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Patients' Preference on Advanced Therapy and Follow-Up Procedure for Inflammatory Bowel Disease in Japan: A Web-Based 3A Survey

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Keywords
Inflammatory bowel disease · Advanced therapy · Examination method · Crohn's disease · Ulcerative colitis

Abstract

Introduction: With the recent increase in number of drugs for treating inflammatory bowel disease (IBD), it has become important to select treatments acceptable to patients. Endoscopy and biomarkers from blood and stool samples are used to evaluate IBD disease activity. This study aimed to clarify the acceptability of usage of advanced therapy and examination methods in patients through an internet-based survey. ***Methods:*** Patients with inflammatory bowel disease were asked via the internet to participate in a survey on the acceptability of nine therapies and three examination methods. The respondents rated acceptability on a scale of 1–10 and specified the most preferred option. ***Results:*** Responses were obtained from 388 patients with ulcerative colitis and 82 with Crohn's disease; 14.5% and 11.5% of the patients underwent intravenous infusions and subcutaneous injections, respectively. Once-daily oral administration had the highest acceptability score, which was significantly different from other administration usages ($p < 0.0001$), regardless of prior treatment history. Oral administration was preferred by 88.9% of patients. The ranking of examination methods from most to least acceptable was blood tests > endoscopy > stool tests, with significant differences among all groups ($p < 0.0001$). Blood testing (76%) and stool testing (4.5%) were the most and least preferred methods, respectively. ***Conclusions:*** The most acceptable usage of advanced therapy in patients with inflammatory bowel disease was once-daily oral administration. Treatments that are effective, safe, and acceptable to patients should be selected, and examination methods acceptable to patients should be used.

Introduction

The two inflammatory bowel diseases (IBDs), ulcerative colitis (UC), and Crohn's disease (CD), are intractable diseases of unknown cause [1], and the number of patients with IBD continues to increase. UC and CD are associated with diarrhea, abdominal pain, fever, bloody stools, and other symptoms that greatly impair quality of life [2, 3]. Antitumor necrosis factor antibody, anti-p40 antibody, anti-α4β7 integrin antibody, and Janus kinase inhibitors are currently available for the treatment of refractory IBD. The new drugs can be administered orally, intravenously, or subcutaneously via various routes and at different frequencies [4–7].

Shared decision-making is becoming increasingly important in the treatment of IBD. When selecting a drug, it is important to consider not only efficacy, safety, and drug information but also patient acceptability [8].

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Achieving mucosal healing is associated with improved prognosis in the treatment of IBD, and in recent years, monitoring by using a combination of biomarkers along with endoscopy has been emphasized as a treat-to-target strategy [9, 10]. Fecal biomarkers, such as fecal calprotectin and fecal immunochemical test, have been found to be correlated with endoscopic activity scores [11, 12]. Recently, a blood biomarker, leucine-rich alpha-2 glycoprotein (LRG), has been reported to be a useful biomarker for patients with IBD; LRG assay is currently approved and available for use in Japan [13–16].

We previously reported on the quality of life and acceptability of topical therapy in the 3I and 3T surveys, which were internet surveys of patients with IBD [1, 17]. In this study, we conducted the 3A survey (acceptance about usage of advanced therapy and examination for patients with IBD) to determine the acceptability of usage of drug administration and examination methods in patients with IBD.

Methods

Survey Instruments

From January 26 to February 2, 2023, 1,535 patients with IBD registered with Cross Marketing Co., Ltd. (Tokyo, Japan) were sent an email asking for cooperation in a questionnaire survey conducted via the internet. The survey items included disease (UC/CD), age, sex, area of residence, duration of disease, smoking status, history of bowel resection, occupation, treatment history, attending medical institution (university hospital, general hospital, clinic, or no attending medical institution), current degree of diarrhea and abdominal pain (none, mild, moderate, or severe), frequency of attending medical institution, and preference for each drug administration usage and examination method (on a scale of 1–10), as well as the most preferred methods.

As of August 2022, infliximab [18], adalimumab [19], golimumab [20], ustekinumab [21], vedolizumab [22], tofacitinib [23], and filgotinib [24] were available as advanced therapies for refractory IBD in Japan. The drug name or other information was not provided in the evaluation of acceptability of drug administration usage. Instead, nine comparisons were made: 8-week interval infusion, 4-week interval infusion, 12-week interval subcutaneous injection, 8-week interval subcutaneous injection, 4-week interval subcutaneous injection, 2-week interval subcutaneous injection, 1-week interval subcutaneous injection, once-daily oral administration, and twice-daily oral administration.

Additionally, three examination methods were compared: blood tests, stool tests, and endoscopy. This study was approved by the Ethics Committee of Iwate Medical University (MH2022-103), and informed consent was obtained from all patients.

Outcome

The primary endpoint was the comparison of acceptability scores from 1 (least preferred) to 10 (most preferred) for nine drug administration usages and three examination methods. The

Table 1. Demographics of patients

Patients, *n*	470
UC	82.6% (388/470)
CD	17.4% (82/470)
Sex (male)	69.4% (326/470)
Age (mean±SD)	52.9±11.2 years
Disease duration (mean±SD)	14.8±10.3 years
Working status	
Full-time	49.6% (233/470)
Part-time	15.1% (77/470)
Student	0% (0/470)
Housework	8.9% (42/470)
Other	3.6% (17/470)
Unemployed	22.8% (107/470)
Smoking	
Present	50.9% (239/470)
Past	18.7% (88/470)
Never	30.4% (143/470)
History of resection	18.3% (86/470)
Degree of current symptoms	
None	43.8% (206/470)
Mild	39.8% (187/470)
Moderate	14.7% (69/470)
Severe	1.7% (8/470)
Visiting institutions	
University hospital	18.3% (86/470)
General hospital	59.4% (279/470)
Clinic	21.9% (103/470)
No regular visits	0.4% (2/470)
Frequency of visits	
Once a week	0.4% (2/470)
Once every 2 weeks	1.5% (7/470)
Once a month	29.1% (137/470)
Once every 2 months	40.2% (189/470)
Once every 3 months	26.6% (125/470)
Less often than that	1.7% (8/470)
No visits	0.4% (2/470)
Treatment history	
Oral mesalazine	94.3% (443/470)
Nutritional therapy	21.9% (103/470)
Oral steroids	43.6% (205/470)
Infliximab	12.3% (58/470)
Adalimumab	8.3% (39/470)
Golimumab	1.7% (8/470)
Ustekinumab	2.8% (13/470)
Vedolizumab	1.3% (6/470)
Tofacitinib	0.9% (4/470)
Filgotinib	0.2% (1/470)
Budesonide foam	13.8% (65/470)
Suppository	37.7% (177/470)
Enema	33.8% (159/470)
Thiopurine	11.9% (56/470)
Tacrolimus	1.5% (7/470)
Apheresis	9.6% (45/470)
History of intravenous infusion and subcutaneous injection treatment	
None	79.8% (375/470)
Intravenous infusion	14.5% (68/470)
Subcutaneous injection	11.5% (54/470)

