Association of IBD specific treatment and prevalence of pain in the Swiss IBD cohort study

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Abstract

Background
Extraintestinal manifestations (EIM) contribute significantly to the burden of disease in inflammatory bowel disease (IBD). Pain is a leading symptom in IBD and could be seen as an EIM itself. Treatment of IBD associated pain is challenging and insufficiently studied. A better knowledge on the association of pain and IBD specific treatment is warranted to improve the management of IBD patients.

Methods
All patients of the Swiss IBD Cohort Study (SIBDCS) (n = 2152) received a questionnaire regarding pain localization, pain character, and the use of IBD specific medication.

Results
1263 completed questionnaires were received. Twenty-one out of 184 patients (10%) receiving anti-TNF treatment compared to 142 out of 678 patients (21%) not receiving anti-TNF medication reported elbow pain (p = 0.002) while 28 out of 198 patients (14%) receiving steroid treatment significantly more often reported elbow pain compared to 59 from 696 patients (8%) not receiving steroids (p = 0.021). Furthermore, we found significantly more female patients under anti-TNF treatment to report knee/ lower leg pain and ankle/ foot pain compared to their male counterparts (36% vs. 20% and 22% vs. 10%, respectively, p = 0.015 for both comparisons). The frequency of knee, lower leg, ankle and foot pain was especially low in male patients under anti-TNF treatment, indicating a high benefit of male patients from anti-TNF therapy regarding EIM.
Conclusions
The frequency of elbow pain was lower in IBD patients treated with anti-TNF but higher in patients treated with steroids.

Introduction
Pain is a common symptom in patients with inflammatory bowel disease (IBD) [1, 2]. In a recent study we showed that the vast majority of patients (71%) within the Swiss IBD Cohort Study experienced pain during their disease course and that for 52% of the patients pain was a longstanding problem [3]. Abdominal pain can be a direct or indirect consequence of intestinal inflammation; however, extraintestinal manifestations (EIM) of IBD can also cause pain and pain in itself can be seen as an EIM [4–6]. The most common EIM of IBD are arthropathies [5, 7–17]. Also, in our former study we could show that pain has a substantial impact on health-related quality of life (HRQOL) of IBD patients, as the general quality of life was significantly lower in patients suffering from pain compared to those without pain [3]. Such a relationship has also been described in other chronic diseases [18–21].

Treatment of both, IBD and IBD associated pain is challenging. The mainstay of IBD treatment includes systemic immunosuppressive medications, such as corticosteroids, anti-tumor necrosis factor (TNF) antibodies or immunomodulators. Furthermore, the management of an acute flare differs from the strategies for maintenance of remission [22, 23]. Moreover, presence of EIM will also influence the choice of a treatment regime. For instance, anti-TNF therapy is known to be very effective regarding gut inflammation as well as arthropathies/ arthritis. Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) can very effectively mediate pain relieve due to their analgetic and also anti-inflammatory effects. However, due to the risk of disease exacerbation and induction of flares their use in IBD is limited [24–30].

Here, we used the well-characterized patient collective of the Swiss IBD Cohort Study (SIBDCS) to study the association of pain and IBD treatment with a focus on anti-TNF treatment.

Methods
Ethics consideration
Ethics approval was obtained from the regional Swiss Ethics Committees in which cohort participants were enrolled (Commission d’éthique du Canton de Vaud, Lausanne, Switzerland/ Protocol no. 33/06). Written, informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee.

Study design
Patients of the nationwide SIBDCS have been prospectively included since 2006 with a yearly follow-up. The cohort goals and methodology of SIBDC have been described elsewhere[31].

A questionnaire addressing various aspects of pain including pain duration localization and frequency was mailed to 2152 SIBDC patients, representing the entire cohort. The questionnaire also inquired about the use of pain specific medication in detail. Our questionnaire contained several questions from a validated German pain questionnaire [32]. The questionnaire was used in a German and in a French version. Further details of the questionnaires including
the fully originally used French and German versions are described elsewhere [3]. Basic epidemiological and clinical data including the use of IBD specific therapy was retrieved from the SIBDCS databases. All data are stored in Microsoft Access (Microsoft Corporation) databases.

