

A Health Survey of Gastroenterologist Prescribing Practices of Adalimumab for Treatment of Crohn's Disease: Final Results

Samantha Zullow, MD, Mark H. Flasar, MD, MS, Deborah Greenberg, J. Kathleen Tracy, PhD, Ankur Rustgi, MBBS, MPH, and Raymond K. Cross, MD, MS

Dr Zullow is affiliated with the Department of Medicine at the Boston University Medical Center in Boston, Massachusetts. Dr Flasar is an assistant professor of medicine in the Division of Gastroenterology and Hepatology at the University of Maryland in Baltimore, Maryland and is affiliated with Veterans Affairs at the Maryland Health Care System in Baltimore, Maryland. Ms Greenberg is a senior research analyst and Dr Tracy is an associate professor of epidemiology and public health in the Department of Epidemiology at the University of Maryland. Dr Rustgi is a research supervisor in the Division of Gastroenterology and Hepatology at the University of Maryland. Dr Cross is an associate professor of medicine in the Division of Gastroenterology and Hepatology at the University of Maryland.

Address correspondence to:

Dr Raymond K. Cross

100 North Greene Street, Lower Level
Baltimore, MD 21201

Fax: 410-706-4330

Tel: 410-706-3387

E-mail: rcross@medicine.umaryland.edu

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Abstract: Adalimumab (Humira, AbbVie) has efficacy in treatment-naïve and infliximab (Remicade, Janssen)–exposed patients with Crohn's disease (CD). An e-survey was sent to US gastroenterologists who were members of the American Gastroenterological Association. A total of 398 gastroenterologists (3%) completed the survey. Seventy-two percent prescribed adalimumab more than a few times yearly, 58% followed more than 50 patients with CD, and 15% followed 200 or more patients with CD. Ninety percent of gastroenterologists felt that adalimumab had a moderately significant positive impact on patient care. Eighty-two percent correctly identified the US Food and Drug Administration–approved adalimumab induction and maintenance regimens. These gastroenterologists were more likely to follow 200 or more patients with CD ($P=.045$) and prescribe adalimumab more than a few times per year ($P=.037$). Years in practice, practice setting, gender, and region did not impact prescribing. Correct dosing was associated with higher prescribing frequency ($P=.014$) and volume of patients with CD ($P=.025$). The frequency of adalimumab prescribing and volume of patients with CD were predictive of the total number of correct survey answers ($P=.014$ and $P=.017$, respectively). Only 50% of gastroenterologists always administered loading doses when switching to adalimumab from another anti-tumor necrosis factor (TNF) agent; 43.5% reported unclear loading efficacy and 24.3% reported infection concerns from excess anti-TNF as reasons. Eighteen percent of gastroenterologists reported that pharmacies had reduced their prescribed adalimumab doses. To our knowledge, this is the only study evaluating prescribing patterns of adalimumab in patients with CD in the United States. Our findings demonstrate that many gastroenterologists are not using optimal adalimumab dosing strategies, which may lead to a decreased rate of response in patients with CD. Further research is needed to confirm our findings and identify barriers to optimal adalimumab use by gastroenterologists for treatment of CD.

Crohn's disease (CD) is characterized by chronic inflammation of the gastrointestinal tract. Adalimumab (Humira, AbbVie) is the second US Food and Drug Administration (FDA)-approved anti-tumor necrosis factor- α (anti-TNF) agent for use in the treatment of moderate-to-severe active CD. Adalimumab induces and maintains clinical remission and promotes mucosal healing and fistula closure.^{1,2} Adalimumab has efficacy in anti-TNF-naïve patients as well as those who have been previously treated with infliximab.^{2,3}

The CLASSIC-I (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease) trial compared several induction regimens in anti-TNF-naïve patients. The induction strategy of 160 mg at Week 0 followed by 80 mg at Week 2 had superior efficacy compared with 80 mg at Week 0 and 40 mg at Week 2 and placebo at both time points (remission rates at Week 4 of 36%, 24%, and 12%, respectively).³ Furthermore, adalimumab was proven to be safe, with similar adverse event rates at both induction doses compared with placebo.³