CD, Crohn's disease; UC, ulcerative colitis.

secondary endpoints were the preferred drug administration usage and examination methods. In addition, the acceptability scores for drug administration usages and the most preferred drug administration usage were analyzed according to patient treatment history.

Statistical Analysis

Statistical analysis was performed using Student's *t*-test to compare acceptability scores, and statistical significance was set at $p < 0.05$.

Results

Patient Background

The survey was distributed to 1,535 patients, yielding a response rate of 30.6% (470 patients: 388 with UC and 82 with CD). No responses were considered ineligible, and all patients were included in the analysis. The mean age was 52.9 ± 11.2 years; the mean disease duration was 14.8 ± 10.3 years, and 69.4% were males (Table 1). The ratio of CD to UC, sex ratio, disease duration, and status of therapeutic drugs in this survey were similar to those in the general situation in Japan [25]. The occupational statuses were full-time (49.6%), part-time (15.1%), student (0%), housework (8.9%), other (3.6%), and unemployed (22.8%). Sixty-eight (14.5%) patients received intravenous infusions, 54 (11.5%) received subcutaneous injections, and 375 (79.8%) did not receive either treatment.

Acceptability of Drug Administration Usages

Oral once daily had the highest acceptability score, with a mean of 7.9 in the 475 patients evaluated; significant differences were observed between oral twice daily, intravenous infusion at each dosing interval, and subcutaneous injection at each dosing interval ($p < 0.0001$) (Fig. 1). Comparison of each administration usage revealed a significant difference ($p < 0.05$) between all administration usages, except for intravenous infusion at 8-week intervals versus subcutaneous injection at 8-week intervals ($p = 0.430$) and intravenous infusion at 4-week intervals versus subcutaneous injection at 2-week intervals ($p = 0.233$). Patients with a history of intravenous infusion or subcutaneous injection reported a higher acceptability score for intravenous infusion and subcutaneous injection than those without a history of treatment; however, once-daily oral administration had the highest acceptability score, with a significant difference among all administration usages ($p < 0.0001$) (Fig. 2).

Most Preferred Drug Administration Usage

Once-daily oral administration was the most preferred usage of administration (80.4%), and when twice daily was included, 88.9% of the patients indicated oral administration as the most preferred method (Fig. 3). The proportion of patients who preferred intravenous infusion or subcutaneous injection increased among those with a history of intravenous infusion or subcutaneous injection. Oral administration was the most preferred treatment (Fig. 4).

Acceptability of Examination Methods

The mean acceptability scores for blood test, stool test, and endoscopy were 7.3, 5.1, and 4.3, respectively, with significant differences among all groups ($p < 0.0001$) (Fig. 5).

Most Preferred Examination Method

The preferred examination methods, in descending order, were blood tests (76.0%), endoscopy (19.6%), and stool tests (4.5%) (Fig. 6).

Discussion

With the development of therapeutic agents, treatment options for refractory IBD have increased in recent years [26] Although the efficacy and safety of drugs for refractory IBD has been investigated in network meta-analyses [27–29]. these are indirect comparisons, and direct comparisons are still limited [30, 31] Hence, no clear conclusions can be drawn. Poor adherence to drugs for refractory IBD has been shown to be associated with poor prognosis [32–36]. Patient acceptability is important for obtaining efficacy through good adherence in real-world clinical practice. Therefore, we evaluated the acceptability of nine administration usages of the following drugs available in Japan: infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, tofacitinib, and filgotinib. The highest acceptability score was observed for once-daily oral administration, which was significantly different from the other administration usages. Acceptance scores decreased with increase in frequency of administration and shortening of interval between administrations. Once-daily oral administration was the preferred method of administration (80.4%). When twice-daily administration was included, 88.9% of patients indicated that oral administration was their preferred method of administration.

However, the 11.1% who preferred non-oral therapy also preferred intravenous or subcutaneous formulations, as indicated in the results. Although the reason for this preference was not confirmed, it is assumed to be due to

