

Real-World Impact of Infliximab Precision-Guided Dosing on Management of Patients With IBD

HIGHLIGHTS

- › PredictrPK IFX: A Precision-Guided Dosing Test That Represents a Novel Approach to Dose Optimization
- › PredictrPK IFX Impact on Health Care Provider Decision-Making
- › Benefits and Usefulness of PredictrPK IFX

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Real-World Impact of Infliximab Precision-Guided Dosing on Management of Patients With IBD

OVERVIEW

This supplement to *The American Journal of Managed Care*[®] describes the results of the EMPOWER (Effect on Decision-Making of Precision Optimization in Real-World Evidence Research) study, which demonstrate the real-world clinical utility of PredictrPK IFX, a precision-guided dosing assay, to prompt early treatment decisions to optimize IFX therapy with greater value than standard therapeutic drug monitoring.

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Real-World Impact of Infliximab Precision-Guided Dosing on Management of Patients With IBD

Bincy P. Abraham, MD, MS; David A. Ziring, MD; Thierry Dervieux, PharmD, PhD; Patricia Aragon Han, MD, MAS; Andrew Shim, PharmD, JD; and Robert Battat, MD, CM

Introduction and Objectives

Inflammatory bowel diseases (IBD), including Crohn disease (CD) and ulcerative colitis (UC), are chronic debilitating lifelong conditions involving inflammation/injury to the gut mucosa, dysbiosis, and potentially lethal complications resulting from progressive bowel damage.^{1,2} Effective, optimal, and personalized therapy for IBD can maximize the likelihood of healing and relieve symptoms. The rising prevalence, particularly in young adults (peak incidence between 15-30 years)³ and older adults (> 60 years),⁴ places a substantial burden on patients and health care systems due to substantial IBD-related total cost of care.

Anti-TNF α therapies have revolutionized IBD care, are considered when other conventional therapies have failed, and are often used as first-line treatment in moderate to severe IBD. However, 40% of patients may experience primary nonresponse to anti-TNF α therapies such as infliximab (IFX).⁵ Among patients who do respond, almost 40% experience secondary loss of response within 1 year⁵ and up to 55% receive treatment intensification upon loss of response.⁶

Moreover, in recent studies, 80% of patients had at least 1 end point indicative of suboptimal therapy (defined as having at least 1 of the following treatment changes or events: dose escalation, switch or discontinuation except for corticosteroid initiation, augmentation, inadequate loading, prolonged corticosteroid use, disease-related surgery, or disease-related hospitalization), indicating substantial shortcomings in treatments, even among patients not classified with loss of response.⁶

The health care cost of IBD is substantial, highlighting the importance of optimizing the use of biologics and biosimilars. Results of a Truven MarketScan Database analysis of 415,405 patients with IBD (2007-2015) reported that the average patient who was taking biologics accounted for \$36,051 and \$41,109 per member per year (PMPY) in 2015 for adults and pediatric patients, respectively.⁷ The US Centers for Disease Control and Prevention (CDC) estimates that adults with IBD in 2015 and 2016 had higher health service use compared with adults who did not have IBD.⁸ The results of another study evaluating data from 2007 to 2016 from commercial and Medicare Advantage patients reported 3-fold greater direct health

ABSTRACT

OBJECTIVES: Evaluate the clinical utility of a precision-guided dosing test for infliximab (IFX) and its impact on treatment decision-making for inflammatory bowel disease (IBD).

STUDY DESIGN: Prospective, multisite, clinical experience program.

METHODS: Health care providers were given access to PredictrPK IFX, a precision-guided dosing test, for their patients with IBD on maintenance IFX therapy. Blood samples were drawn 20 to 56 days post infusion. A Bayesian data assimilation tool used clinical and serologic data to generate individual pharmacokinetic profiles and forecast trough IFX. Results were reported to providers to aid in-therapy management decisions and the decision-making process was assessed through questionnaires. Relationships between forecasted IFX concentration, disease activity, and therapy management decisions were analyzed by logistic regression.

RESULTS: PredictrPK IFX was used for 275 patients with IBD by 37 providers. In 58% of cases, providers modified treatment plans based on the results, including dose modifications (41%; of these, one-third decreased dose) and discontinuation (8%) of IFX. Of the 42% where treatment was not modified, 99.1% had IFX levels of 5 $\mu\text{g}/\text{mL}$ or greater. Patients with IFX concentrations less than 5 $\mu\text{g}/\text{mL}$ were 3 and 7.3 times more likely to have active disease or discontinue IFX, respectively. There was unanimous agreement among providers who completed a postprogram survey that PredictrPK IFX was beneficial in guiding treatment decisions and added more value to their practice than routine therapeutic drug monitoring.

