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Quality of life during one year of postoperative prophylactic drug therapy after intestinal resection in Crohn's patients: Results of the APPRECIA trial

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ABSTRACT

Background: In APPRECIA trial, Crohn's disease (CD) patients undergoing intestinal resection were randomized to postoperative adalimumab (ADA) or azathioprine (AZA).
Aims: To evaluate health-related quality of life (HRQoL) in APPRECIA trial.
Methods: HRQoL was evaluated using disease-specific shortened Spanish version of the IBDQ (SIBDQ-9) and generic European Quality of Life-5 Dimensions (EQ-5D) questionnaires, completed at baseline and at weeks 24 and 52.
Results: Sixty-one patients (37 ADA and 24 AZA) had evaluable data for HRQoL. Patients treated with ADA or AZA had significant improvement from baseline to weeks 24 and 52 in SIBDQ-9 and EQ-5D ($p < 0.001$ and $p \leq 0.006$ for all comparisons, respectively). There were no differences between treatment arms in mean change in SIBDQ-9 and EQ-5D at weeks 24 and 52 vs baseline. Only patients without endoscopic recurrence had significant improvement in SIBDQ-9 ($p < 0.001$) and EQ-5D ($p < 0.001$) at week 52.

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At week 52, there was a high to moderate negative correlation between CDAI score with SIBDQ-9 score (Pearson's *r*: −0.768) and with EQ-5D index (*r*: −0.644).
Conclusion: HRQoL improved after intestinal resection in CD, irrespective of the postoperative therapy used (ADA or AZA). Outcomes in HRQoL were associated with prevention of endoscopic recurrence, since improvements in HRQoL were only significant in patients with endoscopic remission at 1 year.

1. Introduction

Crohn's disease (CD) is an incurable inflammatory bowel disease characterised by alternating periods of relapse and remission. Clinical features of active CD such as diarrhoea, abdominal pain and malaise have been shown in large questionnaire-based studies to have a substantial impact on patients health-related quality of life (HRQoL), including their functioning and well-being [1]. Accordingly, achievement of disease remission by drug therapies is associated with improvements in HRQoL [2,3]. Therefore, HRQoL assessment has been recommended for clinical trials evaluating CD, as it directly reflects patient-perceived benefits of treatment.

Despite the growing use of immunosuppressive and biologic therapies, urgent or elective surgery continues to play a significant role in the management of CD [4]. Intestinal resection, usually in the form of an ileocecal or ileocolonic resection, is the most commonly performed operation for CD. Intestinal resection in CD patients is associated with improved HRQoL [5], being the benefits evident as early as 30 days after resection [6]. However, high rates of clinical and endoscopic recurrence can affect the long-term durability of improved HRQoL following surgery [7,8]. The effects of prophylactic postoperative drug therapy in improving HRQoL after intestinal resection were not associated with endoscopic recurrence or the type of therapy [9].

The randomised controlled trial APPRECIA analysed the early postoperative use of adalimumab (ADA) or azathioprine (AZA) in the prevention of postoperative endoscopic recurrence in CD [10]. The primary endpoint of the trial was the postoperative endoscopic recurrence at 1 year (Rutgeerts score i2b, i3, i4), as evaluated by a blinded central reader. The study showed that ADA is as efficacious as AZA in the prophylaxis of postoperative endoscopic recurrence [10]. The aim of the present study was to evaluate changes in HRQoL in the CD patients undergoing intestinal resection included in the APPRECIA trial who were randomized to postoperative therapy with ADA or AZA.

2. Materials and methods

2.1. Study design and patients

In APPRECIA Study, a phase 3, multicentre, randomised, evaluator-blind, superiority trial sponsored by GETECCU (Spanish Working Group on Crohn's Disease and Ulcerative Colitis), CD patients with ileocaecal or ileocolonic intestinal resection were randomised either to ADA or AZA for 52 weeks, both associated with metronidazole for 12 weeks [10]. The primary endpoint of the trial was postoperative endoscopic recurrence at 1 year. Change in HRQoL was a secondary endpoint of the study. The trial was approved by the Institutional Review Board of the coordinating centre (Hospital La Fe, Valencia, Spain; EudractCT number: 2011-000885-36; ClinicalTrials.gov number: NCT01564823) and confirmed by the local ethics committees. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written, informed consent was obtained from each patient included in the study. The study period ranged from January 2012 to January 2015.