Statistical analysis

Descriptive statistical analyses were performed: Categorical variables were summarized as frequencies and percentages, whereas quantitative variables as median and range. To assess differences in categorical data distribution between groups of different sizes, Fisher’s exact test was used.

The statistical analysis was performed using GraphPad Prism 7 for MacOS. A p-value of <0.05 was considered statistically significant.

Results

Patient’s characteristics

The patients’ characteristics shown in Table 1 have been described previously [3]. In brief: 1263 out of 2152 patients completed the questionnaires (response rate 59%). 599 out of 1263 patients were male (47%) and 664 female (53%). The median age was 47 years. Extraintestinal manifestations (EIM) of IBD were present in 699 patients (55%). The median IBD disease duration was 15 years (mean: 15 years, range: 0–57 years). The vast majority of patients (894/1263, 71%) reported the experience of pain in general during the course of the disease. Table 2 shows the frequency of IBD specific treatment.

Association between IBD specific treatment and pain localization

When comparing the use of IBD specific medication and ten different pain localizations, we found several significant differences. Regarding elbow pain, only 21 patients (10%) receiving anti-TNF treatment compared to 142 patients (21%) not receiving anti-TNF were affected (p = 0.002). Other pain localizations did not reveal significant differences regarding anti-TNF treatment (Table 3).

Comparing other IBD specific therapy and the different pain localization, we found patients not receiving steroid treatment significantly less often to be suffering from elbow pain compared to patients receiving steroids (8% vs. 14%; p = 0.021). For the evaluation of other pain localizations, we found several significant differences. Regarding elbow pain, only 21 patients (10%) receiving anti-TNF treatment compared to 142 patients (21%) not receiving anti-TNF were affected (p = 0.002). Other pain localizations did not reveal significant differences regarding anti-TNF treatment (Table 3).

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Table 1. Patient characteristics.

| Patient characteristics | Number of patients (%) |
|-------------------------|------------------------|
| Gender                  |                        |
| Female                  | 664 (53)               |
| Male                    | 599 (47)               |
| Diagnosis               |                        |
| CD                      | 679 (54)               |
| UC                      | 556 (44)               |
| IC                      | 28 (2)                 |
| Sum                     | 1263 (100)             |
| Pain                    |                        |
| Yes                     | 894 (71)               |
| No                      | 369 (29)               |
| EIM                     |                        |
| Yes                     | 699 (55)               |
| No                      | 564 (45)               |
| Disease duration (Years)|                        |
| Average                 | 15                     |
| Min-Max                 | 0–57                   |

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localizations and other IBD specific therapy (5-ASA, calcineurin-inhibitors, immunomodulators) no significant differences were observed (S1–S5 Tables).

Association between IBD specific treatment and duration of pain

Duration of pain did not differ between patients on anti-TNF treatment versus those not on anti-TNF treatment (Table 4). The duration of pain was also not influenced by other IBD specific medications (Steroids, 5-ASA, Antibiotics, Calcineurin-inhibitors, Immunomodulators) also, no significant differences were observed (S6–S10 Tables).

Association between IBD specific treatment and frequency of pain

The frequency of pain in patients with and without anti-TNF treatment did not significantly differ (Table 5). When comparing the pain frequencies of patients taking other IBD specific medications (steroids, 5-ASA, antibiotics, calcineurin-inhibitors, immunomodulators), also no significant differences were observed (S11–S15 Tables).

Association between IBD specific treatment and pain character

Further, there was no association between the pain character and the use of IBD specific medication. 36 patients (20%) on anti-TNF treatment described their pain to be constant with slight fluctuations compared to 115 patients (19%) without anti-TNF treatment (p > 0.999). Constant pain with strong fluctuations was reported by 15 patients (8%) using anti-TNF treatment and by 64 patients (11%) not receiving anti-TNF treatment (p = 0.331). 115 patients (61%) with TNF treatment and 349 (58%) without anti-TNF treatment experienced pain attacks with pain

Table 2. IBD specific treatment.