Adalimumab also can be used to induce remission in patients who have either lost response or become tolerant to infliximab. A randomized, double-blind, placebo-controlled trial demonstrated that induction with adalimumab 160 mg at Week 0 and 80 mg at Week 2 resulted in a 21% clinical remission rate compared with 7% in patients treated with placebo.⁴ The efficacy of maintenance dosing with adalimumab was assessed in the CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial, in which patients were randomized after open-label induction therapy to receive either placebo or 1 of 2 maintenance regimens: 40 mg weekly or 40 mg every other week. Remission rates were significantly higher with continuous dosing of 40 mg every other week or 40 mg every week, with rates of 51% and 49%, respectively, compared with a rate of 38% with placebo.⁵

The importance of using the FDA-approved 160/80-mg induction dosing strategy was demonstrated in a study looking at predictors of adalimumab dose escalation during the maintenance phase of therapy. Patients who received the 160/80-mg induction regimen had half the risk of escalation to weekly dosing in the subsequent year compared with patients who received the 80/40-mg regimen.⁶ Hence, gastroenterologists who do not use the FDA-approved adalimumab induction regimen may be risking decreased efficacy, accelerated time to loss of response, and higher likelihood of dose escalation in their patients with CD.

To our knowledge, no study to date has attempted to assess gastroenterologist prescribing practices of adalimumab in the United States. Our health survey was designed to evaluate whether gastroenterologists were using the FDA-approved induction and maintenance strategies in

clinical practice. In addition, we assessed whether gastroenterologists alter induction and maintenance dosing based on clinical variables such as patient body weight and prior anti-TNF exposure. Finally, we sought to evaluate whether there were any gastroenterologist characteristics that were associated with FDA-approved adalimumab prescribing.

Patients and Methods

Study Population

An online survey created by Remark Web Survey Version 5 (Gravic, Inc) was sent, via e-mail, to 14,831 gastroenterologists who were members of the American Gastroenterological Association (AGA) living in the United States. No information other than e-mail addresses was extracted. Duplicate e-mail addresses were removed from the e-mail list before the survey was sent.

Study Design

E-mail blasts were sent on December 1, 2011, December 15, 2011, and January 1, 2012. The e-mails included a link to the questionnaire, information about the purpose of the study, and information about an iPad giveaway incentive for completing the survey. Participants were also given the opportunity to opt-out of future e-mail blasts. Approximately 1800 e-mails were undeliverable, leaving 13,031 eligible participants.

Each e-mail was given a unique username and password that could be used only once to access the survey. Participants did not have to complete the survey in 1 sitting; they retained access for 48 hours after they first signed into the survey. In each subsequent e-mail blast, e-mail addresses that had been used to access the survey were removed from the list. The Remark Web Survey software randomly changed the order of the answers to clinical scenario questions for each participant.

Participants

Participants were required to have a valid e-mail address and to have either an MD or DO title. Members with a RN, CRNP, or PA title were excluded. In addition, members who reported 0 years of practice experience and being in an academic setting were excluded, as these members were presumed to be trainees.

Survey Development

The electronic questionnaire was developed based on 2 previous studies that our group had done on gastroenterologist prescribing practices of infliximab (Remicade, Janssen).^{7,8} The survey was validated for content by 3 gastroenterologists who are nationally recognized experts in the field of CD. The survey was revised based on feedback from these experts.

The final survey consisted of 18 multiple-choice questions regarding demographics and practice information, knowledge of the FDA-approved adalimumab dosing strategy, and adalimumab prescribing based on a number of clinical scenarios, including patient body weight and prior exposure to anti-TNF agents. Several clinical scenarios were developed to examine their influence on adalimumab prescribing. Three questions were designed to see whether gastroenterologists would change dosing based on patient body weight.