2.2. Outcome measures

Patients included in APPRECIA who received at least one dose of the study drug were eligible. The study population for HRQoL assessment were patients who completed the questionnaires and had evaluable data. Validated disease-specific and generic questionnaires were completed by patients at baseline (2 weeks after surgery) and at weeks 24 and 52. The shortened Spanish version of the Inflammatory Bowel Disease Questionnaire (SIBDQ-9) was administered. It consists of nine items assessing the effect of IBD on social, emotional, and physical well-being [11]. The overall score is obtained by summing up each item score and the result is transformed into a 0–100 scale, where 0 represents the worst health. The SIBDQ-9 score has proven its validity and reproducibility [11], as well as an excellent correlation with IBDQ-36 [12]. An increase in the SIBDQ-9 score of ≥9 points from baseline was considered the minimal clinically meaningful difference (MCMD) [11,12,13]. The European Quality of Life-5 Dimensions (EQ-5D) is a generic HRQoL instrument that provides a standardised measure of health status, comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [14]. The total index score ranges from −0.594 to 1.000, where higher scores indicate better HRQoL. The EQ-5D visual analogue scale (VAS) ranges from 0 to 100, where 0 represents the worst imaginable health state and 100 the best imaginable one.

Mean changes in SIBDQ-9 score and EQ-5D index from baseline to weeks 24 and 52 were compared for patients receiving ADA or AZA. Changes in HRQoL from baseline at week 52 were also compared for patients with or without endoscopic recurrence at 1 year. We analysed index at week 52 with Crohn's Disease Activity Index (CDAI) score at week 52.

2.3. Statistical analysis

Changes from baseline in SIBDQ-9 score and EQ-5D index were assessed using one-sample t-test. Differences in changes from baseline between treatment arms were evaluated by two-sample t-test for SIBDQ-9 and Wilcoxon rank-sum test for EQ-5D index. Differences according to the presence of endoscopic recurrence were assessed by ANOVA test for both SIBDQ-9 score and EQ-5D index. Chi square test was used to estimate differences between treatment arms for the 9 individual items of SIBDQ-9 and the 5 individual dimensions of EQ-5D. Linear correlation between HRQoL total scores and CDAI score was assessed using Pearson's correlation coefficient. A *p*-value less than 0.05 was considered statistically significant. All analyses were conducted using SAS 9.4 software.

3. Results

3.1. Study population and baseline characteristics

The intention to treat population of the APPRECIA trial included 84 patients (45 randomised in the ADA group and 39 in the AZA

Table 1
Baseline demographic and clinical characteristics of patients randomized to postoperative adalimumab or azathioprine.

	Adalimumab [n = 37]	Azathioprine [n = 24]	*p*
Age—years			0.379
Median	35.0	36.0	
Interquartile range	(30.0, 40.0)	(31.0, 43.0)	
Male gender—no. [%]	15 [40.5]	15 [62.5]	0.094
Current smoker—no. [%]	8 [21.6]	3 [12.5]	0.282
Duration of disease—years mean (SD)	8.22 (6.70)	5.63 (5.13)	0.138
BMI[a]—kg/m^2 mean (SD)	22.74 (4.87)	22.13 (2.16)	0.843
Crohn's disease phenotype			
Localisation—no. [%]			0.807
-L1 ileal	19 [51.4]	12 [50.0]	
-L3 ileum + colon	16 [43.2]	10 [41.7]	
-L4 upper digestive tract	2 [5.4]	2 [8.3]	
Behaviour—no. [%]			
-B3	17 [45.9]	7 [29.2]	0.190
-Perianal	4 [10.8]	5 [20.8]	0.281
Previous resections—no. [%]	3 [8.1]	1 [4.2]	1.000
Any risk factor [smoking, B3, previous resection] — no. [%]	33 [89.2]	19 [79.2]	0.281
Centimetres of ileum resected			0.400
Median	27.0	32.0	
Interquartile range	(16.0, 34.0)	(15.0, 47.5)	
Therapies before surgery—no. [%]			
-Glucocorticoids	35 [94.6]	23 [95.8]	1.000
-Immunosuppressants [thiopurines or methotrexate]	30 [81.1]	17 [70.8]	0.765
-Anti TNFα	23 [62.2]	14 [58.3]	0.352

CDAI, Crohn's Disease Activity Index; STD, standard deviation.
[a] The body-mass index [BMI] is the weight in kilograms divided by the square of the height in meters.