| IBD treatment          | Number of patients (%) with pain | Without pain |
|------------------------|----------------------------------|--------------|
| Anti-TNF               | 216 (24.2)                      | 100 (27.1)   |
| Steroids               | 198 (22.1)                      | 73 (19.8)    |
| 5-aminosalicylic acid (5-ASA) | 334 (37.4)          | 136 (36.9)   |
| Antibiotics            | 11 (1.2)                        | 6 (1.6)      |
| Calcineurin-Inhibitors | 12 (1.3)                        | 5 (1.4)      |
| Immunomodulators       | 316 (35.3)                      | 125 (33.9)   |

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Table 3. Pain localization.

| Pain localization | Anti-TNF | No anti-TNF | p-value |
|-------------------|----------|-------------|---------|
| Head              | 56 (26)  | 147 (21.7)  | 0.193   |
| Neck              | 28 (13)  | 95 (14)     | 0.735   |
| Finger/hand       | 53 (24.5)| 142 (20.9)  | 0.297   |
| Elbow             | 21 (9.7) | 142 (20.9)  | 0.002   |
| Shoulder          | 44 (20.4)| 138 (20.4)  | >0.999  |
| Back              | 77 (35.6)| 236 (34.8)  | 0.869   |
| Hip/thigh         | 52 (24)  | 162 (23.9)  | >0.999  |
| Knee/leg          | 61 (28.2)| 181 (26.7)  | 0.660   |
| Ankle/foot        | 35 (16.2)| 109 (16.1)  | >0.999  |
| Abdomen           | 105 (48.6)| 375 (55.3)  | 0.099   |

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free intervals (p = 0.554). Pain attacks with constant pain were reported by 30 patients (16%) receiving anti-TNF treatment compared to 75 (12%) not receiving anti-TNF (p = 0.268). When comparing the pain character of patients receiving other IBD specific medication (steroids, 5-ASA, antibiotics, calcineurin-inhibitors, immunomodulators), no significant differences across treatment groups were seen (S16–S21 Tables).

**Association between IBD specific treatment and duration of pain attacks**

Moreover, the duration of pain attacks was not influenced by IBD specific medication (Table 6), neither with regards to anti-TNF nor other agents to treat IBD, including steroids, 5-ASA, Antibiotics, Calcineurin-Inhibitors, Immunmodulators (S22–S26 Tables).

**Comparison of pain localization of male and female patients with and without anti-TNF therapy**

From a total of 894 patients, a similar fraction of male and female patients (24% for both) received anti-TNF therapy (Fig 1).

When comparing the pain localizations of male and female patients receiving anti-TNF treatment significantly fewer male patients with anti-TNF treatment suffered from knee/lower leg pain compared to female patients receiving anti-TNF therapy (20% vs. 36%; p = 0.015). Also, significantly fewer male patients receiving anti-TNF treatment reported ankle/foot pain compared to female patients with anti-TNF treatment (10% vs. 22%; p = 0.015). For the other pain localizations, no differences regarding gender were seen (Table 7).

We did not observe any differences in pain localizations in patients with versus without anti-TNF-therapy, neither in male nor female patients (Tables 8 and 9).

### Table 4. Duration of pain.

| Pain period     | Anti-TNF N (%) | No anti-TNF N (%) | p-value |
|-----------------|----------------|-------------------|---------|
| <1 month        | 6 (2.7)        | 9 (1.3)           | 0.218   |
| 1 month–½ year  | 20 (9.3)       | 37 (5.5)          | 0.054   |
| ½ year–1 year   | 13 (6)         | 46 (6.8)          | 0.608   |
| 1–2 years       | 18 (8.3)       | 61 (9)            | 0.890   |
| 2–5 years       | 51 (23.6)      | 164 (24.2)        | 0.927   |
| >5 years        | 108 (50)       | 361 (53.2)        | 0.434   |

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### Table 5. Frequency of pain.

| Pain Frequency       | Anti-TNF N (%) | No anti-TNF N (%) | p-value |
|----------------------|----------------|-------------------|---------|
| Several times daily  | 49 (28.2)      | 115 (22)          | 0.099   |
| 1x/day               | 11 (6.3)       | 34 (6.5)          | >0.999  |
| Several times per week| 34 (19.5)     | 100 (19.1)        | 0.911   |
| 1x/week              | 11 (6.3)       | 26 (5)            | 0.557   |
| Several times per month | 28 (16.1)   | 102 (19.5)        | 0.369   |
| 1x/month             | 12 (6.9)       | 55 (10.5)         | 0.182   |
| <1x/month            | 29 (16.7)      | 91 (17.4)         | 0.907   |