Clinical scenarios included an underweight patient with a body mass index (BMI) of 16.8 kg/m², a patient with a normal BMI of 23.4 kg/m², and an obese patient with a BMI of 36.7 kg/m². There were also 3 questions to address whether gastroenterologists changed their dosing based on prior exposure to infliximab. Clinical scenarios included a patient who had lost response to infliximab, a patient who had good response to infliximab but wanted to switch to adalimumab for convenience, and a patient who had experienced an infusion reaction to infliximab.

Answer choices for each clinical scenario question consisted of “40 mg every 2 weeks,” “80 mg at Week 0, followed by 40 mg every 2 weeks,” “160 mg at Week 0, 80 mg at Week 2, followed by 40 mg every 2 weeks,” “160 mg at Week 0, 80 mg at Week 2, followed by 40 mg each week,” and “320 mg at Week 0, 160 mg at Week 2, followed by 80 mg every 2 weeks.” These answer choices were put in random order for each clinical scenario question for each participant. In addition, after each clinical scenario, gastroenterologists were asked how long they would wait to initiate adalimumab after the last dose of infliximab, assuming immediate approval for the drug. The answer choices were “≤2 weeks,” “2 to <4 weeks,” “4 to <6 weeks,” “6 to <8 weeks,” and “≥8 weeks.”

We also evaluated whether gastroenterologists administered loading doses when they switched from 1 anti-TNF agent to another. If they did not administer loading doses, a subsequent question asked for a reason. Answer choices included “risk of infusion/injection site reaction,” “cost of loading an anti-TNF agent,” “unclear efficacy of loading doses,” and “risk of infection secondary to excess anti-TNF therapy.” Respondents were allowed to check all reasons that applied as well as write in an answer if their reason was not listed. In addition, if a gastroenterologist did use loading doses after switching from another anti-TNF agent, we asked what the rationale was. Respondents could check all reasons that applied, with answer choices including “increased response rate to adalimumab,” “decreased risk of injection site reactions,” “decreased risk of adverse events,” “decreased risk of immunogenicity,” “I don't know,” and a write-in “other” box. Lastly, a question asked whether and how often pharmacies substituted the prescribed adalimumab dosing for another dosing strategy without the gastroenterologist's knowledge.

Outcome and Predictor Variables

The primary outcome variable for the study was the prescribing of adalimumab according to the FDA-approved dosing strategy for CD (160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week). We evaluated demographic characteristics of gastroenterologists that could be associated with the approved dosing strategy, including years in practice, practice setting, region in the United States, number of patients with CD in their practice, and frequency of adalimumab prescribing. Years in practice were ascertained with a write-in box for the following question: “Not counting your fellowship training, how long have you been practicing as a gastroenterologist (years)?” The practice setting choices included “community solo practice,” “community group practice,” “community hospital–owned practice,” “community health maintenance organization,” “academic,” and “military (Veterans Affairs and others),” and respondents could select more than 1 practice setting. The region of the United States was obtained using a drop-down menu of states, which were then put into the categories of Northeast, Midwest, South, and West for analysis. The number of patients with CD followed by the gastroenterologist was selected from a multiple-choice question. The answer choices were “50 or less,” “51 to 200,” “201 to 350,” “351-500,” and “501 or more.”

The frequency of adalimumab prescribing was measured categorically by how often a gastroenterologist initiated treatment. Choices included “never,” “a few times since adalimumab has been FDA-approved,” “a few times a year,” and “a few times a month.”

Statistical Analysis

Data were collected through the Remark Web Survey software, and statistical analysis was performed using Stata 9 (StataCorp LP) software. Frequency counts were constructed for each survey question. Bivariate analyses were conducted to examine differences between demographic variables and the primary outcome of interest. In addition, variables associated with the outcome of interest at a *P* value of no more than .10 were identified for inclusion in regression models. Differences between groups were assessed with the chi-square test for categorical variables. Using the outcome of the preliminary descriptive analyses, it was found that the frequency of prescribing adalimumab and the number of patients with CD were important factors in choosing the FDA-approved strategy. A logistic regression model was built based on these results. The region was included as a variable because previous research indicated that this factor affected prescribing practices.⁶ Finally, linear regression analysis was performed to explore the association between the number of correct answers on the survey and demographic characteristics such as the frequency of prescribing and the number of patients with CD followed.