Table 2
Baseline demographic and clinical characteristics of patients without or with endoscopic recurrence at 1 year.

	Without endoscopic recurrence [n = 42]	With endoscopic recurrence [n = 19]	*p*
Age—years			0.566
Median	35.0	35.0	
Interquartile range	(31.0, 43.0)	(30.0, 41.0)	
Male gender—no. [%]	20 [47.6]	10 [52.6]	0.717
Current smoker—no. [%]	7 [16.7]	4 [21.1]	0.394
Duration of disease—years mean (SD)	7.79 (6.79)	5.89 (4.63)	0.495
BMI[a]—kg/m^2 mean (SD)	22.41 (3.86)	22.69 (4.41)	0.981
Crohn's disease phenotype			
Localisation—no. [%]			
-L1 ileal	21 [50.0]	10 [52.6]	
-L3 ileum + colon	19 [45.2]	7 [36.8]	
-L4 upper digestive tract	2 [4.8]	2 [10.6]	
Behaviour—no. [%]			
-B3	18 [42.9]	6 [31.6]	0.404
-Perianal	6 [14.3]	3 [15.8]	0.878
Previous resections—no. [%]	3 [7.1]	1 [5.3]	1.000
Any risk factor [smoking, B3, previous resection]—no. [%]	36 [85.7]	16 [84.2]	0.878
Centimetres of ileum resected			0.756
Median	29.5	25.0	
Interquartile range	(15.0, 40.0)	(20.0, 40.0)	
Therapies before surgery—no. [%]			
-Glucocorticoids	39 [92.9]	19 [100.0]	0.546
-Immunosuppressants [thiopurines or methotrexate]	32 [76.2]	15 [78.9]	0.813
-Anti TNFα	24 [57.1]	13 [68.4]	0.403

CDAI, Crohn's Disease Activity Index; STD, standard deviation.
[a] The body-mass index [BMI] is the weight in kilograms divided by the square of the height in meters.

group) recruited from 22 centres. Of these, 61 patients (receiving 37 ADA and 24 AZA) who had evaluable data for HRQoL outcomes composed the study population. The cohorts were similar regarding baseline characteristics, including smoking status, previous resections, CD phenotype, previous perianal disease, and previous drug exposure (Table 1). At baseline, there were no differences in mean SIBDQ-9 total score between the cohorts of patients randomized to ADA (60.6, 95% CI: 55.2–65.9) or to AZA (60.4, 95% CI: 53.6–67.2; $p = 0.9$). Mean baseline EQ-5D total index was no different between the ADA group (64.8, 95% CI: 58.8–70.9) and the AZA group (67.3, 95% CI: 59.5–75.2; $p = 0.604$).

Nineteen patients had endoscopic recurrence at 1 year and 42 patients did not, as reported in the APPRECIA trial. Baseline demographic and clinical characteristics of patients without or with endoscopic recurrence are summarized in Table 2. At baseline, mean SIBDQ-9 total score was 60.0 (95% CI: 55.4–64.5) and 61.7 (95% CI: 52.7–70.6) for the cohorts of patients without or with endoscopic recurrence at 1 year, respectively ($p = 0.485$). Mean baseline EQ-5D total index was 62.6 (95% CI: 57.3–67.9) for patients without endoscopic recurrence and 70.0 (95% CI: 63.9–82.1; $p = 0.036$) for patients with recurrence.