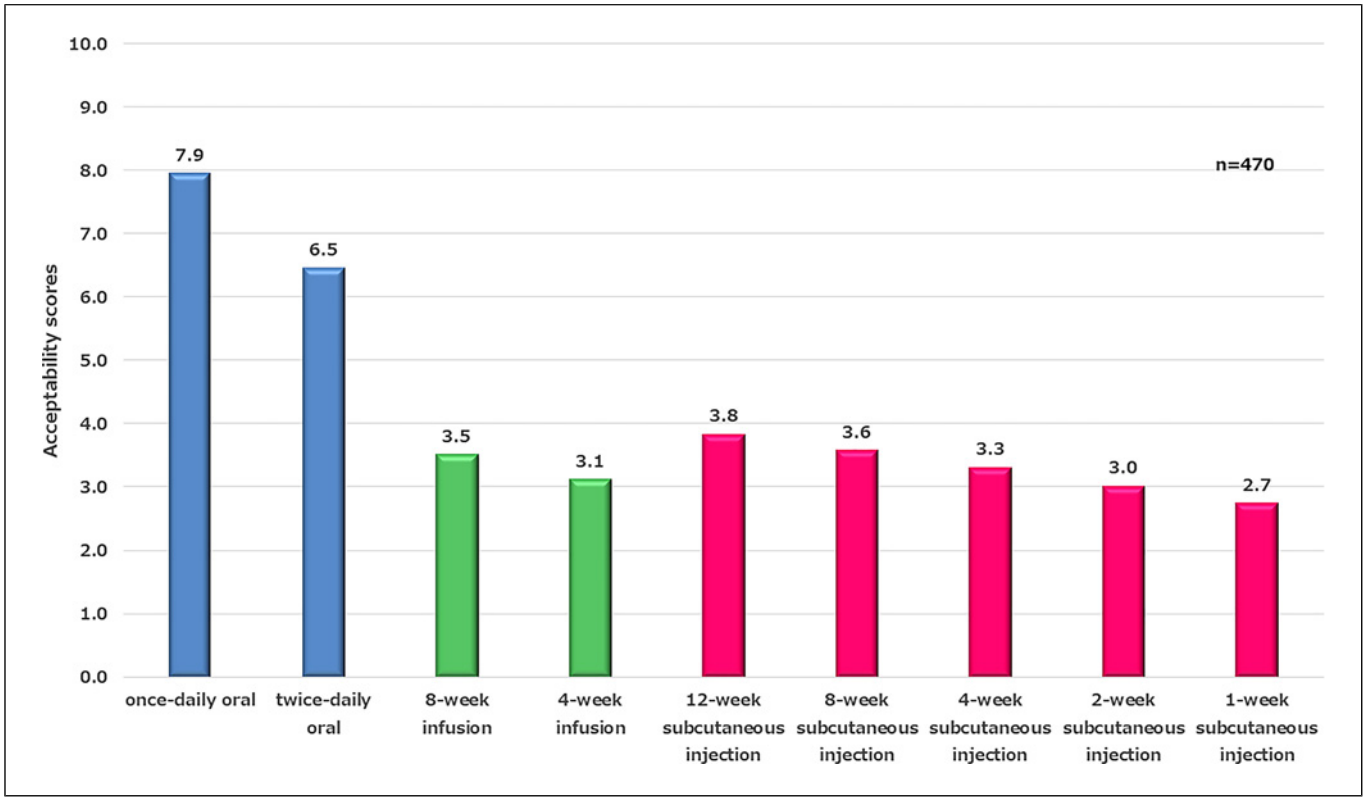

Fig. 1. Acceptability scores by drug administration usages. Comparison between the two groups for each administration usage showed significant differences ($p < 0.05$) between all administration usages except for the 8-week infusion and 8-week subcutaneous injection ($p = 0.430$) and the 4-week infusion and 2-week subcutaneous injection ($p = 0.233$).

the longer administration interval compared with that of oral formulations.

Similar acceptability assessment reports have recently been published in the UK [37] and France [38], with results similar to ours. In a French report, 12- and 8-week intervals of subcutaneous injections were more acceptable than once-daily oral administration by patients with a treatment history of intravenous or subcutaneous injections. In our study, the acceptability of intravenous infusion and subcutaneous injection increased in patients with a history of intravenous or subcutaneous treatment; however, oral administration remained the most preferred method. This may be due to the differences in medical treatment conditions, culture, and national characteristics between Western and Japanese patients.

Filgotinib, a once-daily oral drug, available in Japan since March 2022, has been shown to be effective against UC in clinical trials [24, 39–41]. However, data have not yet been fully accumulated. In addition to the risk of herpes zoster, tofacitinib has been associated with an increased risk of cardiovascular events and malignancy in rheumatoid arthritis, and safety data in IBD are currently being accumulated [42–45]. Although there is good safety data for filgotinib in rheumatoid arthritis treatment [46], there is a need for more safety data, especially in IBD. The results of a detailed study on abnormal spermatogenesis are also awaited [47].

Mucosal healing has been shown to be associated with improved prognosis in IBD treatment [48, 49]. To achieve mucosal healing, treat-to-target strategy using biomarkers is important [50]. As a biomarker reflecting mucosal healing, C-reactive protein is insufficient. The usefulness of fecal calprotectin and fecal immunochemical test has been reported, and they are widely used [11, 12, 51–53]. The new blood biomarker, LRG, showed good correlation with endoscopy activity scores as well as fecal calprotectin and fecal immunochemical test. LRG assay has been available in Japan since June 2020 [13–16, 54–56].

The acceptability of blood test, stool test, and endoscopy was evaluated in this study. Blood tests, stool tests, and endoscopy were ranked in the descending order of acceptability; 76.0% of the respondents indicated that blood