Results

Data Collection

In total, 398 participants completed the survey, representing a 3% response rate. However, 54 participants were excluded from the data analysis because they reported both 0 years of practice experience and an academic setting as their only practice setting. Three hundred forty-four practicing gastroenterologists were used in the subsequent analyses (3%).

Demographics

These respondents were well distributed throughout the United States, with 28% coming from the Northeast, 19% from the Midwest, 35% from the South, and the remaining 19% from the West. Respondents reported an average of 13.2±11.1 years of gastroenterology practice. Ninety-one percent reported only 1 practice setting. Thirty-seven percent of respondents reported an academic practice setting, 44% reported a community group practice setting, 9% reported a community hospital–owned practice setting, 7% reported a military practice setting, 6% reported a community solo practice setting, and 3% reported a community health maintenance organization practice setting. Eighty-six percent of respondents were male.

Adalimumab Prescribing in Clinical Practice

Six percent of surveyed gastroenterologists reported having never initiated treatment with adalimumab, 22% initiated adalimumab a few times since FDA approval, 54% initiated adalimumab a few times a year, and 19% initiated adalimumab a few times a month. Fifty-eight percent of gastroenterologists were currently following more than 50 patients with CD, with 15% following 200 or more patients with CD. Ninety percent of respondents reported believing that adalimumab had a moderately to significantly positive impact on patient care since being approved by the FDA in 2007. Eighty-two percent of gastroenterologists chose the appropriate FDA-approved adalimumab induction and maintenance strategies for CD. Seven percent of respondents chose the 80/40-mg induction regimen; 5% chose the correct induction regimen followed by 40 mg every week; 1% chose 320 mg at Week 0, 160 mg at Week 2, followed by 40 mg every other week; less than 1% chose 40 mg every 2 weeks; and 3% did not respond to this question.

Chi-square analysis indicated that FDA-approved adalimumab dosing was significantly associated with higher frequency of prescribing adalimumab and higher volume of patients with CD. Of the respondents who prescribed adalimumab more than a few times a year, 88% chose the approved loading strategy as opposed to 78% of those who prescribed adalimumab a few times a year or less ($P=.037$).

Ninety-four percent of gastroenterologists who reported following 200 or more patients with CD identified the correct induction and maintenance regimens as opposed to 84% of those reporting that they followed fewer than 200 patients with CD ($P=.045$). Geographic region, gender, academic setting, and years in practice were not significantly associated with selecting the FDA-approved dosing strategy for adalimumab. Eighteen percent of gastroenterologists reported that the pharmacy substituted a different dose of adalimumab than that prescribed; 9% of gastroenterologists reported that this substitution occurred from 1% to 25% of the time.

Prescribing According to Patient Body Weight When evaluating the results from various clinical scenarios, approximately 78% of gastroenterologists identified FDA-approved dosing of adalimumab in a patient of normal body weight with moderate-to-severe CD refractory to corticosteroid therapy. Gastroenterologists who prescribed adalimumab more frequently and those with a higher volume of patients with CD were more likely to identify the approved adalimumab dose ($P<.001$ and $P=.008$, respectively). For an obese patient with a BMI of 36.7 kg/m², 71% of gastroenterologists chose the appropriate dosing strategy, and 16% selected the correct induction dose but preferred maintenance doses of 40 mg every week. FDA-approved prescribing was associated with higher frequency of adalimumab prescribing ($P=.039$). For an underweight patient with a BMI of 16.8 kg/m², 69% of gastroenterologists chose the correct induction and maintenance doses. Thirteen percent chose 80 mg at Week 0 followed by 40 mg every other week, and 12% chose the correct induction dose but maintenance doses of 40 mg every week. Based on chi-square analysis, there was a significant association between the number of patients followed and correctly choosing the FDA-approved dosing strategy. Eighty-three percent of gastroenterologists who follow 200 or more patients chose the correct answer; conversely, 69% of those who follow fewer than 200 patients chose the correct answer ($P=.043$).

