acute pancreatitis: A prospective, multicentre, exact-matched cohort analysis. Pancreatology. 2022; 22(8):1071-1078. **Q1 IF: 3,977 (2021)**

7.2. Other publications

Kriszta Katinka Boros, Gábor Veres, Orsolya Cseprekál, Hajnalka Krisztina Pintér, Éva Richter, Áron Cseh, Antal Dezsőfi-Gottl, András Arató, György Reusz, **Dóra Dohos**, Katalin Eszter Müller. Body composition, physical activity, and quality of life in pediatric patients with inflammatory bowel disease on anti-TNF therapy-an observational follow-up study. Eur J Clin Nutr. 2023; 77(3):380-385. **Q1 IF (2021): 4,884**

Katalin Eszter Müller, **Dóra Dohos**, Zoltán Sipos, Szabolcs Kiss, Fanni Dembrovszky, Norbert Kovács, Margit Solymár, Bálint Erőss, Péter Hegyi, Patrícia Sarlós. Immune response to influenza and pneumococcal vaccines in adults with inflammatory bowel disease: A systematic review and meta-analysis of 1429 patients. Vaccine. 2022; 18;40(13):2076-2086. **Q1 IF (2021): 4,169**

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Fanni Dembrovszky, Noémi Gede, Zsolt Szakács, Péter Hegyi, Szabolcs Kiss, Nelli Farkas, Zsolt Molnár, Marcell Imrei, **Dóra Dohos**, Zoltán Péterfi. Fecal Microbiota Transplantation May Be the Best Option in Treating Multiple Clostridioides difficile Infection: A Network Meta-Analysis. Infect Dis Ther. 2021; 10(1):201-211. **Q1 IF: 6,119**

Fanni Dembrovszky, Szilárd Váncsa, Nelli Farkas, Bálint Erőss, Lajos Szakó, Brigitta Teutsch, Stefania Bunduc, Rita Nagy, **Dóra Dohos**, Szabolcs Kiss, Andrea Párniczky, Zsófia Vinkó, Zoltán Péterfi, Péter Hegyi. Immunoglobulin Response and Prognostic Factors in Repeated SARS-CoV-2 Positive Patients: A Systematic Review and Meta-Analysis. Viruses. 2021; 30;13(5):809. **Q1 IF: 5,818**

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Adrienn Erős, **Dóra Dohos**, Gábor Veres, András Tárnok, Áron Vincze, Alexandra Tészás, Noémi Zádori, Noémi Gede, Péter Hegyi, Patrícia Sarlós. Effect of joint transition visits on quality of life in adolescents with inflammatory bowel diseases: a protocol for a prospective, randomised, multicentre, controlled trial (TRANS-IBD). BMJ Open. 2020; 6;10(10):e038410. **Q1 IF: 2,692**

Dohos Dóra, Kálmán Dóra, Boros Kriszta Katinka, Béres Nóra, Veres Gábor. Purpura nélküli melaena, mint a Schönlein-Henoch-purpura első tünete. GYERMEKGYÓGYÁSZAT. 2018; 69: 6 pp. 403-407., 5 p.

Dohos Dóra, Veres Gábor. Urzodeoxikólsav alkalmazása gyermekekben. GYERMEKGYÓGYÁSZAT. 2018; 3 pp. 133-136., 3 p.

Summary

Impact factors of publicated papers supporting the dissertation: **19.171**
Impact factors of publicated papers (without citable abstracts): **50.763**
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