CONCLUSIONS: PredictrPK IFX enables earlier and more precise dose optimization of IFX in patients with IBD, exerting a substantial impact on treatment decisions that may result in improved health outcomes and overall cost savings.

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For author information and disclosures, see end of text.

TAKEAWAY POINTS

- Precision-guided dosing of anti-tumor necrosis factor alpha (anti-TNF α) therapy has been associated with improved health outcomes in patients with IBD.
- The EMPOWER (Effect on Decision-Making of Precision Optimization in Real-World Evidence Research) study demonstrates the real-world clinical utility of PredictrPK IFX, a precision-guided dosing assay, to prompt early treatment decisions to optimize IFX therapy with greater value than standard therapeutic drug monitoring.
- Using PredictrPK IFX in the management of IBD may lead to a net decrease in health care expenditures by more rapidly optimizing IFX dosing, reducing unnecessary IFX use, avoiding disease-related adverse outcomes and treatment delays, and enhancing the durability of response to IFX compared with empiric dosing.

care costs among patients with IBD compared with those who did not have IBD (\$22,987 vs \$6956); key drivers of cost included drug costs; emergency department use; and other services associated with relapsing disease, anemia, or mental health comorbidity.⁹ Among patients with CD who were treated with biologics between January 2004 and March 2019, 79.4% had 1 or more suboptimal treatment indicators (eg, nonadherence, dose escalation, chronic corticosteroid use, augmentation, ≥ 1 CD surgery, ≥ 2 CD emergency department visits, ≥ 1 CD inpatient stay, switch, cycling, restart, inadequate induction) with mean PMPY costs ranging from \$46,100 (no indicator) to \$68,572 (≥ 4 indicators).¹⁰

A useful approach to biologic optimization in IBD is therapeutic drug monitoring (TDM), which involves assessing serum levels of drug and anti-drug antibodies to guide dosing decisions and to improve the probability of sustained remission. Compared with empiric changes in dosing that have been shown to lack correlation with disease activity,¹¹ TDM is considered to be both the standard of care and more advantageous.¹²

Multiple publications describe the value of TDM in mitigating loss of response¹²⁻¹⁵ and guidelines recommend using TDM in patients with primary nonresponse or secondary loss of response to determine when optimization of current therapies or change to alternate therapies may be needed. Additionally, guidelines affirm the medical value of TDM and benefits associated with improved clinical, mucosal, and endoscopic remission.^{13,16-18} However, TDM is limited in that clinical decision-making is inherently reactive to measured drug and anti-drug antibody levels. In a patient with active disease, the need to wait for several weeks to measure a

trough concentration for TDM often limits the use of this strategy. In contrast, proactive TDM involves measuring drug levels in asymptomatic patients without objective evidence of active disease (ie, endoscopic, biochemical, and preemptively targeting specific clinically defined thresholds). It is associated with higher treatment persistence and lower health care resource utilization compared with reactive or empiric monitoring.¹⁹

Precision-guided dosing enables estimations of trough serum IFX concentrations without the need to wait for trough concentrations for testing. Thus, it permits expedited and informed clinical decision-making by clinicians. The clinical utility of precision-guided dosing was recently demonstrated in the PRECISION trial (NCT02624037), the results of which showed that 69% of patients with IBD treated with IFX were predicted to benefit from dose optimization during the induction phase of therapy and at week 52, 68% of the intent-to-treat group was still on IFX therapy.²⁰ This increased to 81% when data for patients who were lost to follow-up were removed. In addition, 97% of patients who were still on IFX at week 52 were in steroid-free clinical remission.²¹ For those patients who did not adhere to dose optimization as suggested by the precision-guided dosing tool, IFX durability was significantly reduced.²⁰

PredictrPK IFX (Prometheus Laboratories Inc) is a clinically validated, precision-guided dosing tool that incorporates Bayesian population pharmacokinetic models and patient-specific clinical and serological inputs, including TDM. It enables providers to more rapidly and precisely optimize dosing to achieve target drug levels for individual patients by producing individualized predictive estimates of serum IFX concentration at the next trough, as well as alternative IFX doses and intervals.²¹ To demonstrate the real-world clinical utility of PredictrPK IFX and its impact on treatment for patients with IBD, a prospective, multisite, clinical experience program (CEP) was conducted among US health care providers (HCPs).

Methods

EMPOWER (Effect on Decision-Making of Precision Optimization in Real-World Evidence Research) was a prospective, multisite, survey-based study that enrolled academic and community HCPs treating pediatric and adult patients with IBD (**Figure 1**).