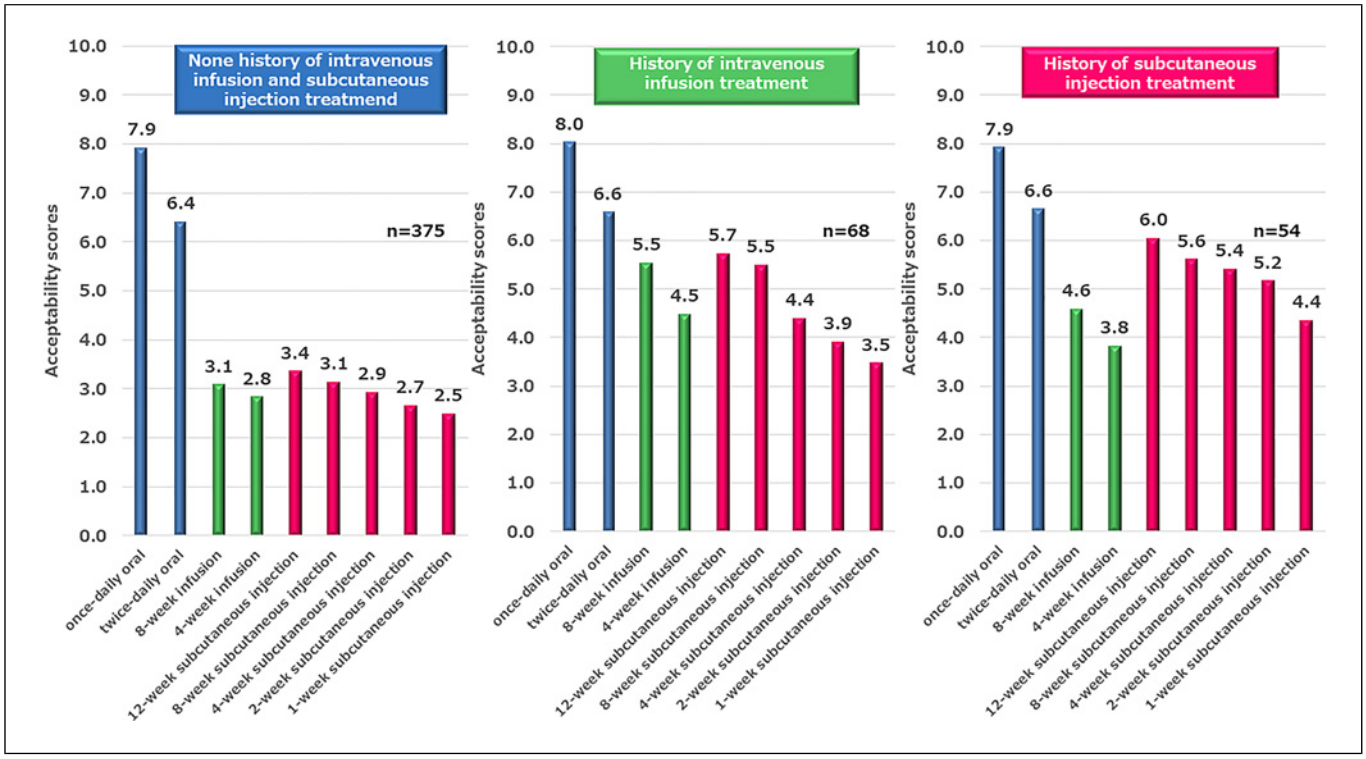

Fig. 2. Acceptability scores of drug administration usages by treatment history. The acceptability of once-daily oral administration was significantly higher than that of other administration methods, regardless of the treatment history of intravenous infusion or subcutaneous injection ($p < 0.0001$).

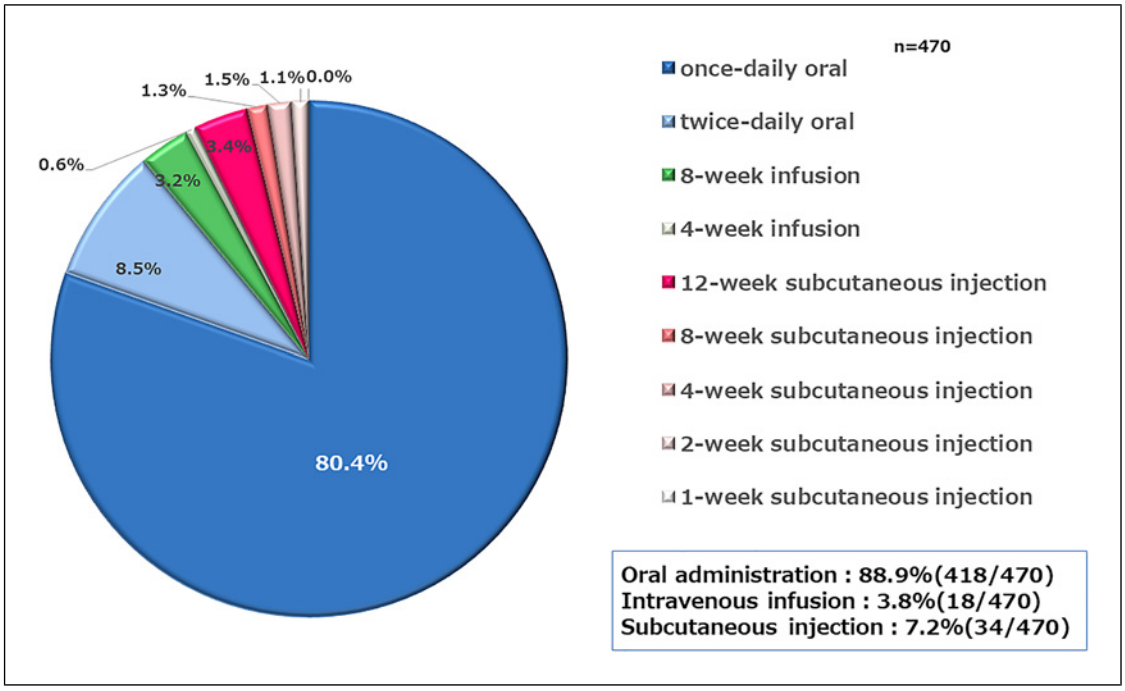

Fig. 3. Most preferred drug administration usage.

