Fecal Lactoferrin Predicts Primary Nonresponse to Biologic Agents in Inflammatory Bowel Disease

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Keywords

Biomarkers · Inflammatory bowel diseases · Treatment response · Fecal lactoferrin · Biologics

Abstract

Introduction: Fecal lactoferrin (FL) is a timely and accurate marker of inflammation in ulcerative colitis (UC) and Crohn's disease (CD). The aim of this study was to verify whether FL can predict primary nonresponse (PNR) to biologic agents during induction. **Methods:** Retrospective outcome review in 27 patients (13 with CD and 14 with UC) tested for baseline FL and retested within a week after the first and second induction doses. Clinical/biochemical outcomes were evaluated at end of induction and at follow-up (3–24 months). **Results:** Compared to baseline, changes of the Harvey-Bradshaw (CD) and Partial Mayo Scoring (UC) indices at end of induction separated responders (18/27 or 67%) from nonresponders (9/17 or 33%). In all patients, the initial FL value at induction decreased compared to baseline, continuing to decrease after the following dose in clinical responders while bouncing back in the others. Models targeting the 2 consecutively decreased FL values or the second FL value compared to baseline or the second FL value compared to the first were able to accurately predict response at end of induction. Follow-up assessment confirmed clinical remission in

initial responders (with FL values reduced on the average by $94 \pm 10\%$ compared to baseline). **Conclusions:** In CD and UC patients during induction with biologic agents, early FL measurements accurately separate clinical responders from those experiencing PNR. The method described here offers several potential advantages over other strategies to assess and manage these patients.

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Introduction

Primary response to biologic induction in inflammatory bowel disease (IBD) – both ulcerative colitis (UC) and Crohn's disease (CD) – has been traditionally evaluated by the attenuation of clinical symptoms after 12 weeks [1, 2]. More recently, the measurement of drug trough levels (TL) and of antidrug antibodies (ADA), a strategy known as therapeutic drug monitoring (TDM), has been used to evaluate possible loss of response (LOR) [3] and proposed by some to proactively reduce primary nonresponse (PNR) and LOR incidence [4–6]. Although proactive TDM-based management might improve outcomes in IBD [4–6], this strategy is expensive and has practical shortcomings [7–11] and it is unclear whether it

is truly superior to reactive TDM or to the clinically based management [12, 13]. Ideally, it is the individual patient disease burden that should be targeted by therapy [14–16]. Fecal lactoferrin (FL) and calprotectin (FC) are accurate indicators of intestinal mucosa inflammation [17], but their role in the management of therapeutic response is still evolving [18]. A necessary feature of any strategy for the management of LOR and PNR is the test time sensitivity, that is, the immediate responsiveness to drug-induced changes in mucosa inflammation. We have published evidence that FC levels in IBD patients on biologics timely and sensibly reflect the increasing inflammatory activity during the therapeutic interval due to the progressive neutralization of the medication [19]. Indeed, fecal marker levels in stool are directly related to neutrophil translocation to the mucosa of the GI tract – a process quickly modulated by medications acting on the activity of the inflammatory process [20]. We have since leveraged on those findings to routinely evaluate the immediate response to treatment in patients undergoing biologic induction. In this retrospective study, we report the relevant data.

Methods

Study Design and Study Population

This retrospective study enrolled 27 consecutive patients with UC or CD diagnosed and staged according to established criteria [21], to be treated with biologic monotherapy (infliximab, adalimumab, certolizumab, and vedolizumab) as standard of care in our IBD center and enrolled within a 2-year period (2018–2020). No steroids or other medications were prescribed before the index FL tests and the end of induction. All patients tested negative for tuberculosis and hepatitis B and C as well as stool culture and *C. difficile*.

FL levels as well as clinical/laboratory data were collected from the patients' electronic medical records. Data collected involved patients (both naïve and biologic experienced) undergoing biologic induction. In these patients, FL was measured at baseline (within 1 month of starting therapy), then within a week after drug administration for at least 2 consecutive infusions/injections during the induction phase (comprising 3 infusions for infliximab and vedolizumab [weeks 0, 2, and 6], 2 injections for adalimumab [weeks 0 and 2], and 3 injections for certolizumab [weeks 0, 2, and 4]). Management of these patients was based on clinical outcomes and scores (see below) after completion of the induction phase. Follow-up was 3–24 months – on the average 8 months – and included clinical and biochemical (postinduction FL levels) assessment.