Clinical Experience Program

Prior to program initiation, HCPs were presented with PredictrPK IFX validation data and test criteria. HCPs completed a prestudy survey that explored practice details and how IFX TDM was currently utilized in their practice. Subsequently, HCPs were provided access to 10 PredictrPK IFX precision-guided dosing tests to utilize in the clinical scenarios of their choosing during the maintenance phase of IFX therapy. Tests could be used in different patients or for repeat testing in the same patient. HCPs completed a posttest survey for each patient after receiving PredictrPK IFX test results. The survey

captured patient phenotype, how and why the test was ordered, how results were used, and whether the results were considered beneficial for guiding patient care. HCPs also completed a post-program survey to share overall feedback about the usefulness of PredictrPK IFX. National Institutes of Health criteria for exemption from human subject regulations (category 4) were met because all personal information was removed to protect privacy.²²

PredictrPK IFX

PredictrPK IFX includes a determination of IFX serum levels (> 1.0 µg/mL), antibodies-to-IFX (ATI) (> 3.1 U/mL), and albumin (g/dL). All assays were performed in a CLIA-certified laboratory (Prometheus Laboratories Inc, San Diego, CA). Assay results, patient dosing provided by the HCP, and patient weight were included in a validated Bayesian data assimilation tool that produces pharmacokinetic profiles.²¹ PredictrPK results included forecasted IFX trough levels based on the actual dosing, as well as patient-specific alternative dosing regimens.

PredictrPK IFX tests were used on patients for whom the physician would have otherwise ordered TDM and utilized the following EMPOWER inclusion criteria: a) confirmed diagnosis of IBD; b) received IFX treatment with or without concomitant immunotherapy; and c) received IFX treatment for at least 14 continuous weeks (maintenance phase). Blood samples for PredictrPK IFX could be collected any time from 20 days postinfusion until immediately prior to the subsequent infusion.

Data Analyses

Relationships between patient characteristics and therapy discontinuation were assessed by univariate and bivariate analyses (Table 1). Simple logistic regression was used to quantify the risk associated with estimated drug concentration, clearance, disease activity, and therapy discontinuation. Results were reported as odds ratios and confidence intervals.

Results

Characteristics of Clinical Practice

A total of 37 HCPs specializing in IBD from academic and community settings in 19 states and Puerto Rico participated in EMPOWER. HCPs were highly experienced in treating patients with IBD using biologics, with 62% of HCPs in practice for 10 years or more, 36 of 37 treating at least 10 patients with IBD per month, and 59% treating 50 or more patients per month. Biologics were used in 21% to 40% of patients by 73% of HCP practices (see eAppendix Table 1 for complete presurvey results. eAppendices available at AJMC.com). HCPs most frequently ordered PredictrPK IFX to optimize IFX therapy in the absence of symptoms (61%; proactive TDM); the test was also ordered to assess the need for change in a symptomatic patient (47%; reactive TDM), soon after initiating IFX therapy (7%; early proactive), after an infusion reaction (4%), or after another type of adverse event (4%). HCPs were allowed to provide more than 1 explanation for ordering the test. Thus, the sum of responses is greater than 100% (Figure 2).

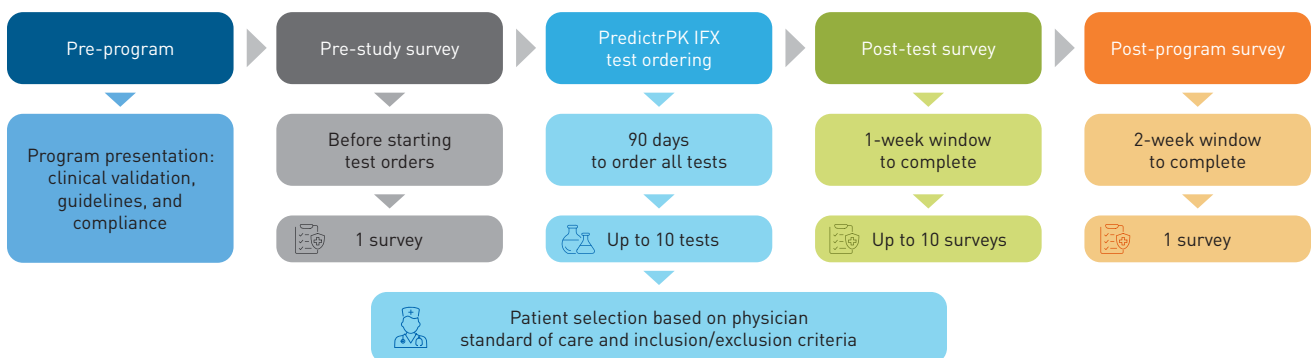
Characteristics of Patient Cohort

The median age of patients (N = 275) was 32 years; 45% of patients were female; 64% had CD, 34% had UC, and 1.5% had an indeterminate colitis (Table 1). At study entry, 32% of the patients were classified as being in remission, 38% as having mild-to-moderate disease, and 29% as having moderate to severe disease by physician global assessment (PGA); 52% had been on IFX therapy for at least 24 months, and 30% of patients had exposure to prior biologics.