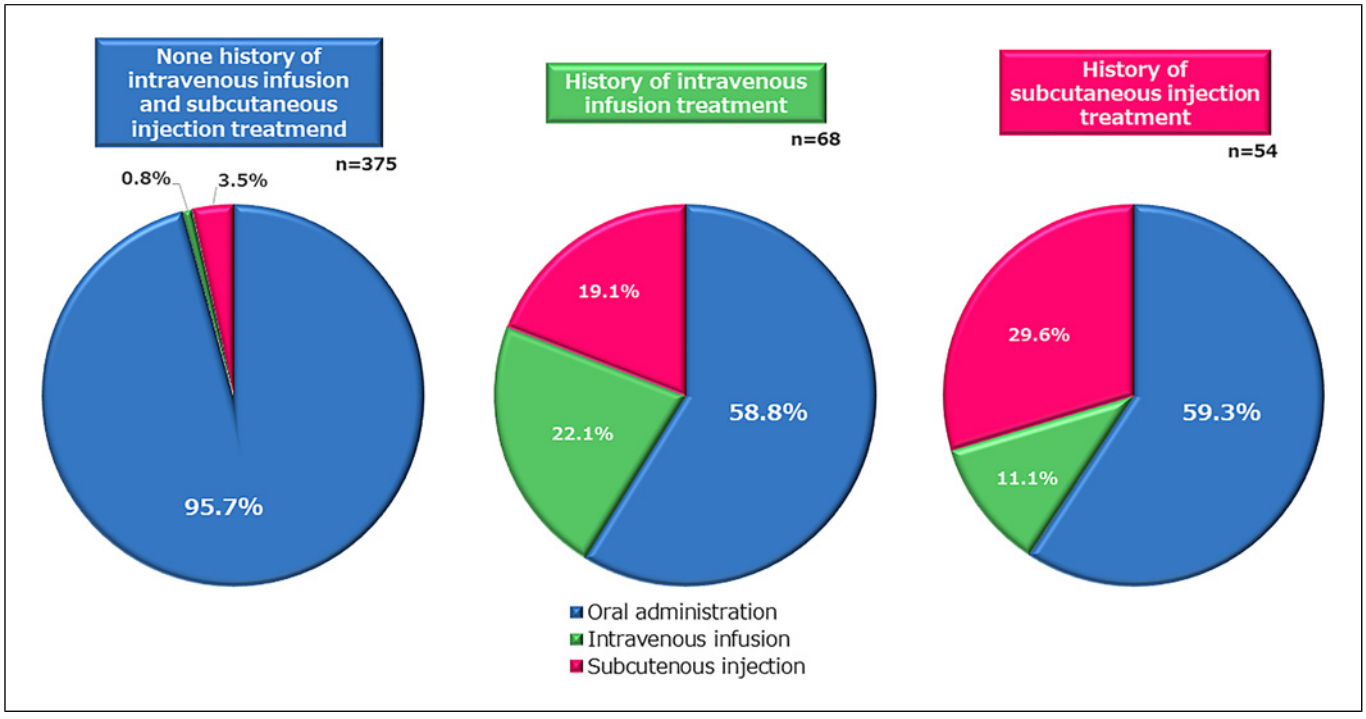

Fig. 4. Most preferred drug administration usage by treatment history.

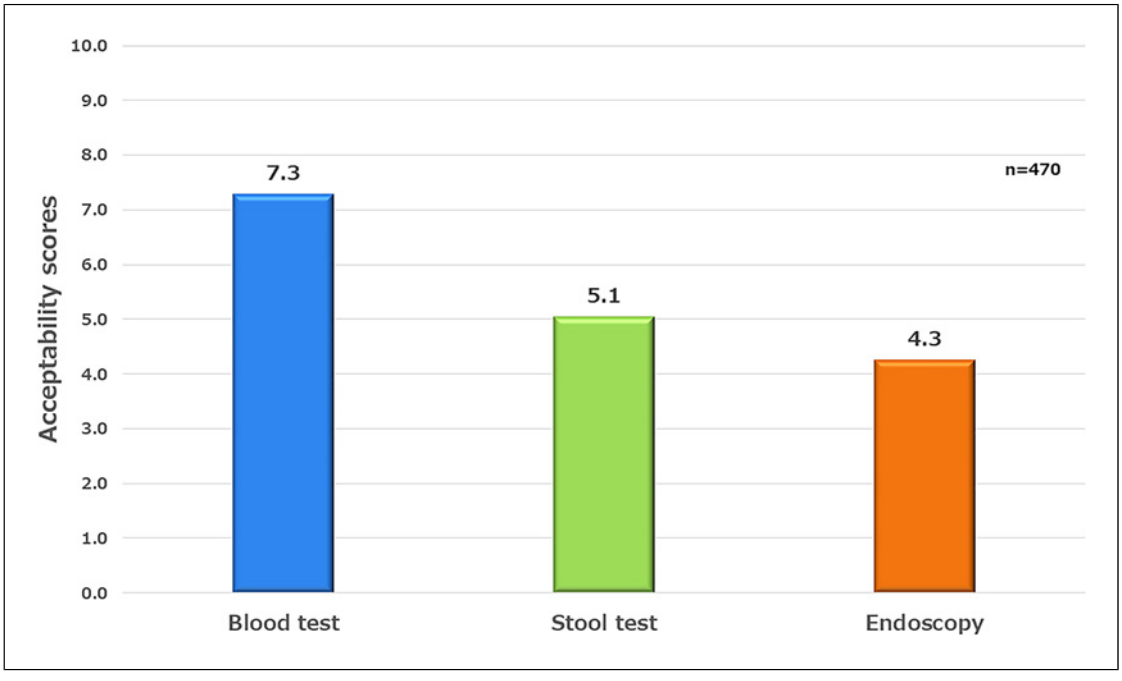

Fig. 5. Acceptability scores of examination methods. There was a significant difference between all examination methods ($p < 0.0001$).

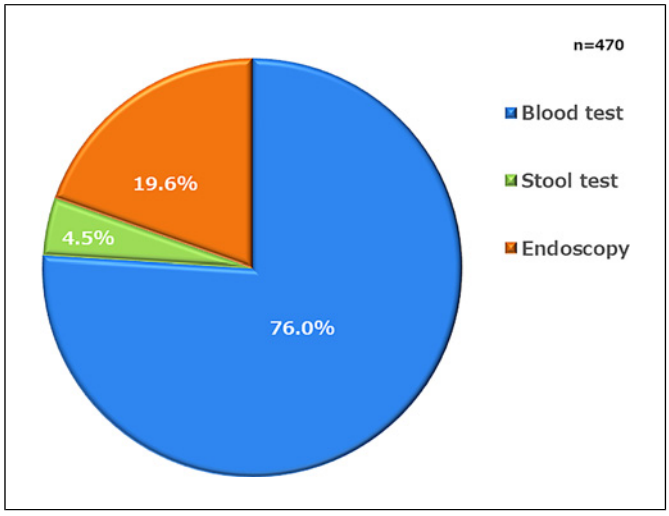

Fig. 6. Most preferred examination method.

tests were the most preferred examination method. Stool testing was the least preferred examination method (4.5%). We believe that resistance to bringing stool samples and the burden of collecting stool samples and bringing them to medical institutions may have influenced these results. Comparison between endoscopy and other modalities, such as computed tomography enterography, magnetic resonance enterography, capsule endoscopy, and ultrasound, is a future challenge. The usefulness of prostaglandin E-major urinary metabolites as new biomarkers has recently been reported [57–59] and should be compared with urinalysis.

Similar acceptability assessment reports have recently been published in New Zealand [60], where blood tests were reported as the most prescribed, completed, and comfortable tests and had the least worrying test results. Conversely, endoscopy was rated as the least comfortable and generated the most worry compared to the stool test.