Biomarker Testing

FL was measured in samples collected during the first bowel movement of the day by the LACTOFERRIN SCAN (TECHLAB, Blacksburg, VA, USA), an ELISA. Values ≤ 7.24 $\mu\text{g/mL}$ are considered normal [22]. At Carilion Clinic Laboratory, the lower limit to which the linearity of results has been validated is 6.25 $\mu\text{g/mL}$,

which is the absolute value reported and analyzed for results ≤ 6.25 $\mu\text{g/mL}$. FL values are presented by standard decimal approximations of the actual number by excess or defect. Routine blood and stool studies were performed using established methods.

Assessment of Clinical Disease Activity

Clinical assessment was performed during clinic visits at baseline, within a week of completing induction and at follow-up and was based on the Harvey-Bradshaw Index (HBI) for CD and the Partial Mayo Scoring Index (PMSI) for UC [23]. For HBI, scores of <5 , 5–7, 8–16, and >16 define remission, mild, moderate, and severe disease activity. The same activities are defined by the scores of 0–1, 2–4, 4–6, and 7–9 for PMSI. Clinical response in UC was defined as a decrease of ≥ 3 of the partial Mayo score [24] plus a decrease of at least 30% from the baseline score, accompanied by a decrease of ≥ 1 in the rectal bleeding scale or an absolute rectal bleeding score of 0 or 1 [25]. Response in CD was defined as a decrease of ≥ 3 of the HBI [26].

Statistical Analysis

Patients were separated in 2 groups based on the postinduction clinical response. To uniformly analyze HBI and PMSI, these indices were rescaled to be between 0 and 1 by dividing each score by the maximum value for each scale with the value of “16” used as the maximum value for the HBI since all the scores above 16 are considered severe (and 16 was also the highest value of the HBI in the data set). Analysis of these rescaled HBI and PMSI before and after induction treatment was performed using a nonparametric sign test within each group due to nonnormality of these values; a Mann-Whitney U test was used to compare baseline values. We also used nonparametric Mann-Whitney U test to compare the baseline FL values and the initial FL drop in the 2 groups of patients.

Various combinations of FL measures were used to predict whether an individual would respond clinically (based on the criteria outlined in the previous section) following the entire induction cycle. The first of these measures was a dichotomous measure where participants were labeled as FL responders if they experienced 2 consecutive drops in FL compared to their baseline measurement and labeled as FL nonresponders if they did not. The remaining measures were all numeric measures of FL (generally based on % of baseline measure), including FL values following the first induction dose (as a percentage of baseline values), FL values following the second induction dose (as a percentage of baseline values), the baseline FL measure itself (in raw units), and the difference between the first and the second FL values (as a percentage of the baseline value).

Logistic regression models were used to examine the relationships of each of these predictors to the outcome of remission. For all models, area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, and FL cutoff values were calculated.

Results

There were 27 patients who underwent biologic induction (Table 1) with 14/27 being biologic naïve. The median age was 51 years, 48% had CD (with approxi-

Table 1. Patient features

<i>Demographics</i>	<i>N = 27</i>
Age, median (IQR), years	51 (32.5)
Males-females	15-12
Smoker (current, former, and never), %	18, 30, and 52
<i>Disease characteristics</i>	
Disease type	
CD, <i>N</i> (%)	13 (48)
UC, <i>N</i> (%)	14 (52)
Disease duration, median (IQR), years	6 (8)
Biologic naïve (yes/no)	14/13
Biologic induction	
Infliximab, <i>n</i> (%)	15 (55)
Vedolizumab, <i>n</i> (%)	7 (30)
Adalimumab, <i>n</i> (%)	4 (15)
Certolizumab, <i>n</i> (%)	1 (4)
CD location, %	
L1: ileal	30
L2: colonic	30
L3: ileocolonic	40
CD behavior, %	
B1: nonstricturing, nonpenetrating	85
B2: stricturing	15
B3: penetrating	0
UC location, %	
E1: ulcerative proctitis	15
E2: left sided (distal)	21
E3: extensive (pancolitis)	64

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

mately equally distributed ileal, ileocolonic, and colonic disease), and 52% had UC (2/3 with pancolitis). In CD patients the disease was mostly nonstricturing/nonpenetrating.