PredictrPK IFX Impact on Health Care Provider Decision-Making

Of the 275 patients in the study, HCPs decreased the IFX dose or increased the dosing interval in 36 (13%) patients who had elevated measured (28 µg/mL) and forecasted (30 µg/mL) trough IFX concentrations. HCPs increased the dose or shortened the interval in 75 (28%)

FIGURE 1. EMPOWER Program Outline



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TABLE 1. Patient Characteristics and PredictrPK IFX Assay Data

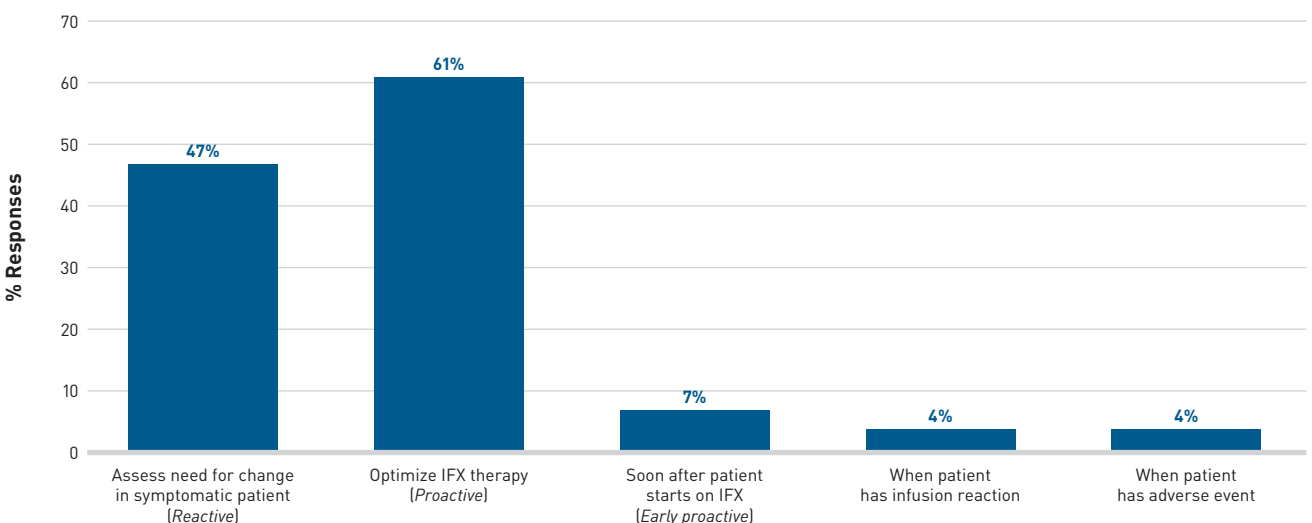
Clinic-pharmacologic characteristic	Physician decision on IFX therapy					P Value ^a
	Overall N=275 (100%)	Decrease n=36 (13%)	Continue n=141 (51%)	Increase n=75 (28%)	Discontinue n=23 (8%)	
Age (years), median (IQR)	32 (20-49)	24 (16-40)	35 (20-49)	32 (20-50)	41 (22-52)	.12
Female, n (%)	122 (45)	13 (36)	63 (45)	34 (46)	12 (52)	.65
Diagnoses, n (%)						.075
Crohn disease	177 (64)	23 (64)	98 (70)	43 (57)	13 (57)	
Ulcerative colitis	94 (34)	11 (31)	42 (30)	32 (43)	9 (39)	
Indeterminate colitis	4 (1.5)	2 (5.6)	1 (0.7)	0 (0)	1 (4.3)	
Weight (kg), median (IQR)	74 (60-89)	70 (58-78)	78 (62-93)	69 (59-86)	68 (59-75)	.022
Physician global assessment of remission, n (%)	89 (32)	21 (58)	52 (37)	13 (17)	3 (13) ^b	< .001
IFX dose (mg/kg), median (IQR)	9.3 (5.3-10.0)	10.1 (9.3-10.6)	9.4 (5.4-10.0)	6.2 (5.0-10.0)	9.6 (6.0-10.0) ^b	< .001
Interdose interval (wk), median (IQR)	8 (6-8)	6 (4-7)	7 (6-8)	8 (8-8)	8 (7-8) ^b	< .001
Time specimen collection (d), median (IQR)	41 (27-55)	32 (27-43)	41 (28-56)	40 (27-56)	42 (28-50)	.45
Measured IFX (µg/mL), median (IQR)	14 (7-24)	28 (19-48)	17 (10-24)	8 (5-15)	3 (1-10) ^b	< .001
Forecasted trough (µg/mL), median (IQR)	12 (7-20)	30 (24-40)	14 (10-20)	6 (3-9)	3 (1-9) ^b	< .001
Albumin (g/dL), median (IQR)	3.9 (3.6-4.2)	4.2 (3.9-4.3)	4.0 (3.7-4.2)	3.8 (3.5-4.0)	3.6 (3.2-3.8) ^b	< .001
ATI (>3.1 U/mL), n (%)	25 (9.1)	0 (0)	1 (0.7)	11 (15)	13 (57) ^b	< .001
Clearance (L/d), median (IQR)	0.26 (0.20-0.34)	0.21 (0.16-0.25)	0.26 (0.19-0.32)	0.29 (0.24-0.37)	0.38 (0.29-0.56) ^b	< .001