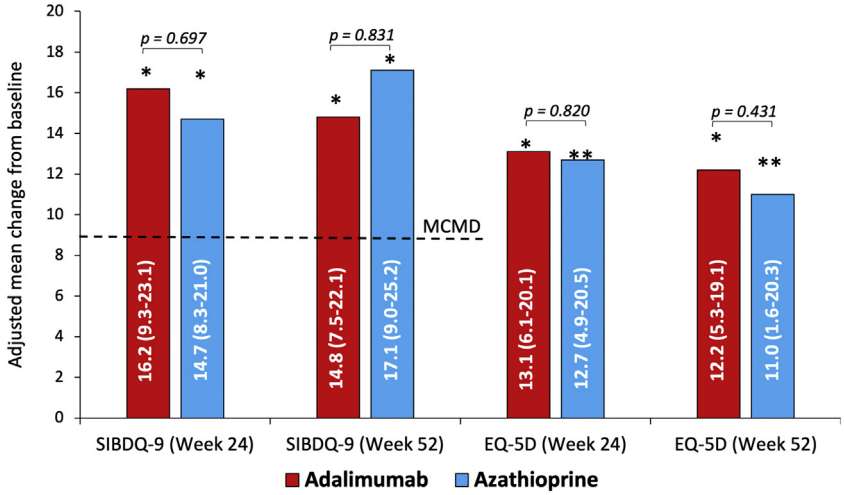

Fig. 1. Adjusted mean change in Short Inflammatory Bowel Disease Questionnaire [SIBDQ-9] score and in European Quality of Life-5 Dimensions [EQ-5D] index from baseline to weeks 24 and 52 in the cohorts of patients treated with adalimumab or with azathioprine [mean (95% CI)].
*$p < 0.0001$ versus baseline; **$p = 0.002$ versus baseline; ***$p = 0.006$ versus baseline. MCMD: minimal clinically meaningful difference in the SIBDQ-9 score.

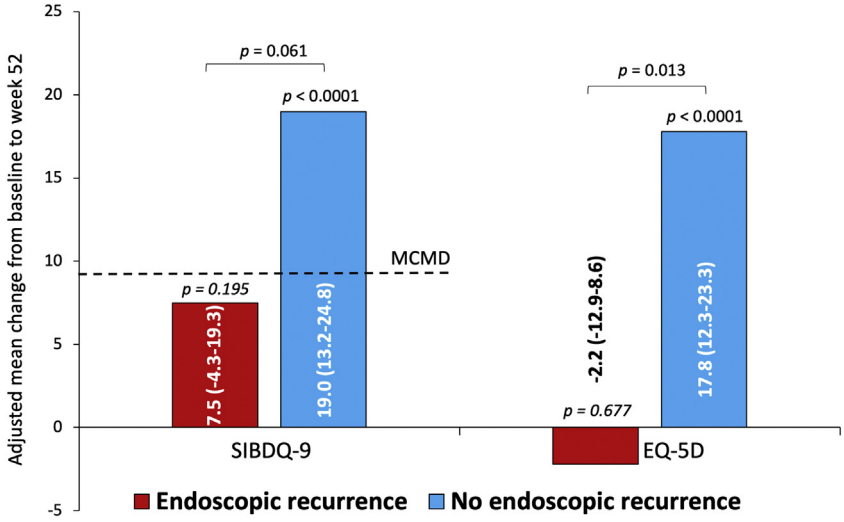

Fig. 2. Adjusted mean change in Short Inflammatory Bowel Disease Questionnaire [SIBDQ-9] score and in European Quality of Life-5 Dimensions [EQ-5D] score from baseline to week 52 in patients with or without endoscopic recurrence at 1 year.
*$p < 0.0001$ versus baseline; **$p = 0.195$ versus baseline; ***$p = 0.319$ versus baseline. MCMD: minimal clinically meaningful difference in the SIBDQ-9 score.

3.2. HRQoL outcomes by treatment arm

Patients treated with ADA or AZA showed a statistically significant improvement from baseline at weeks 24 and 52 in HRQoL outcomes measured with SIBDQ-9 score ($p < 0.0001$ for all comparisons) and EQ-5D index (Fig. 1). No differences were observed between patients receiving ADA or AZA in the adjusted mean change in SIBDQ-9 score and EQ-5D index at weeks 24 and 52 from baseline (Fig. 1). There were no differences in the 5 individual dimensions of EQ-5D according to the treatment arm. At week 24, there were no differences in mean SIBDQ-9 total score between patients randomized to ADA (76.8, 95% CI: 70.8–82.7) or to AZA (75.1, 95% CI: 68.5–81.6; $p = 0.462$). Mean EQ-5D total index at week 24 was no different between the ADA (77.9, 95% CI: 72.4–83.4) and the AZA cohort (80.0, 95% CI: 74.3–85.8; $p = 0.710$). At week 52, mean SIBDQ-9 total score was 76.0 (95% CI: 69.1–82.8) and 76.2 (95% CI: 68.5–83.9) for patients randomized to ADA or to AZA, respectively ($p = 0.731$). Mean EQ-5D total index at week 52 was no different between the ADA group (77.9, 95% CI: 71.2-84.5) and the AZA group (77.7, 95% CI: 72.0–83.4; $p = 0.513$).