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Discussion

In our study population 5-aminosalicylic acid (5-ASA) (37%) was the most frequently used IBD specific medication, followed by immunomodulators (35%) and anti-TNF antibodies (24%). As for anti-TNF, Vavricka et al. showed that in more than 40% of the cases, this therapy regime is initiated to treat EIM rather than bowel inflammation and over 70% showed a clinical response of EIM to anti-TNF therapy [6]. Our study supports these findings: we could show that significantly less patients on anti-TNF reported elbow pain compared to patients not on anti-TNF. Of note, significantly more patients on steroid treatment reported elbow pain. References to support these findings are lacking.

Regarding gender specific differences in treatment of EIM/ pain in IBD patients, data is not consistent. Concerning IBD treatment, Lopetusa et al. found no general influence of the gender on the therapy of ulcerative colitis (UC) with anti-TNF (infliximab) [33]. However, female patients with steroid-refractory UC and successive anti-TNF treatment showed an increased 1-year remission rate and a cumulative non-colectomy rate. In contradiction, Lopetusa et al. found a lower rate of response to treatment and of disease remission in female patients under TNF inhibitors with axial spondyloarthritis [34]. As for possible explanations, Nguyen et al. showed that the three biomarkers prealbumin, platelet factor 4 and S100A12 accurately predict the response of patients with rheumatoid arthritis to TNF inhibitors [35]. Further studies about a gender-specific correlation of these markers could reveal useful findings. In our study, we found that statistically significant less male patients with anti-TNF treatment reported knee/ lower leg and foot/ ankle pain compared to female patients with anti-TNF. This data may indicate that there is a gender difference regarding the effect of anti-TNF therapy for EIM.

One strength of our study is the size of the cohort with 1263 completed questionnaires. Together with our former study evaluating pain in the SIBDCS [3] it is, to the best of our knowledge, the largest evaluation of pain and the use of IBD specific therapy in IBD up to date.

However, our study also has limitations. Due to the study design and the lack of control regarding unreturned questionnaires, a reporting bias cannot be excluded. Patients who actually suffer from pain due to IBD therefore might be overrepresented compared to patients without pain, since the former might be more motivated to return the questionnaire. The patients not responding to the survey might have represented a different phenotype regarding our topic of interest. The existing data of the SIBDCS doesn’t include any information about pain, preventing us from comparing pain specific parameters between responders and non-responders. Furthermore, regarding the use of IBD specific therapy and pain localizations, we do not have information on the reason to initiate medical therapy (i.e. EIM vs. intestinal activity of IBD or both) and how high the prevalence of pain has been before treatment initiation. Our statistical evaluation of the data represents another limitation. We have performed a mostly descriptive analysis of the dataset. To remain a high response rate and not no

Table 6. Duration of pain attacks.

| Duration of pain attacks | Anti-TNF  | No anti-TNF | p-value |
|-------------------------|---------|------------|---------|
| Seconds                 | 26 (14.9) | 61 (11.9) | 0.295   |
| Minutes                 | 56 (32)  | 158 (30.8) | 0.777   |
| Hours                   | 55 (31.4) | 175 (34)  | 0.577   |
| <3 days                 | 21 (12)  | 67 (13)    | 0.793   |
| >5 days                 | 17 (9.7) | 53 (10.3)  | 0.885   |

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overstrain the goodwill of the patients, we intended to keep our questionnaire on a simplistic level. We further see the sizes of our subgroups as a potential limitation. We are aware that small subgroups may be linked to random positive findings. In comparison to other studies about pain in IBD, the subgroups examined here are not considerably small. Furthermore, we aimed to include as many pain localizations as possible to thoroughly analyse the distribution of pain. Additionally, our findings, particularly regarding Anti-TNF, match the clinical observations, depicting a genuine outcome.