Prescribing According to Prior Infliximab Exposure For a patient who had previously entered remission with infliximab but then had a progressive loss of response despite infliximab dose escalation, 63% of gastroenterologists chose the correct dosing strategy; 15% selected the appropriate loading dose but favored maintenance doses of adalimumab 40 mg every week. Selecting the correct answer was significantly associated with the volume of patients with CD. Based on chi-square analysis, 77% of gastroenterologists who reported following 200 or more patients with CD chose the correct answer, compared with 63% of those who reported following fewer than 200 patients with CD ($P=.052$).

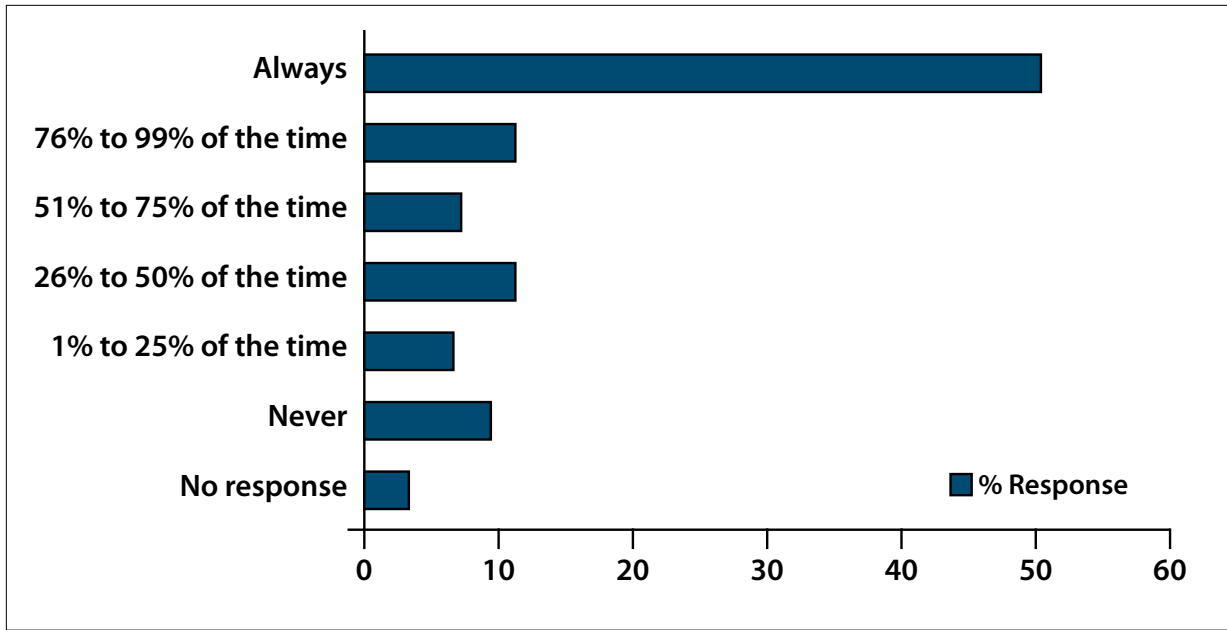


Figure. Response to the survey question “Do you administer loading doses when switching from one anti-TNF agent to another?” TNF, tumor necrosis factor.

The convenience-switch scenario involved a patient who had been on infliximab for 2 years and maintained remission; however, the patient wanted to switch to adalimumab for convenience. For this scenario, 56% of gastroenterologists chose the correct induction and maintenance regimens of adalimumab, 18% chose to go straight to maintenance of adalimumab 40 mg every other week without loading, and 11% chose adalimumab 80 mg at Week 0 followed by 40 mg every other week. Chi-square analysis demonstrated that selecting the approved loading strategy was associated with following 200 or more patients with CD ($P=.014$). For a patient who achieved remission with infliximab but had an infusion reaction on the second and third maintenance infusions, 54% of gastroenterologists selected the approved induction and maintenance doses for adalimumab. Seventeen percent of gastroenterologists chose not to use any adalimumab induction but instead preferred to go straight to maintenance adalimumab 40 mg every other week. The frequency of prescribing adalimumab and the volume of patients with CD were not significantly associated with choosing the correct dosing strategy.