This survey has several limitations. The first is the possibility of a biased population as this is an internet-based patient survey. Although there was a high proportion of males in this survey conducted by the commercial company Cross Marketing Co., Ltd., it was similar to the general sex ratio and age structure of patients with IBD in Japan and other East Asian countries [25, 61–63] and did not differ from our two previous surveys in Japan [2, 17]. Therefore, we assume this bias to be relatively small. Second, because this was a web-based survey, there was the problem of response accuracy. Regarding consistency of web-based surveys in IBD, Randell et al. [64] reported the consistency of patient and physician ratings by CCFA partners, and Kelstrup et al. [65] reported the consistency of patient ratings and medical records in web-based surveys. Although we were unable to confirm consistency with medical records in this survey, we assume that the consistency of web-based surveys in IBD is relatively high based on these reports. The third limitation is the patients' subjective evaluation in the comparison of drug administration usages and not the actual adherence to treatment. Nonetheless, we believe that our survey is informative because there are only a limited number of reports comparing the acceptability of each drug administration usage, which may differ between countries. Fourth, concerning examination methods, endoscopy and blood tests have different targets in the treat-to-target (T2T) strategies of Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) guidelines [10], and comparing them in the same category may, therefore, be inappropriate. However, as both are clinically important, we believe that they have considerable clinical significance.

Despite the abovementioned limitations, the web-based survey showed a high acceptance of once-daily oral administration of advanced therapies and blood tests in Japanese patients with IBD. These observations provide clues to improve the management of outpatients with IBD.

Acknowledgment

This survey was supported by the Cross Marketing Co., Ltd. (Tokyo, Japan).

Statement of Ethics

All the procedures were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The study design was observational. This study was approved by the Ethics Committee of our institution (Institutional Review Board of Iwate Medical University). The IRB Approval No. MH2022-103. The study was performed in accordance with the ethics guidelines of Japan and was allowed to be implemented without obtaining written informed consent. The study was announced on the homepages of the participating institutions. Written informed consent to participate was not directly obtained but inferred by completion of the questionnaire. Patients who expressed unwillingness to participate in the study were excluded.

Conflict of Interest Statement

The authors do not have conflicts of interest to declare.

Funding Sources

The authors have no funding support to declare.

Author Contributions

Toshifumi Morishita: study design, data collection, data analysis, and writing the first draft of the manuscript; Shunichi Yanai, Yosuke Toya, and Takayuki Matsumoto: study design and data analysis. All the authors have read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [T.M.] upon reasonable request.

References

1 Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011;140(6):1785–94. https://doi.org/10.1053/j.gastro.2011.01.055
2 Murakami Y, Nishiwaki Y, Oba MS, Asakura K, Ohfuji S, Fukushima W, et al. Estimated prevalence of ulcerative colitis and Crohn's disease in Japan in 2014: an analysis of a nationwide survey. J Gastroenterol. 2019;54(12):1070–7. https://doi.org/10.1007/s00535-019-01603-8
3 Matsumoto T, Yanai S, Toya Y, Ueno M, Nakamura S. Internet-orientated assessment of QOL and actual treatment status in Japanese patients with inflammatory bowel disease: the 3I survey. J Crohns Colitis. 2015;9(6):477–82. https://doi.org/10.1093/ecco-jcc/jjv052
4 Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. J Crohns Colitis. 2022;16(1):2–17. https://doi.org/10.1093/ecco-jcc/jjab178
5 Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. J Crohns Colitis. 2020;14(1):4–22. https://doi.org/10.1093/ecco-jcc/jjz180
6 Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019;114(3):384–413. https://doi.org/10.14309/ajg.0000000000000152
7 Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018;113(4):481–517. https://doi.org/10.1038/ajg.2018.27
8 Siegel CA. Shared decision making in inflammatory bowel disease: helping patients understand the tradeoffs between treatment options. Gut. 2012;61(3):459–65. https://doi.org/10.1136/gutjnl-2011-300988
9 Neurath MF, Travis SPL. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61(11):1619–35. https://doi.org/10.1136/gutjnl-2012-302830
10 Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology. 2021;160(5):1570–83. https://doi.org/10.1053/j.gastro.2020.12.031
11 Takashima S, Kato J, Hiraoka S, Nakarai A, Takei D, Inokuchi T, et al. Evaluation of mucosal healing in ulcerative colitis by fecal calprotectin vs. fecal immunochemical test. Am J Gastroenterol. 2015;110(6):873–80. https://doi.org/10.1038/ajg.2015.66
12 Naganuma M, Kobayashi T, Nasuno M, Motoya S, Kato S, Matsuoka K, et al. Significance of conducting 2 types of fecal tests in patients with ulcerative colitis. Clin Gastroenterol Hepatol. 2020;18(5):1102–11.e5. https://doi.org/10.1016/j.cgh.2019.07.054
13 Serada S, Fujimoto M, Terabe F, Iijima H, Shinzaki S, Matsuzaki S, et al. Serum leucine-rich alpha-2 glycoprotein is a disease activity biomarker in ulcerative colitis. Inflamm Bowel Dis. 2012;18(11):2169–79. https://doi.org/10.1002/ibd.22936
14 Shinzaki S, Matsuoka K, Iijima H, Mizuno S, Serada S, Fujimoto M, et al. Leucine-rich Alpha-2 glycoprotein is a serum biomarker of mucosal healing in ulcerative colitis. J Crohns Colitis. 2017;11(1):84–91. https://doi.org/10.1093/ecco-jcc/jjw132
15 Shinzaki S, Matsuoka K, Tanaka H, Takeshima F, Kato S, Torisu T, et al. Leucine-rich alpha-2 glycoprotein is a potential biomarker to monitor disease activity in inflammatory bowel disease receiving adalimumab: PLANET study. J Gastroenterol. 2021;56(6):560–9. https://doi.org/10.1007/s00535-021-01793-0
16 Yanai S, Shinzaki S, Matsuoka K, Mizuno S, Iijima H, Naka T, et al. Leucine-rich Alpha-2 glycoprotein may be predictive of the adalimumab trough level and antidrug antibody development for patients with inflammatory bowel disease: a sub-analysis of the PLANET study. Digestion. 2021;102(6):929–37. https://doi.org/10.1159/000517339
17 Yanai S, Toya Y, Nakamura S, Matsumoto T. Patients' preference of topical therapy for ulcerative colitis in Japan: a web-based 3T survey. J Crohns Colitis. 2020;2:otaa030 published online Apr 17. https://doi.org/10.1093/crocol/otaa030
18 Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462–76. https://doi.org/10.1056/NEJMoa050516
19 Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142(2):257–65.e653. https://doi.org/10.1053/j.gastro.2011.10.032
20 Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):85–e15; quiz e14. https://doi.org/10.1053/j.gastro.2013.05.048
21 Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2019;381(13):1201–14. https://doi.org/10.1056/NEJMoa1900750
22 Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710. https://doi.org/10.1056/NEJMoa1215734
23 Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723–36. https://doi.org/10.1056/NEJMoa1606910
24 Feagan BG, Danese S, Loftus EV Jr, Vermeire S, Schreiber S, Ritter T, et al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. Lancet. 2021;397(10292):2372–84. https://doi.org/10.1016/S0140-6736(21)00666-8
25 Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, Takebayashi T. Prevalence of ulcerative colitis and Crohn's disease in Japan. J Gastroenterol. 2009;44(7):659–65. https://doi.org/10.1007/s00535-009-0057-3
26 Alsoud D, Verstockt B, Fiocchi C, Vermeire S. Breaking the therapeutic ceiling in drug development in ulcerative colitis. Lancet Gastroenterol Hepatol. 2021;6(7):589–95. https://doi.org/10.1016/S2468-1253(21)00065-0
27 Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2022;7(2):161–70. https://doi.org/10.1016/S2468-1253(21)00377-0