ATI, antibodies to infliximab; IFX, infliximab; IQR, interquartile range.

^aFactors associated with discontinuation of IFX therapy; comparisons by Kruskal-Wallis rank sum test, Pearson chi-squared test, or Fisher exact test, as appropriate.

^bVariables significantly associated ($P < .001$) with IFX therapy discontinuation on bivariate analysis.

FIGURE 2. Reasons for Ordering PredictrPK IFX Test^a



IFX, infliximab.

^aShown are the percentages of health care provider responses to each category. Health care providers were allowed to provide more than 1 explanation for ordering the test. Thus, the sum of responses is greater than 100%.

patients who had lower measured (8 µg/mL) and forecasted (6 µg/mL) trough IFX concentrations (Table 1 and Figure 3). No patients who had their IFX dose decreased had detectable antibodies to infliximab (ATI) and only 1 of 141 patients (0.7%) who had no change to their IFX dose had detectable ATI. Of those patients who had their IFX dose increased, 15% had detectable ATI prior to dose escalation. In patients who were switched to a different primary therapy, 57% had detectable ATI prior to the switch. In patients with dose de-escalation or unchanged dosing, 58% and 37% were in remission, respectively.

A forecasted IFX trough of less than 5 µg/mL was associated with 7.3 times the odds of IFX discontinuation and 3.0 times the odds of active disease compared with a forecasted IFX concentration of more than 5 µg/mL on logistic regression (Table 2). Similarly, a clearance rate of more than 0.294 L/day was associated with 4.1 times the odds of IFX discontinuation and 3.2 times the odds of active disease compared with a clearance rate of less than 0.294 L/day. As shown in Table 1 and Figure 3, other clinicopharmacologic features associated with the decision to stop IFX (8%) were albumin and ATI levels.

After receiving the results of PredictrPK IFX, HCPs modified their treatment plan in 58% of cases (Figure 4). Treatment modifications can be further broken down by the type of change: 41% modified biologic dosing (68% dose escalated and 32% dose de-escalated), 8% switched biologic or therapy, 6% adjusted immunosuppressant therapy (add, remove, or change dose), 9% ordered colonoscopy or other imaging, 7% added additional tests (ie, fecal calprotectin), and 2% made other changes (ie, surgery). These numbers are not additive, as HCPs may have made multiple modifications. Among 42% of cases with no treatment modification, 83.6% had IFX trough concentrations of at least 10 µg/mL, 15.5% had IFX trough concentrations of 5 to 10 µg/mL, and 0.9% had IFX trough concentrations of less than 5 µg/mL.

Benefits and Usefulness of PredictrPK IFX

In the postprogram survey, 83.8% of HCPs responded. Among these HCPs, 100% indicated PredictrPK IFX was deemed beneficial for ongoing treatment decisions, 97% reported utility for determining optimal dose/interval, and 77% reported utility for providing confidence for maintaining current dose/interval (eAppendix Table 2). When asked about the usefulness in specific situations, the strongest levels of agreement were for consideration of dose increase in primary nonresponse or secondary loss of response, followed by consideration for dose decrease, patients on maintenance IFX, and patients starting on a biologic (ie, postinduction, first maintenance dose) (Figure 5). PredictrPK IFX was also helpful in providing justification for adjustments with insurance providers (55%) or assisting in discussions with patients regarding adverse events (32%). HCPs unanimously agreed that PredictrPK IFX added more value to their practice than standard TDM.