When gastroenterologists were asked if they administered loading doses when switching from infliximab to adalimumab, 50% reported always loading adalimumab, whereas 10% never used adalimumab loading (Figure). There were various reasons reported for not loading adalimumab in patients previously exposed to infliximab. Forty-four percent of gastroenterologists reported that there was unclear efficacy of loading doses, 23% thought

that there could be a higher risk of infection secondary to excess anti-TNF therapy, 14% were concerned about the cost of loading adalimumab, and 7% reported concerns about the risk of infusion or injection site reaction.

In contrast, if the gastroenterologist used loading doses of adalimumab in patients previously exposed to infliximab, 65% reported doing so because loading doses of adalimumab increased the overall response rate to adalimumab. Thirteen percent thought that loading doses decreased immunogenicity, and 9% did not know why loading doses were important. For each infliximab exposure scenario, responses varied widely with how long gastroenterologists would wait to initiate adalimumab in patients previously exposed to infliximab (data not shown).

Association of Demographic Characteristics of Gastroenterologists With the Number of Correct Survey Responses

Linear regression indicates that both the frequency of prescribing adalimumab and the number of patients with CD significantly predict the total number of correct answers with a positive association. After adjusting for the region, gastroenterologists with a higher frequency of prescribing adalimumab ($P=.014$) and those following more patients with CD ($P=.017$) were significantly more likely to have more correct answers. These characteristics were also positively significantly associated with correct answers to the 3 weight-based scenarios ($P=.014$ and $P=.025$). Interestingly, there were no predictors that were associated with correct answers to the questions regarding patients with prior anti-TNF exposure.

Discussion

In our study, nearly 20% of gastroenterologists did not use the FDA-approved induction and maintenance doses of adalimumab for CD in clinical practice. FDA-approved prescribing was more likely in gastroenterologists who prescribe adalimumab more than a few times per year and in gastroenterologists who follow more than 200 patients with CD. Experience, gender, practice setting, and region of the United States were not associated with FDA-approved induction and maintenance doses of adalimumab. FDA-approved prescribing of adalimumab appeared to vary most in clinical scenarios involving underweight patients and patients previously exposed to anti-TNF therapy. No clinical variables were associated with FDA-approved loading of adalimumab in clinical scenarios based on prior exposure to infliximab. Gastroenterologists reported unclear efficacy of adalimumab loading and fear of infectious complications as reasons for not loading adalimumab in patients previously exposed to infliximab. Surprisingly, up to 20% of gastroenterologists reported substitution of their adalimumab dosing schedule by the pharmacy.

Use of adalimumab 160 mg at Week 0 and 80 mg at Week 2 as an induction strategy is supported by multiple studies showing increased efficacy with these loading doses. Data from the CLASSIC I study demonstrated higher rates of remission after induction if patients were given adalimumab 160 mg at Week 0 and 80 mg at Week 2.³ Patients given different induction doses are less likely to go into and maintain remission and have a higher likelihood of hospitalization as well as rate of escalation to weekly dosing in the future.^{6,9}

According to our study, only half of gastroenterologists reported always administering loading doses when switching from 1 anti-TNF agent to another. This is consistent with a health survey from France published in 2009, in which participants were asked which dosing strategy they would use when switching from infliximab to adalimumab.¹⁰ Fifty-three percent of respondents used 160 mg at Week 0 and 80 mg at Week 2, whereas 39% reported using 80 mg at Week 0 and 40 mg at Week 2. Our respondents reported unclear efficacy of loading doses as well as risk of infection secondary to excess anti-TNF therapy as reasons for not using any induction dosing. Despite our respondents' concerns over infection, the GAIN (Gauging Adalimumab Efficacy in Infliximab Nonresponders) study did not demonstrate higher rates of overall adverse events or infectious complications in patients with CD receiving adalimumab after a prior loss of response to infliximab compared with placebo-treated patients.⁴ However, patients in this study underwent an 8-week washout period from infliximab before starting adalimumab.