Of the 27 patients, 18 (67%) responded clinically to induction with normalized clinical scores dropping from 0.71 ± 0.16 to 0.05 ± 0.06 , ($p < 0.0001$) (Table 2). In all cases the numerical value of both HBI and PMSI fell within the definition of remission. In 9/27 (33%) patients, normalized clinical scores remained unchanged after induction (0.79 ± 0.19 vs. 0.71 ± 0.13 , $p = 0.06$). Baseline clinical score values were very similar among the 2 groups ($p = 0.28$). Although FL substantially decreased (by up to 98% of baseline levels) in all patients after the first infusion/injection, subsequent FL levels further decreased (or stayed within normal values/did not increase) only in clinical responders during induction (Table 2). In clinical nonresponders, subsequent FL levels increased, in some cases reaching levels close or superior to baseline values (Table 2). The data for all patients are graphically reported in Figure 1. No changes in management were made in

the first group of patients since they responded to induction. However, the patients in the second group continued to experience severe symptoms after induction and were reinduced with other biologics or underwent surgery if they had failed multiple biologics.

The baseline FL values were greater in the nonresponders group compared to responders ($2,221 \pm 1,910$ vs. $773 \pm 1,054$ $\mu\text{g/mL}$, $p = 0.02$). Likewise, the initial FL drop was less on the average in the nonresponders although the difference was not statistically significant (62 ± 36 vs. $83 \pm 16\%$, $p = 0.09$).

Diagnostic accuracy for FL in predicting clinical response was calculated for different models (see Methods). Using the drop in FL values after the first induction dose (as a percentage of the baseline FL), the AUC associated with the receiver operating curve is 0.710 with a 95% CI of 0.497–0.923 (see online suppl. Fig. 1; see www.karger.com/doi/10.1159/000515432 for all online suppl. material). The FL cutoff (probability of clinical response >0.5) is 45.6% of baseline with sensitivity of 1 and 95% CI of 0.847–1 and specificity of 0.333 and 95% CI of 0.075–0.701. Using the drop in FL value after the second drug dose (as a percentage of baseline FL), the AUC is estimated to be 1 (online suppl. Fig. 2). In this case, the FL cutoff is 42.7% of baseline with a sensitivity of 1 (95% CI = 0.847, 1) and specificity of 1 (95% CI = 0.717, 1). Baseline FL ($\mu\text{g/mL}$) was also able to predict clinical response at end of induction with AUC of 0.778 (95% CI = 0.570–0.986), sensitivity of 0.762 (95% CI = 0.528, 0.918), specificity of 0.444 (95% CI = 0.137, 0.788), and baseline FL cutoff of 2,334.07 $\mu\text{g/mL}$ (online suppl. Fig. 3). Using the change in FL value after the second drug dose compared to the value after the first drug dose, the AUC is estimated to be 1 with a sensitivity of 1 (95% CI = 0.847, 1), a specificity of 1 (95% CI = 0.717, 1), and a FL cutoff of 25% of baseline FL (online suppl. Fig. 4). Finally, using the 2 consecutive FL drops as a criterion to predict remission, the AUC is estimated to be 1 with a sensitivity of 1 (95% CI = 0.847, 1) and a specificity of 1 (95% CI = 0.717, 1) (online suppl. Fig. 5).

Follow-up data were available for all patients from a minimum of 3 months to a maximum of 24 months. All the patients in the first group remained in clinical remission (<5 for HBI and 0–1 for PMSI) at follow-up with clinical scores superimposable to those postinduction and FL levels (measured at the reported follow-up times [Table 2] within a week after drug administration) reduced on the average by $93.5 \pm 9.8\%$ (67–99.9) compared to baseline values.