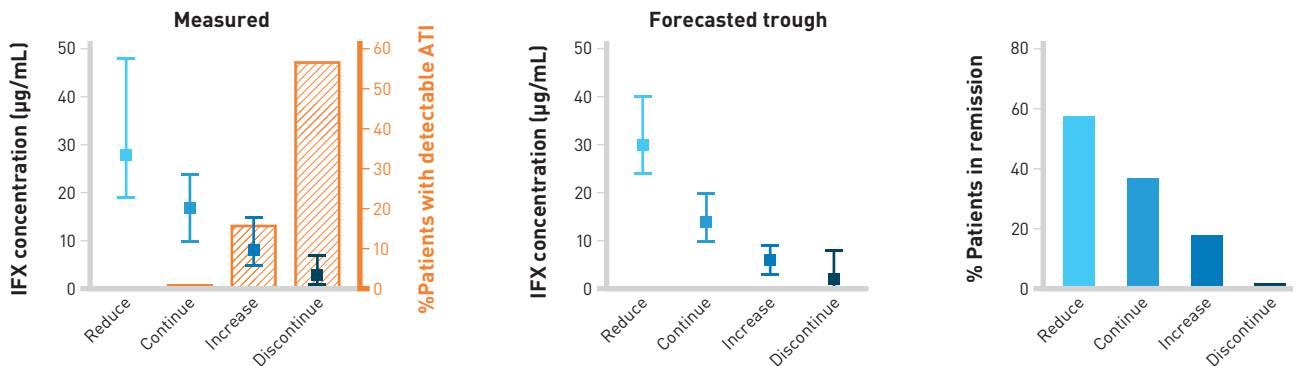
Almost all HCPs reported that ordering PredictrPK IFX was easy (90%), results were received in reasonable time (97%) to support/impact their clinical decision-making, and the test report was easy to understand and informative (100%).

The survey responses in the postprogram survey were more subjective, as the survey looked at overall experience with the test across multiple samples and patients. However, the objective data were captured following the individual postsample surveys.

Discussion

EMPOWER included a geographically diverse group of gastroenterology practitioners treating pediatric and adult patients in academic and community settings. PredictrPK IFX was ordered to optimize IFX therapy, both proactively (61%) and reactively to assess the need for change in symptomatic patients (47%), suggesting that clinicians

FIGURE 3. Associations Between PredictrPK IFX Test Results (Measured and Forecasted Trough Values), Patient Disease Status, and Changes to IFX Dosing Regimens*



ATI, antibodies to infliximab; IFX, infliximab.

*Infliximab concentrations are shown as median values with interquartile ranges. The percentage of patients with detectable antibodies to infliximab are indicated by the superimposed orange bars.

TABLE 2. Relationships Between Physician Decision-Making and PredictrPK IFX Test Results and Status of Patient Disease Activity Calculated by Simple Logistic Regression

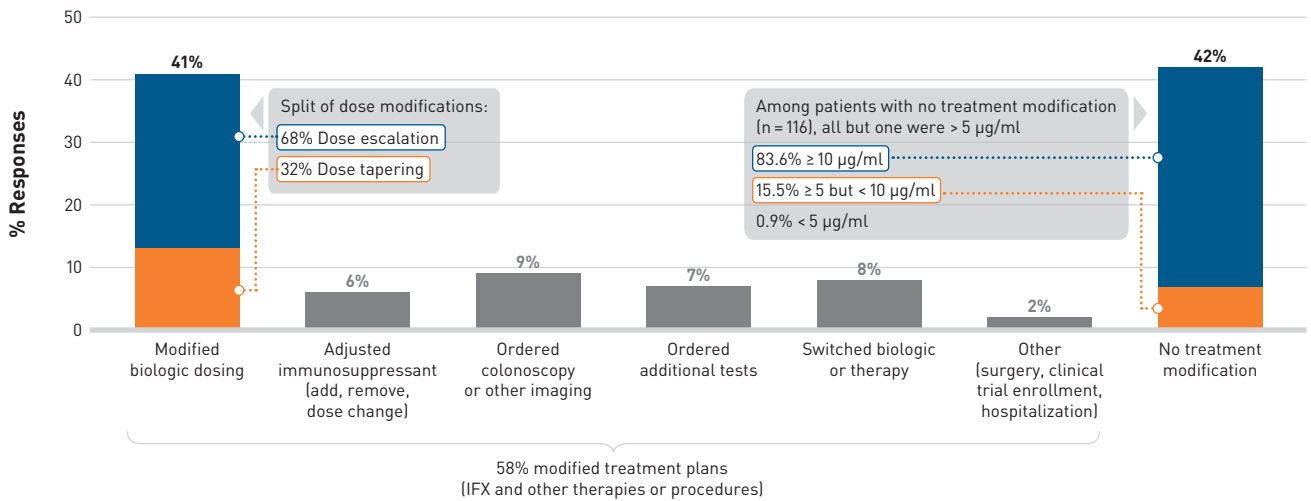
Association	Odds ratio	95% CI	P Value
Forecasted IFX concentration < 5 µg/mL			
Active disease	3.0	1.4-7.3	<.01
Discontinue IFX therapy	7.3	3.1-18.3	<.01
Clearance rate > 0.294 L/day			
Active disease	3.2	1.8-5.9	<.01
Discontinue IFX therapy	4.1	1.7-11.0	<.01

IFX, infliximab.

were comfortable in adopting a precision-guided dosing method in a variety of clinical scenarios.