3.3. HRQoL outcomes according to the presence of endoscopic recurrence

Only patients with endoscopic remission (Rutgeerts score i0, i1, i2a) at 1 year had a significant improvement in SIBDQ-9 score ($p < 0.0001$) and EQ-5D index ($p < 0.0001$) mean change at week 52 from baseline (Fig. 2). Mean change from baseline to week 52 in the EQ-5D index was significantly greater in patients without endoscopic recurrence at 1 year (17.8, 95% CI: 12.3–23.3) compared to those with recurrence (−2.1, 95% CI: −12.9 to 8.6; $p = 0.013$) (Fig. 2). At week 52, patients without endoscopic recurrence (19.0, 95% CI: 13.2–24.8) had a numerically greater improvement in SIBDQ-9 mean change from baseline compared to those with recurrence (7.5, 95% CI: −4.3 to −19.3; $p = 0.061$). At week 52, there were no significant differences in mean SIBDQ-9 total score between patients without endoscopic recurrence (78.5, 95% CI: 72.9–84.2) or those with recurrence (70.0, 95% CI: 59.4–80.7; $p = 0.174$). EQ-5D total index at week 52 was 79.9 (95% CI: 74.5–85.4) and 72.9 (95% CI: 64.8–81.1) for patients without or with endoscopic recurrence, respectively ($p = 0.101$).

Table 3
Linear correlations (at baseline, at week 52, and changes from baseline to week 52) between health-related quality of life total scores and Crohn's Disease Activity Index (Pearson's correlation coefficient).

Pearson's *r*	EQ-5D			SIBQD-9		
CDAI	Baseline	Week 52	Changes	Baseline	Week 52	Changes
Baseline	−0.407*			−0.304*		
Week 52		−0.644*			−0.768*	
Changes			−0.326*			−0.544*

CDAI, Crohn's Disease Activity Index; EQ-5D, European Quality of Life-5 Dimensions; SIBQD-9, Shortened Spanish version of the Inflammatory Bowel Disease Questionnaire.
* $p < 0.001$.

3.4. Interaction between the treatment arm and the presence of endoscopic recurrence

After stratifying by endoscopic recurrence and treatment, for both ADA and AZA arms only patients without endoscopic recurrence had a significantly greater improvement in mean change from baseline in SIBDQ-9 score and EQ-5D index (Fig. 3). In the ADA group, improvement in both questionnaires was significantly greater at week 52 in patients without endoscopic recurrence compared to those with recurrence (Fig. 3).

3.5. Correlation of HRQoL outcomes with CDAI

At baseline, mean CDAI score was 172.8 and 128.8 for patients without endoscopic recurrence or those with endoscopic recurrence, respectively ($p = 0.074$). At week 52, mean CDAI score was 67.0 and 84.9 for patients without endoscopic recurrence or those with endoscopic recurrence, respectively ($p = 0.250$). Thus, the mean change in CDAI score was −105.0 and −33.5 for patients without endoscopic recurrence and those with endoscopic recurrence, respectively ($p = 0.004$).

At week 52, there was a high negative correlation between the total SIBDQ-9 score and the CDAI score (Pearson's *r*: −0.768; $p < 0.001$), and a moderate negative correlation between the total EQ-5D index and the CDAI score (Pearson's *r*: −0.644; $p < 0.001$) (Table 3). There was a moderate negative correlation between the mean change from baseline to week 52 of SIBDQ-9 score and CDAI score (Pearson's *r*: −0.544; $p < 0.001$), and a weak negative correlation between the mean change from baseline to week 52 of EQ-5D index and CDAI score (Pearson's *r*: −0.326; $p < 0.001$) (Table 3).