Table 2. FL and induction with biologic agents: management and follow-up

Pt #	Disease type	Biologic naïve	Baseline FL, µg/mL	FL after first induction dose, µg/mL	FL after second induction dose, µg/mL	Medication*	HBI (pre/postinduction)*	PMSI (pre/postinduction)*	Change in care	Follow-up, clinical outcome (index) and FL, µg/mL
<i>Responders</i>										
1	CD	Yes	337	47	27	Infliximab	8/0	na	None	12 months. Clinical remission [^] (0). 6.25
2	CD	Yes	4,262	483	6.25	Infliximab	14/2	na	None	24 months. Clinical remission (0). 6.25
3	UC	No	1,306	82	6.25	Infliximab	na	6/0	None	11 months. Clinical remission (1). 62
4	CD	Yes	68	6.25	6.25	Infliximab	13/0	na	None	10 months. Clinical remission (0). 6.25
5	UC	No	386	173	94	Infliximab	na	9/1	None	6 months. Clinical remission (0). 6.25
6	UC	No	753	283	15	Vedolizumab	na	5/0	None	12 months. Clinical remission (0). 6.25
7	CD	Yes	159	51	27	Adalimumab	8/2	na	None	12 months. Clinical remission (2). 23
8	CD	Yes	229	6.25	6.25	Infliximab	14/1	na	None	6 months. Clinical remission (1). 6.25
9	UC	Yes	454	6.25	6.25	Vedolizumab	na	5/0	None	8 months. Clinical remission (0). 6.25
10	CD	No	43	6.25	6.25	Adalimumab	12/3	na	None	6 months. Clinical remission (0). 6.25
11	UC	No	2,585	44	32	Infliximab	na	5/0	None	9 months. Clinical remission (1). 65
12	CD	No	181	38	20	Infliximab	13/1	na	None	8 months. Clinical remission (2). 61
13	CD	Yes	819	23	14	Adalimumab	12/0	na	None	7 months. Clinical remission (0). 6.25
14	CD	No	597	77	8	Adalimumab	11/1	na	None	3 months. Clinical remission (0). 6.25
15	CD	No	227	6.25	6.25	Infliximab	8/0	na	None	12 months. Clinical remission (0). 6.25
16	UC	Yes	673	299	280	Vedolizumab	na	8/0	None	6 months. Clinical remission (0). 7.3
17	UC	No	600	217	59	Infliximab	na	8/1	None	3 months. Clinical remission (0). 6.25
18	CD	Yes	228	6.25	6.25	Infliximab	10/1	na	None	18 months. Clinical remission (0). 6.25
<i>Nonresponders</i>										
19	UC	No	1,130	46	732	Vedolizumab	na	5/5	Therapy change	4 months. Failed 2 more biologics (5). Considering surgery
20	UC	Yes	3,811	775	3,529	Infliximab	na	8/7	Total abdominal colectomy	4 months. Surgical remission (1)
21	UC	Yes	5,851	219	3,143	Infliximab	na	9/8	Total abdominal colectomy	6 months. Surgical remission (1)
22	UC	No	1,423	1,155	2,140	Infliximab	na	5/5	Therapy change	3 months. Currently in remission with ustekinumab (1)
23	UC	Yes	277	248	386	Vedolizumab	na	6/6	Therapy change	3 months. Currently in remission with ustekinumab (1)
24	UC	No	3,637	927	2,805	Vedolizumab	na	9/7	Therapy change	3 months. Currently in remission with infliximab (1)
25	CD	No	221	190	357	Infliximab	16/14	na	Small bowel resection	7 months. Surgical remission (2)
26	CD	Yes	936	151	442	Certolizumab	12/10	na	-	3 months. (9) considering surgery
27	UC	Yes	2,700	433	2,447	Vedolizumab	na	6/6	-	3 months. (5). Surgery scheduled

FL, fecal lactoferrin; HBI, Harvey-Bradshaw Index; PMSI, Partial Mayo Scoring Index; UC, ulcerative colitis; CD, Crohn's disease; na, not applicable. * Infliximab and vedolizumab are administered as 3 induction infusions at weeks 0, 2, and 6; adalimumab as 2 injections at weeks 0 and 2; and certolizumab as 3 injections at weeks 0, 2, and 4. [^] Pre/postinduction: before starting therapy and at the end of the induction. [^] Clinical remission defined as a score <5 (HBI) or 0–1 (PMSI).

By contrast, of the 9 patients who did not respond to induction with rebounding FL, 4 were reinduced with new biologics (with 3 of them responding) while the others either underwent immediate surgery or are planning to undergo surgery due to previous or new multiple biologic failures.

Discussion

LOR and PNR to biologic agents represent an important and frequent event in IBD [1, 2]. Symptomatic improvement after 12 weeks of initial biologic induction has been traditionally used to evaluate response to therapy [1,

Fig. 1. FL levels in IBD patients at baseline (before therapy) and during biologic induction. **a** Patients showing a progressive FL decrease. These patients showed clinical response after induction and continued to be in full remission at follow-up. **b** Patients showing an initial FL drop with a subsequent increase. These patients did not respond clinically to induction, and therapy was changed to a different biologic or they underwent surgery. FL, fecal lactoferrin.

2]. More recently, proactive TDM has been proposed as a tool to optimize initial drug treatment in these patients [4–6]. With proactive TDM, target TL are stipulated before induction and – when measured and found subtherapeutic (in the absence of ADA) during and after induction – the drug dose is progressively increased. A number of studies have indeed shown that this interesting strategy could reduce PNR incidence and improve long-term outcomes [4–6]. However, solid evidence for routine clinical use is still lacking [12, 13]. In addition, this strategy is expensive and has some practical shortcomings [7–9, 27], in particular in the USA [11]. One of the issues with this strategy is the assumption that there is a universal therapeutic TL that can be applied to all patients. However, establishing universal, practically useful therapeutic TL has been proven challenging since TL vary according to a number of factors [9], most importantly the individual disease burden [14]. Indeed, using a priori stipulated values, a substantial proportion of patients on biologics are either in remission with “subtherapeutic” TL or might experience PNR/LOR with “therapeutic” TL [7, 9, 14, 16, 19, 27, 28].