Overall, PredictrPK IFX showed clinical utility in health care provider decision-making. In 58% of cases, test results were utilized in the decision to modify treatment plans and to confirm existing therapy plans where dosing was appropriately controlling IBD. Our EMPOWER data demonstrate that the most common treatment modification was a change in biologic dosing (41%) and that within this group, 32% had dose de-escalation (Figure 4). This is an important finding, showing that TDM may be a valuable tool to avoid unnecessary biologic drug use when dose reduction is warranted based on the combination of clinical symptoms and

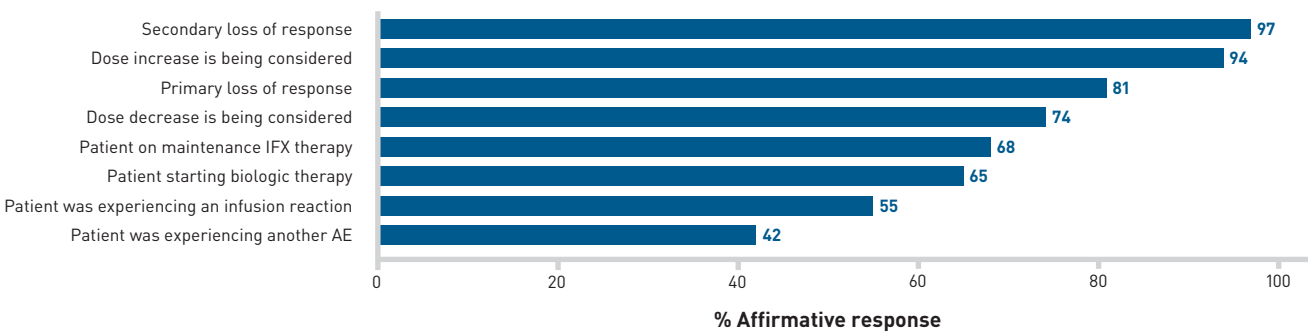
FIGURE 4. Impact of PredictrPK IFX Test Results on Clinical Decision-Making^a



IFX, infliximab.

^aHealth care providers may have made multiple modifications to the treatment plan of any given patient. Thus, the sum of responses is greater than 100%.

FIGURE 5. Usefulness of the PredictrPK IFX Test^a



AE, adverse event; IFX, infliximab.

^aShown are the percentages of health care providers (n=31) responding "yes" for the usefulness of the test in the various circumstances listed.

results of individualized pharmacokinetic profiles from PredictrPK IFX testing. Among patients with no treatment modification (42%), 83.6% had serum IFX of at least 10 µg/mL, which has been associated with corticosteroid-free clinical remission in 97% of patients still on IFX at week 52.²⁰ In addition, 15.5% of patients with no treatment modification had IFX trough concentrations between 5 and less than 10 µg/mL and only 0.9% had serum IFX of less than 5 µg/mL, concentrations that are associated with active disease and result in the discontinuation of IFX.²⁰

In the postprogram survey, HCPs unanimously agreed that PredictrPK IFX was beneficial for ongoing treatment decisions. They also had a high level of agreement that the test was beneficial for optimizing IFX dosage/interval and providing confidence for maintaining the current IFX dose and/or interval. Almost all HCPs believed that it was easy to order PredictrPK IFX, understand the test report, and receive it within a reasonable time. Importantly, HCPs unanimously agreed that PredictrPK IFX precision-guided dosing added more value to their practice than standard TDM. Given the diverse group of clinical specialists, the findings suggest that precision-guided dosing tools will likely be accepted and valued by the broader gastroenterology community.

The adoption of TDM has been variable among different practices due to knowledge gaps in clinicians' understanding of optimal target drug concentration and the need for ideal (trough) timing of measurement.^{23,24} However, a recent expert consensus statement on biologics in IBD recommended that TDM should be performed for patients treated with anti-TNF α therapies at least once during the maintenance phase and specifically when IFX dose reduction is being considered for patients in remission.²⁴ PredictrPK IFX provides increased utility relative to TDM by forecasting trough IFX in blood samples drawn at least 20 days post infusion and prior to the next IFX infusion. This precision-guided approach provides predictive data in a timely manner, which helps to avoid delays in therapeutic decision-making. In addition, PredictrPK IFX simultaneously generates a personalized profile unique to each patient, affording clinicians an opportunity to make decisions about dose or interval adjustments prior to the next infusion without having to estimate future levels and outcomes.