Because adalimumab can be given at home, many patients prefer it to infliximab, which is generally given in an office- or hospital-based infusion clinic. Not surprisingly, patients often inquire about electively switching from infliximab to adalimumab for convenience and, at times, for insurance-related reasons. Unfortunately, data from the SWITCH (Randomized-controlled Trial of Switching to Alternative Tumour-Necrosis Factor-Blocking Drugs or Abatacept or Rituximab in Patients with Rheumatoid Arthritis Who Have Failed an Initial TNF-blocking Drug) trial found that elective switching from infliximab to adalimumab in patients in clinical remission results in unacceptably high rates of flare. Seventy-three patients with CD with ongoing response to infliximab for at least 6 months were randomized to continue infliximab or switch to adalimumab.¹¹ At 1 year, 47% of patients in the adalimumab group required dose optimization or interruption of treatment compared with 16% of infliximab-treated patients.

Five serious adverse events occurred, all of which were related to CD complications. All adverse events occurred in patients randomized to adalimumab.¹¹ However, this study used the approved induction regimen in Europe for adalimumab (80 mg at Week 0 followed by 40 mg every other week). It is possible that use of lower adalimumab induction doses contributed to the high rates of loss of response or drug interruption over time.

Our study has several strengths. First, we assessed content validity of the survey with 3 experts in the field. Second, we distributed the survey to all members of the AGA with valid e-mail addresses. Third, we performed adjusted analyses for each question to account for potentially confounding variables.

Our study also has several limitations. First, the response rate of 3% was low. Although disappointing, a low response rate is common for surveys of physicians, especially surveys in an electronic format. Based on the low response rate, it is possible that our results are not representative of the overall gastroenterologist community. We think this is likely and hypothesize that our findings are, in fact, a best-case scenario, as providers with an interest in inflammatory bowel disease were more likely to complete the survey. Furthermore, 37% of respondents reported an academic practice setting. Therefore, results in the community at large may be more discouraging than our study findings.

Second, because this is a survey, we are not actually measuring prescribing of adalimumab but gastroenterologists' reports of prescribing. It is possible that gastroenterologists may prescribe quite differently in real life. We attempted to assess our hypothesis that our results represented a best-case scenario and not real-life prescribing of adalimumab using data supplied to us from a Symphony Health Solutions' Patient Transactional Dataset. New adalimumab

prescriptions (defined as prescriptions for adalimumab in patients who had not used biologics in the preceding 12- to 24-month period) for patients with CD were captured from January 2009 through December 2012. Using the FDA-approved induction dosing strategy of adalimumab, patients with CD filled either the CD starter pack or a starter pack equivalent (3 maintenance packs including 6 pens) in the first 21 days of therapy initiation. During this time period, 63% of patients received an adalimumab CD starter pack or starter pack equivalent.

These real-life findings support our results and conclusions that lack of adherence to FDA-approved induction dosing of adalimumab is a significant problem among gastroenterologists. Our clinical scenarios were thought to be representative of real-life cases (confirmed by expert review); however, it is possible that our scenarios did not accurately reflect decision-making based on patient weight and/or prior exposure to infliximab. It is also possible that factors affect prescribing other than those included in the survey. We found that predictors of correct prescribing include gastroenterologists who have a higher frequency of adalimumab prescribing and who follow a higher number of patients with CD. It is possible that providing educational information specifically targeting gastroenterologists who have less experience with adalimumab and CD may increase rates of correct prescribing and optimize response to treatment.

To our knowledge, this is the only study evaluating prescribing patterns of adalimumab in patients with CD in the United States. Our findings demonstrate that many gastroenterologists are not using optimal adalimumab dosing strategies, which may lead to a decreased rate of response in patients with CD. Further research is needed to confirm our findings and identify barriers to optimal adalimumab use by gastroenterologists for treatment of CD.

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