4. Discussion

This study reports HRQoL changes in the CD patients randomized in the APPRECIA trial to ADA or AZA to prevent endoscopic recurrence after elective ileocolonic resection. Improvement in disease-specific and generic HRQoL was sustained, and clinically meaningful. A statistically significant improvement in SIBDQ-9 score and EQ-5D index was seen as early as week 24 and was maintained through week 52. The effect on patient-reported HRQoL was similar in the ADA and AZA arms. This was to be expected since in the APPRECIA trial no significant differences were observed between the treatment groups for clinical, endoscopic or radiological recurrence [10].

Patient-reported HRQoL outcomes provide valuable information about the impact of treatment on CD patient health status and well-being. Therefore, ideal assessment of efficacy for CD therapies should comprise clinical and endoscopic evaluation, complemented by patient-reported HRQoL. HRQoL improvement over the long-term after intestinal resection for complicated CD is uncertain, due to the high rate of postoperative clinical and endoscopic recurrence [7,8,15].

Surgery has been described as a reset of disease course, and this window of opportunity could make a strategy based on preventive immunosuppressants and/or biological therapy an attractive option [16]. Prospective studies evaluating impact of postoperative prophylactic therapy on patient-reported HRQoL in CD are scarce. The POCER study has shown that intestinal resection of all macroscopic CD followed by prophylactic drug therapy was associated with a significant and durable improvement both in general and disease-specific HRQoL [9]. As in our work, authors reported that the benefit in HRQoL was irrespective of the type of therapy (ADA or thiopurines). In another study with a smaller sample, patients receiving postoperative prophylactic therapy with ADA showed a greater improvement in HRQoL compared to those treated with AZA or mesalazine. In this study, with a 2-year follow-up that doubles that of the APPRECIA trial, the rate of endoscopic or clinical recurrence was significantly lower in the ADA compared with the AZA and mesalamine groups, a fact that explains the differences in the gain of HRQoL between arms [17]. A meta-analysis of controlled trials reported that anti-TNF agents may be more effective in preventing clinical and endoscopic postoperative Crohn's disease recurrence than control treatment (thiopurines or mesalamine), but HRQoL outcomes were not evaluated [18].

The most relevant and novel finding of our study is the evidence that endoscopic remission at 1 year (defined as Rutgeerts score i0, i1, i2a) was predictive of a greater benefit on HRQoL outcomes. In fact, improvement from baseline to week 52 in SIBDQ-9 score and EQ-5D index was only significant in patients with endoscopic remission. Improvement from baseline to week 52 in the SIBDQ-9 score was clinically meaningful only for patients with endoscopic remission at 1 year. Moreover, in both ADA and AZA arms the effect on perceived HRQoL was significant for patients achieving remission at 1 year and not for those with endoscopic recurrence, a fact that gives consistency to our results. This finding is intriguing, since in the APPRECIA trial no significant differences were observed at week 52 for the absolute CDAI score or the proportion of patients with CDAI <150 between the population with endoscopic remission or endoscopic recurrence at 1 year. As a possible explanation, in our study mean reduction in CDAI score at week 52 was significantly greater in patients without endoscopic recurrence at 1 year compared to those with recurrence.

In our study, there was a high to moderate negative correlation between absolute HRQoL scores and CDAI score (patients with a higher CDAI score had a lower SIBDQ-9 score and a lower EQ-5D index). In a previous study in CD patients with ileocolonic resection, multivariate analysis showed that changes in HRQoL scores had a strong linear relationship with CDAI score [7]. However, even in the absence of active disease, HRQoL could be impaired in patients with CD [19]. Furthermore, although changes in clinical indexes of activity may correlate with HRQoL [20], some CD patients' HRQoL may still be impaired despite achieving clinical goals such as mucosal healing [21]. Patient-reported HRQoL is a global measure of the patient's perceptions, illness experience, and functional status. It is not always associated with CD clinical activity, and may be more sensitive to other changes affecting patients rather than clinical outcomes. Our study is the first to report an association between improvement in HRQoL and postoperative endoscopic recurrence in CD patients undergoing intestinal resection. In the CD population included in the POCER study, improvement in HRQoL was sustained at 18 months postoperatively, irrespective of endoscopic recurrence [9].

A limitation of our study is the lack of a placebo-controlled arm to assess if the observed benefits in HRQoL depend on the postoperative prophylactic drugs used or on the surgery itself [22]. In this sense, the main findings of a recent systematic review are that patients with CD report a significant improvement in HRQOL as early as 30 days and up to 5 years after intestinal resection [14].