In summary, we could show that the frequency of elbow pain was lower in patients treated with anti-TNF but higher under steroid treatment. There were no significant differences regarding the use IBD specific therapy and the character, duration and frequency of pain. Furthermore, our data point towards a higher treatment benefit of anti-TNF with regards to EIM in male patients which should be followed up in future studies.

Table 7. Pain localization of male vs. female patients with anti-TNF.

| Pain localization      | Anti-TNF/ male | Anti-TNF/ female | p-value |
|------------------------|----------------|------------------|---------|
| Back                   | 32 (30.8)      | 45 (40.2)        | 0.158   |
| Knee/lower leg         | 21 (20.2)      | 40 (35.7)        | **0.015** |
| Elbow                  | 11 (10.6)      | 10 (8.9)         | 0.819   |
| Hip/thigh              | 22 (21.2)      | 30 (26.8)        | 0.344   |
| Finger/hand            | 21 (20.2)      | 32 (28.6)        | 0.158   |
| Ankle/foot             | 10 (9.6)       | 25 (22.3)        | **0.015** |

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Table 8. Pain localization of male patients with vs. without anti-TNF.

| Pain localization | Anti-TNF/ male | No anti-TNF/ male | p-value |
|-------------------|----------------|-------------------|---------|
| Back              | 32 (30.8)      | 122 (38)          | 0.198   |
| Knee/ lower leg   | 21 (20.2)      | 89 (27.7)         | 0.156   |
| Elbow             | 11 (10.6)      | 28 (8.7)          | 0.561   |
| Hip/thigh         | 22 (21.2)      | 73 (22.7)         | 0.787   |
| Finger/ hand      | 21 (20.2)      | 69 (21.5)         | 0.890   |
| Ankle/ foot       | 10 (9.6)       | 51 (15.9)         | 0.146   |

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Table 9. Pain localization of female patients with vs. without anti-TNF.

| Pain localization | anti-TNF/female | No anti-TNF/female | p-value |
|-------------------|-----------------|-------------------|---------|
| Back              | 45 (40.2)       | 114 (31.9)        | 0.110   |
| Knee/ lower leg   | 40 (35.7)       | 92 (25.8)         | 0.053   |
| Elbow             | 10 (8.9)        | 38 (10.6)         | 0.721   |
| Hip/thigh         | 30 (26.8)       | 89 (24.9)         | 0.709   |
| Finger/ hand      | 32 (28.6)       | 73 (20.4)         | 0.090   |
| Ankle/ foot       | 25 (22.3)       | 58 (16.2)         | 0.156   |

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Supporting information

S1 Table. Pain localization (Steroids).
(PDF)

S2 Table. Pain localization (5-aminosalicylic acid).
(PDF)

S3 Table. Pain localization (Immunomodulators).
(PDF)

S4 Table. Pain localization (Antibiotics).
(PDF)

S5 Table. Pain localization (Calcineurin-Inhibitors).
(PDF)

S6 Table. Duration of pain (Steroids).
(PDF)

S7 Table. Duration of pain (5-aminosalicylic acid).
(PDF)

S8 Table. Duration of pain (Antibiotics).
(PDF)

S9 Table. Duration of pain (Calcineurin-Inhibitors).
(PDF)

S10 Table. Duration of pain (Immunomodulators).
(PDF)
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References

1. Wagtmans MJ, Verspaget HW, Lamers CB, van Hogezand RA. Crohn’s disease in the elderly: a comparison with young adults. J Clin Gastroenterol. 1998; 27(2):129–33. PMID: 9754773.
2. Aghazadeh R, Zail MR, Bahari A, Amin K, Ghaighaie F, Firozzi F. Inflammatory bowel disease in Iran: a review of 457 cases. J Gastroenterol Hepatol. 2005; 20(11):1691–5. https://doi.org/10.1111/j.1440-1746.2005.03905.x PMID: 16246187.

3. Zeitz J, Ak M, Muller-Mottet S, Scharl S, Biedermann L, Fournier N, et al. Pain in IBD Patients: Very Frequent and Frequently Insufficiently Taken into Account. PLoS One. 2016; 11(6):e0156666. Epub 2016/06/23. https://doi.org/10.1371/journal.pone.0156666 PMID: 27332879; PubMed Central PMID: PMCPMC4917102.

4. Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. J Clin Gastroenterol. 1996; 23(1):29–34. PMID: 8835896.

5. Lakatos L, Pandur T, David G, Balogh Z, Kuronya P, Tollas A, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. World journal of gastroenterology: WJG. 2003; 9(10):2300–7. https://doi.org/10.3748/wjg.v9.i10.2300 PMID: 14562397; PubMed Central PMID: PMCPMC4656482.

6. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extrainestinal Manifestations of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015; 21(8):1982–92. Epub 2015/07/15. https://doi.org/10.1097/MIB.0000000000000392 PMID: 26154136; PubMed Central PMID: PMCPMC4611685.

7. Salvarani C, Vilchonikolis IG, van der Heijde DM, Fornaciari G, Macchioni P, Beltrami M, et al. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. Scandinavian journal of gastroenterology. 2001; 36(12):1307–13. PMID: 11761022.

8. Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011; 106(1):110–9. https://doi.org/10.1038/ajg.2010.345 PMID: 20808297.

9. Palm O, Bermklev T, Mourn B, Gran JT. Non-inflammatory joint pain in patients with inflammatory bowel disease is prevalent and has a significant impact on health related quality of life. The Journal of rheumatology. 2005; 32(9):1755–9. PMID: 16142874.

10. D’Inca R, Podswiadek M, Ferronato A, Punzi L, Salvagnini M, Stumiolo GC. Articular manifestations in inflammatory bowel disease patients: a prospective study. Dig Liver Dis. 2009; 41(8):565–9. https://doi.org/10.1016/j.dld.2009.01.013 PMID: 19278908.

11. Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal manifestations of inflammatory bowel disease: a population-based study. Am J Gastroenterol. 2001; 96(4):1116–22. https://doi.org/10.1111/j.1572-0241.2001.03756.x PMID: 11316157.

12. Lanna CC, Ferrari Mde L, Rocha SL, Nascimento E, de Carvalho MA, da Cunha AS. A cross-sectional study of 130 Brazilian patients with Crohn’s disease and ulcerative colitis: analysis of articular and ophthalmologic manifestations. Clin Rheumatol. 2008; 27(4):503–8. https://doi.org/10.1007/s10067-007-0797-5 PMID: 18097711.

13. Turkcapar N, Toruner M, Soykan I, Aydintogut OT, Cetinkaya H, Duzgun N, et al. The prevalence of extra-intestinal manifestations and HLA association in patients with inflammatory bowel disease. Rheumatology international. 2006; 26(7):663–8. https://doi.org/10.1007/s00296-005-0044-9 PMID: 16136311.

14. de Vlaminck H, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. J Rheumatol. 2000; 27(12):2860–5. Epub 2000/12/29. PMID: 11128677.

15. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. Gut. 1998; 42(3):387–91. PMID: 9577346; PubMed Central PMID: PMCPMC1727027.

16. Brynskov J, Binder V. Arthritis and the gut. Eur J Gastroenterol Hepatol. 1999; 11(9):997–9. PMID: 10509836.

17. van Erp SJ, Brakenhoff LK, van Gaalen FA, van den Berg R, Fiddler HH, Verspaget HW, et al. Classifying Back Pain and Peripheral Joint Complaints in Inflammatory Bowel Disease Patients: A Prospective Longitudinal Follow-up Study. Journal of Crohn’s & colitis. 2015. https://doi.org/10.1093/ecco-jcc/jv5195 PMID: 26512134.

18. Kuukreja M, Bryant AS, Cleveland DC, Dabal R, Hingorani N, Kirklin JK. Health-Related Quality of Life in Adult Survivors After the Fontan Operation. Semin Thorac Cardiovasc Surg. 2015; 27(3):299–306. https://doi.org/10.1053/j.semtcvs.2015.08.007 PMID: 26708372.

19. Hussain KB, Fontana RJ, Moyer CA, Su GL, Sneed-Pee N, Lok AS. Comorbid illness is an important determinant of health-related quality of life in patients with chronic hepatitis C. Am J Gastroenterol. 2001; 96(9):2737–44. https://doi.org/10.1111/j.1572-0241.2001.04133.x PMID: 11569704.