28 Burr NE, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis. Gut. 2021;71(10):1976–87. https://doi.org/10.1136/gutjnl-2021-326390
29 Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, et al. Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(12):1002–14. https://doi.org/10.1016/S2468-1253(21)00312-5
30 Sands BE, Peyrin-Biroulet L, Loftus EV Jr, Danese S, Colombel JF, Törüner M, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med. 2019;381(13):1215–26. https://doi.org/10.1056/NEJMoa1905725
31 Sands BE, Irving PM, Hoops T, Izanec JL, Gao LL, Gasink C, et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. Lancet. 2022;399(10342):2200–11. https://doi.org/10.1016/S0140-6736(22)00688-2
32 Kane SV, Chao J, Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. Adv Ther. 2009;26(10):936–46. https://doi.org/10.1007/s12325-009-0069-7
33 Carter CT, Waters HC, Smith DB. Effect of a continuous measure of adherence with infliximab maintenance treatment on inpatient outcomes in Crohn's disease. Patient Prefer Adherence. 2012;6:417–26. https://doi.org/10.2147/PPA.S31115
34 Carter CT, Waters HC, Smith DB. Impact of infliximab adherence on Crohn's disease-related healthcare utilization and inpatient costs. Adv Ther. 2011;28(8):671–83. https://doi.org/10.1007/s12325-011-0048-7
35 Stein DJ, Ananthakrishnan AN, Issa M, Williams JB, Beaulieu DB, Zadvornova Y, et al. Impact of prior irregular infliximab dosing on performance of long-term infliximab maintenance therapy in Crohn's disease. Inflamm Bowel Dis. 2010;16(7):1173–9. https://doi.org/10.1002/ibd.21164
36 Billioud V, Laharie D, Filippi J, Roblin X, Oussalah A, Chevaux JB, et al. Adherence to adalimumab therapy in Crohn's disease: a French multicenter experience. Inflamm Bowel Dis. 2011;17(1):152–9. https://doi.org/10.1002/ibd.21491
37 Denesh D, Carbonell J, Kane JS, Gracie D, Selinger CP. Patients with inflammatory bowel disease (IBD) prefer oral tablets over other modes of medicine administration. Expert Rev Gastroenterol Hepatol. 2021;15(9):1091–6. https://doi.org/10.1080/17474124.2021.1898944
38 Buisson A, Serrero M, Orsat L, Nancey S, Rivière P, Altwegg R, et al. Comparative acceptability of therapeutic maintenance regimens in patients with inflammatory bowel disease: results from the nationwide ACCEPT2 study. Inflamm Bowel Dis. 2023;29(4):579–88. https://doi.org/10.1093/ibd/izac119
39 Hibi T, Motoya S, Hisamatsu T, Hirai F, Watanabe K, Matsuoka K, et al. Efficacy and safety of filgotinib as induction and maintenance therapy for Japanese patients with moderately to severely active ulcerative colitis: a post-hoc analysis of the phase 2b/3 SELECTION trial. Intest Res. 2023;21(1):110–25. https://doi.org/10.5217/ir.2021.00143
40 Loftus EV, Vermeire S, Feagan BG, Le Brun FO, Oortwijn A, Moerch U, et al. Corticosteroid-sparing effects of filgotinib in moderately to severely active ulcerative colitis: data from the phase 2b/3 SELECTION study. J Crohns Colitis. 2023;17(2):211–20. https://doi.org/10.1093/ecco-jcc/jjac122
41 Danese S, Ferrante M, Feagan BG, Peyrin-Biroulet L, Hibi T, Sandborn WJ, et al. Rapid and sustained symptom relief in patients with ulcerative colitis treated with filgotinib: data from the phase 2b/3 SELECTION trial. Am J Gastroenterol. 2023;118(1):138–47. https://doi.org/10.14309/ajg.0000000000001979
42 Winthrop KL, Vermeire S, Long MD, Panés J, Ng SC, Kulisek N, et al. Long-term risk of herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. Inflamm Bowel Dis. 2023;29(1):85–96. https://doi.org/10.1093/ibd/izac063
43 Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386(4):316–26. https://doi.org/10.1056/NEJMoa2109927
44 Sandborn WJ, Panés J, D'haens GR, Sands BE, Su C, Moscariello M, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. Clin Gastroenterol Hepatol. 2019;17(8):1541–50. https://doi.org/10.1016/j.cgh.2018.11.035
45 Lichtenstein GR, Rogler G, Ciorba MA, Su C, Chan G, Pedersen RD, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancy (excluding nonmelanoma skin cancer) events across the ulcerative colitis clinical program. Inflam Bowel Dis. 2021;27(6):816–25. https://doi.org/10.1093/ibd/izaa199
46 Winthrop KL, Tanaka Y, Takeuchi T, Kivitz A, Matzkies F, Genovese MC, et al. Integrated safety analysis of filgotinib in patients with moderately to severely active rheumatoid arthritis receiving treatment over a median of 1.6 years. Ann Rheum Dis. 2022;81(2):184–92. https://doi.org/10.1136/annrheumdis-2021-221051
47 Hellstrom WJG, Dolhain RJEM, Ritter TE, Watkins TR, Arterburn SJ, Dekkers G, et al. MANTA and MANTA-RAy: rationale and design of trials evaluating effects of filgotinib on semen parameters in patients with inflammatory diseases. Adv Ther. 2022;39(7):3403–22. https://doi.org/10.1007/s12325-022-02168-4
48 Shah SC, Colombel JF, Sands BE, Narula N. Mucosal healing is associated with improved long-term outcomes of patients with ulcerative colitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14(9):1245–55.e8. https://doi.org/10.1016/j.cgh.2016.01.015
49 Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther. 2016;43(3):317–33. https://doi.org/10.1111/apt.13475
50 Colombel JF, Panaccione R, Bossuyt P, Lukas M, Baert F, Vaňásek T, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet. 2017;390(10114):2779–89. https://doi.org/10.1016/S0140-6736(17)32641-7
51 Ma C, Lumb R, Walker EV, Foshaug RR, Dang TT, Verma S, et al. Noninvasive fecal immunochemical testing and fecal calprotectin predict mucosal healing in inflammatory bowel disease: a prospective cohort study. Inflamm Bowel Dis. 2017;23:1643–9. https://doi.org/10.1097/MIB.0000000000001173
52 Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients: a systematic review and meta-analysis. Am J Gastroenterol. 2015;110(6):802–20; quiz 820. https://doi.org/10.1038/ajg.2015.120
53 Shi HY, Chan FKL, Chan AWH, Higashimori A, Kyaw M, Ching JYL, et al. Accuracy of faecal immunochemical test to predict endoscopic and histological healing in ulcerative colitis: a prospective study based on validated histological scores. J Crohns Colitis. 2017;11(9):1071–7. https://doi.org/10.1093/ecco-jcc/jjx088
54 Kawamoto A, Takenaka K, Hibiya S, Ohtsuka K, Okamoto R, Watanabe M. Serum leucine-rich α2 glycoprotein: a novel biomarker for small bowel mucosal activity in Crohn's disease. Clin Gastroenterol Hepatol. 2022;20(5):e1196–200. https://doi.org/10.1016/j.cgh.2021.06.036
55 Kawamura T, Yamamura T, Nakamura M, Maeda K, Sawada T, Ishikawa E, et al. Accuracy of serum leucine-rich Alpha-2 glycoprotein in evaluating endoscopic disease activity in Crohn's disease. Inflamm Bowel Dis. 2023;29(2):245–53. https://doi.org/10.1093/ibd/izac076
56 Abe I, Shiga H, Chiba H, Miyazawa T, Oomori S, Shimoyama Y, et al. Serum leucine-rich alpha-2 glycoprotein as a predictive factor of endoscopic remission in Crohn's disease. J Gastroenterol Hepatol. 2022;37(9):1741–8. https://doi.org/10.1111/jgh.15907