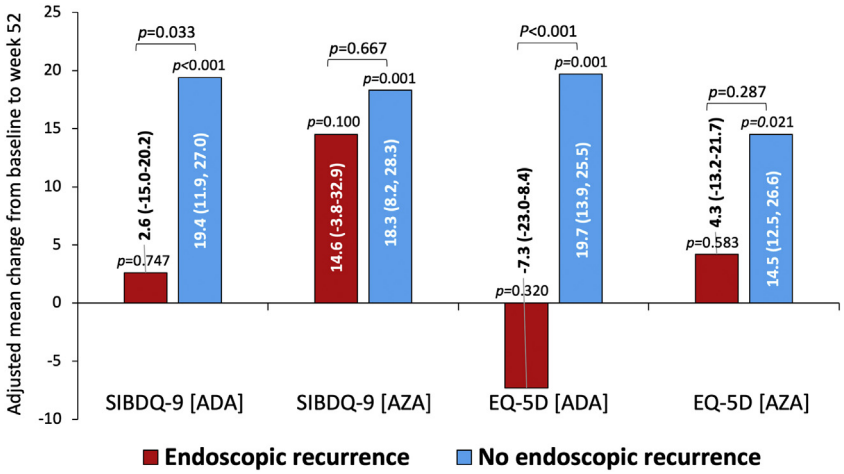

Fig. 3. Adjusted mean change in Short Inflammatory Bowel Disease Questionnaire [SIBDQ-9] score and in European Quality of Life-5 Dimensions [EQ-5D] index from baseline to week 52, stratified by endoscopic recurrence and treatment group [adalimumab (ADA) or azathioprine (AZA)].

In conclusion, disease-specific and generic perceived HRQoL improved after elective ileocaecal or ileocolonic intestinal resection in CD patients. This benefit was independent of the type of postoperative prophylactic therapy used (ADA or AZA) and it may be due to the surgery itself. Outcomes in patient-reported HRQoL were associated with prevention of endoscopic recurrence, since the improvements in HRQoL were only significant in patients who had endoscopic remission at 1 year.

Conflict of interest

CT: reports personal fees from MSD, AbbVie, Pfizer, Janssen, Takeda, Ferring, Tillots-Pharma, Dr. Falk Pharma, outside the submitted work. AL-S: reports grants from AbbVie, during the conduct of the study; grants and personal fees from AbbVie, MSD, Tillotts, personal fees from Ferring, Faes Farma, Shire, Hospira, Kern-Celltrion, Takeda, Pfizer, outside the submitted work. IV-M: reports personal fees from MSD, AbbVie, Shire, Ferring, Takeda, Pfizer, outside the submitted work. ED: reports grants, personal fees, and non-financial support from AbbVie, MSD, personal fees from Takeda, Hospira, Kern, Shire Pharmaceuticals, personal fees and non-financial support from Ferring, Tillots Pharma, Otsuka Pharmaceuticals, personal fees from Pfizer, Celgene, outside the submitted work. JG: reports personal fees from AbbVie, MSD, Shire, Ferring, Kern Pharma, Gebro Pharma, outside the submitted work. ME: reports a collaboration with Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa [GETECCU] during the conduct of the study; other from AbbVie, MSD, Tillots-Pharma, Takeda, outside the submitted work. PM-M: reports personal fees and nonfinancial support from AbbVie, Ferring, Takeda, Otsuka, Shire, outside the submitted work. JPG: has served as a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Hospira, Kern Pharma, Takeda, Janssen, Pfizer, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Vifor Pharma. XC: reports personal fees from AbbVie, Hospira, MSD, Shire, Allergan, outside the submitted work. JB: reports non-financial support from AbbVie, MSD, Ferring, outside the submitted work. MDM-A: reports a collaboration with AbbVie, other from Janssen, other from Takeda, other from MSD, outside the submitted work. FB: reports a collaboration with AbbVie, outside the submitted work. JR: reports grants from Genentech, personal fees from Takeda, Robarts Clinical Trials, grants from AbbVie, outside the submitted work. PN: reports grants and personal fees from MSD, grants from Otsuka, AbbVie, personal fees from Takeda, Kern, Biogen, Janssen, Ferring, outside the submitted work. The remaining authors declare that they have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.01.002.

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