Responses from the postprogram survey indicated that the main benefit of PredictrPK IFX was in providing rationale and guidance for dosing decisions. Patients who discontinued IFX therapy had the lowest concentrations of measured and forecasted serum IFX and were among the highest proportion of patients with detectable levels of ATI (57%), whereas patients who either maintained or decreased their IFX dosing had the highest concentrations of serum IFX and were among the lowest proportion of patients with detectable ATI (<1%). Patients with IBD who were in remission were also more likely to have higher levels of forecasted IFX, exceeding 5 µg/mL. These associations strengthen

the perspective that early dose optimization of IFX may reduce the burden of illness.

Logistic regression coupled with machine learning may be used to estimate the association of an independent variable (ie, risk factor) with the probability or risk of a particular outcome of interest (ie, disease).²⁵ Logistic regression analysis showed that patients who had estimated IFX concentrations of less than 5 µg/mL have 3 and 7 times the odds of active disease and discontinuation therapy, respectively, when compared with IFX concentrations of at least 5 µg/mL. PredictrPK IFX can facilitate timely, clinical decision-making, providing dose optimization that is tailored to the individual patient.

At present, studies examining the relationship between precision-guided dosing and direct impact on health care costs have not yet been initiated. However, cost impact may be cautiously extrapolated based on anticipated impact to IBD-related outcomes when biologics are optimized appropriately. Proactive dose optimization with TDM in patients with IBD has been associated with improved health outcomes (ie, lower rates of IBD-related hospitalization) when compared with empiric dosing or reactive dose optimization.^{23,26,27} Specifically for IFX therapy, proactive TDM has been associated with significantly higher primary response rates and significantly lower rates of adverse clinical outcomes (severe flare, hospitalization, or surgery) when compared with empiric treatment.²⁸ In a study that analyzed data collected from June 2016 to July 2017, TDM (reactive and proactive) was deemed to identify unnecessary use of IFX in 31% of patients with IBD.²⁹

Despite the benefits of proactive TDM, a survey of more than 400 US gastroenterologists indicated that the greatest barriers to TDM were uncertainty about insurance coverage (78%) and high out-of-pocket costs to patients (76%).³⁰ Also, dose escalation accounted for 12% of the reasons given for submitting an insurance prior authorization (PA) request. The low approval rate of 67.6% suggests that PAs do not account for available evidence on the importance of dose modifications to achieve therapeutic trough targets of anti-TNF α therapies for more effective disease management.³¹ It is notable that cost constraints and management thereof constitute the greatest barriers, despite the potential opportunities for overall IBD health care savings that can result from dose optimization of these biologics.

In our study, 13% of tests resulted in dose tapering, which represents a potential reduction in costs by avoiding unnecessary drug utilization. Even IFX dose escalation (28%) represents an opportunity to expediently identify patients at risk of losing response. It also allows HCPs to adjust dosing to enable drug persistence and mitigate adverse clinical outcomes, which is now more important with the availability of biosimilars. In a prospective observational study of CD patients, treatment failure was predicted by low concentrations of anti-TNF α therapies and the development of immunogenicity.³²

The results of a systematic review and meta-analysis of serum IFX levels and outcomes in IBD found that patients in clinical remission had significantly higher mean trough IFX than patients who were not in remission.³³ This is consistent with our findings that patients in remission had a higher likelihood of a forecasted IFX of greater than 5 µg/mL and that higher clearance rates were associated with active disease and patients who discontinued IFX therapy.

Limitations

PredictrPK IFX is intended to provide guidance to clinicians in continuing or modifying their management strategy for any given patient, but currently, guidelines do not address how such testing should be best utilized. Since there is no standard of practice for use of this predictive dosing test, the results may not broadly apply to all HCPs. However, there were diverse participating sites ranging from academic to community practices that treated adult and pediatric patients, so the results were representative of real-world practice.

Also, all survey responses were self-reports with no confirmation of changes to patient care by medical records and no follow-up to determine actual real-world outcomes; however, the program intent was to assess initial treatment decisions rather than a long-term outcome assessment. Lastly, any cost savings are inferred since we did not directly determine economic outcomes.

Conclusions

PredictrPK IFX is a precision-guided dosing test that represents a novel approach to dose optimization by providing predictive pharmacokinetic data to clinicians to generate a personalized profile unique to each patient. Precision-guided dosing allows for earlier optimization of IFX dosing in patients with IBD, is associated with an increased likelihood of remission, reduces unnecessary drug use, and is associated with reduced loss of treatment response. Our data validate the consistent relationship of the PredictrPK IFX test with disease activity and its clinical utility to HCPs in managing patients with IBD who are being treated with IFX or its biosimilars. ■

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