57 Arai Y, Arihiro S, Matsuura T, Kato T, Matsuoka M, Saruta M, et al. Prostaglandin E-major urinary metabolite as a reliable surrogate marker for mucosal inflammation in ulcerative colitis. Inflamm Bowel Dis. 2014;20(7):1208–16. https://doi.org/10.1097/MIB.0000000000000062
58 Ishida N, Tamura S, Miyazu T, Tani S, Yamade M, Iwaizumi M, et al. Comparison between prostaglandin E-major urinary metabolite and C-reactive protein levels to reflect endoscopic scores in patients with ulcerative colitis. Sci Rep. 2021;11(1):16205. https://doi.org/10.1038/s41598-021-95761-6
59 Sakurai T, Akita Y, Miyashita H, Miyazaki R, Maruyama Y, Saito T, et al. Prostaglandin E-major urinary metabolite diagnoses mucosal healing in patients with ulcerative colitis in remission phase. J Gastroenterol Hepatol. 2022;37(5):847–54. https://doi.org/10.1111/jgh.15782
60 Ho SSC, Keenan JI, Day AS. Patient perceptions of current and potential inflammatory bowel disease diagnostic and monitoring tests. Intern Med J. 2022;52(7):1196–202. https://doi.org/10.1111/imj.15298
61 Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology. 2013;145(1):158–65.e2. https://doi.org/10.1053/j.gastro.2013.04.007
62 Ng SC, Kaplan GG, Tang W, Banerjee R, Adigopula B, Underwood FE, et al. Population density and risk of inflammatory bowel disease: a prospective population-based study in 13 countries or regions in Asia-pacific. Am J Gastroenterol. 2019;114(1):107–15. https://doi.org/10.1038/s41395-018-0233-2
63 Kim HJ, Hann HJ, Hong SN, Kim KH, Ahn IM, Song JY, et al. Incidence and natural course of inflammatory bowel disease in Korea, 2006–2012: a nationwide population-based study. Inflamm Bowel Dis. 2015;21(3):623–30. https://doi.org/10.1097/MIB.0000000000000313
64 Randell RL, Long MD, Cook SF, Wrennall CED, Chen W, Martin CF, et al. Validation of an internet-based cohort of inflammatory bowel disease (CCFA partners). Inflamm Bowel Dis. 2014;20(3):541–4. https://doi.org/10.1097/01.MIB.0000441348.32570.34
65 Kelstrup AM, Juillerat P, Korzenik J. The accuracy of self-reported medical history: a preliminary analysis of the promise of internet-based research in inflammatory bowel Diseases. J Crohns Colitis. 2014;8(5):349–56. https://doi.org/10.1016/j.crohns.2013.09.012