20. Naliboff BD, Kim SE, Bolus R, Bernstein CN, Mayer EA, Chang L. Gastrointestinal and psychological mediators of health-related quality of life in IBS and IBD: a structural equation modeling analysis. Am J Gastroenterol. 2010; 105(6):1183–92. Epub 2010/04/07. PMID: 20366138; PubMed Central PMID: PMCPMC2841238.
21. Luo J, Hendryx M, Safford MM, Wallace R, Rosson R, Eaton C, et al. Newly Developed Chronic Conditions and Changes in Health-Related Quality of Life in Postmenopausal Women. J Am Geriatr Soc. 2015; 63(11):2349–57. https://doi.org/10.1111/jgs.13796 PMID: 26503351.

22. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis. 2012; 6(10):991–1030. https://doi.org/10.1016/j.crohns.2012.09.002 PMID: 23040451.

23. Dignass A, Van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010; 4(1):28–62. https://doi.org/10.1016/j.crohns.2009.12.002 PMID: 21122489.

24. Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med. 2012; 156(5):350–9. https://doi.org/10.7326/0003-4819-156-5-201203060-00007 PMID: 22393130; PubMed Central PMCID: PMCPMC3369539.

25. Long MD, Kappelman MD, Martin CF, Chen W, Anton K, Sandler RS. Role of Nonsteroidal Anti-Inflammatory Drugs in Exacerbations of Inflammatory Bowel Disease. J Clin Gastroenterol. 2015. https://doi.org/10.1097/MCG.0000000000000421 PMID: 26485106.

26. Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2006; 4(2):196–202. PMID: 16469680.

27. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflam matory drugs on the small and large intestine in humans. Gastroenterology. 1993; 104(6):183 2–47. PMID: 8500743.

28. Kaufmann HJ, Taubin HL. Nonsteroidal anti-inflammatory drugs activate quiescent inflammatory bowel disease. Ann Intern Med. 1987; 107(4):513–6. PMID: 3498419.

29. Miner PB Jr. Factors influencing the relapse of patients with inflammatory bowel disease. Am J Gastroenterol. 1997; 92(12 Suppl):1S–4S. PMID: 9395345.

30. Kefalakes H, Styliandes TJ, Amanakis G, Kolios G. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? European journal of clinical pharmacology. 2009; 65(10):963–70. https://doi.org/10.1007/s00228-009-0719-3 PMID: 19711064.

31. Pittet V, Juillerat P, Mottet C, Felley C, Ballabeni P, Burnand B, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). Int J Epidemiol. 2009; 38(4):922–31. Epub 2008/09/11. https://doi.org/10.1093/ije/dyn180 PMID: 18782966.

32. Nagel B, Gerbershagen HU, Lindena G, Pfingsten M. [Development and evaluation of the multidimensional German pain questionnaire]. Schmerz. 2002; 16(4):263–70. Epub 2002/08/23. https://doi.org/10.1007/s00482-002-0162-1 PMID: 12192435.

33. LoPetuso LR, Gerardi V, Papa V, Scaldaferr F, Rapaccini GL, Gasbarrini A, et al. Can We Predict the Efficacy of Anti-TNF-alpha Agents? Int J Mol Sci. 2017; 18(9). Epub 2017/09/15. https://doi.org/10.3390/ijms18091973 PMID: 28906475; PubMed Central PMCID: PMCPMC5618622.

34. Lubrano E, Perrotta FM, Manara M, D’Angelo S, Addimanda O, Ramonda R, et al. The Sex Influence on Response to Tumor Necrosis Factor-alpha Inhibitors and Remission in Axial Spondyloarthrits. J Rheumatol. 2018; 45(2):195–201. Epub 2018/02/09. https://doi.org/10.3899/jrheum.170666 PMID: 29419448.

35. Nguyen MVC, Baillet A, Romand X, Trocmé C, Courtier A, Marotte H, et al. Prealbumin, platelet factor 4 and S100A12 combination at baseline predicts good response to TNF alpha inhibitors in rheumatoid arthritis. Joint Bone Spine. 2018. Epub 2018/06/10. https://doi.org/10.1016/j.jbspin.2018.05.006 PMID: 29885551.