A more practical approach to manage patients starting a biologic would be to evaluate whether the medication

directly impacts the disease activity – that is, whether it is effective in reducing inflammation in the individual patient. Fecal markers of inflammation (FL/FC) accurately reflect mucosa inflammation [17, 29, 30] and disease burden [20, 31] in IBD. However, their optimal use in disease management remains unclear [18]. Previous data obtained with FC [19] show that fecal markers timely mirror drug-mediated changes in inflammation since they directly reflect neutrophil translocation to the mucosa of the GI tract – a process quickly modulated by the activity of the inflammatory process [20]. Hence, fecal markers could potentially be used to immediately monitor biologic response in IBD. In our center, we have used this strategy over the years to assess patients with LOR to biologics and to monitor primary response during induction. We have reported here the data related to the latter group of patients.

We show that in all patients undergoing induction, the biologic agent induced an initial drop in FL compared to baseline levels. However, after the following dose, FL levels bounced back in approximately 30% of patients while keeping on decreasing (or remain low) in the others. Only in the latter patients clinical scores significantly dropped into the remission range at the end of induction. In the

former group, the symptoms persisted and the medication was changed or patients underwent (or are planning) surgery if they had failed multiple biologics. Follow-up confirmed persistence of clinical remission (and FL levels reduced on the average by 94%) over time only in initial responders, all of whom had 2 consecutive decreased FL levels during induction. Of the unresponsive patients who changed medication, 3 out of 4 responded to new biologics while the others – due to multiple biologic failures – either underwent immediate surgery or are planning to undergo surgery.

Logistic regression analysis showed that the 2 consecutively decreased FL values after the initial induction doses could predict remission at end of induction. When FL measurements were extended to the third induction dose, the patterns described above (continuous FL decrease vs. initial decrease with subsequent rebound) did not appear to change in individual patients (D. Sorrentino, unpublished). Hence, testing patients only after the second and the third induction dose could be equally informative. Models targeting single FL values (second FL value compared to baseline and second FL value compared to the first) were also able to predict remission. Models using the baseline FL or the FL drop after the first drug dose were less accurate in predicting remission.

Pavlidis et al. [32] have also shown that early postinduction changes in FC predict PNR clinical outcomes in CD. By contrast to us, those authors tested the fecal marker up to 10 weeks after the first induction dose and only studied anti-TNF naïve patients, with more than half of them being on combination therapy. Similarly to us, De Vos et al. [33] have shown that a constant and deep decrease in FC during and after induction predicts remission at week 10 in patients treated with infliximab. Theede et al. [34] tested for FC 16 patients with active UC being treated with steroids and showed that the stool markers dropped immediately in all patients and correlated well with clinical and biochemical parameters. By contrast, Toyonaga et al. [35] in 27 UC patients (mostly treated with steroids with a minority treated with anti-TNF agents or tacrolimus) showed that clinical scores dropped faster than FC levels; this apparently due to daily FC variability. In our study, as discussed above, 2 consecutive FL drops as well as single FL values during induction predicted the response to therapy. These findings are consistent with the traditional clinical approach whereby the lack of clinical improvement after 2 induction doses was considered an indication to switch therapy [1, 2].

The significant drop (up to 98%) in FL levels in all of our patients (including nonresponders) after the initial

infusion/injection was somewhat unexpected. Billiet et al. [16] have reported a similar phenomenon testing different cytokines. It is possible that neutralizing antibodies produced after the first drug dose hamper response to the following drug administration [36]. However, it is also possible that inflammation switches to a different “driver” once a given pathway has been blocked by the medication in susceptible individuals [14, 37]. It is also possible that patients with high inflammatory burden are more likely to experience PNR and might need a higher dose [16]. However, there is no clear evidence that initial induction doses might be insufficient in a proportion of patients due to a very high disease burden. Billiet et al. [16] suggested that some of the nonresponders might have lower tissue concentrations of medication and that – by inference – higher doses could be effective. In theory, it is possible that in our nonresponsive patients inflammation (and FL) increased after an initial drop due to the excessive consumption of medication because of the large disease burden. Indeed, baseline FL levels were higher on the average in nonresponsive patients. However, there was a large overlap among responders and nonresponders and a number of patients with very high baseline FL levels did respond to the same medications/doses/therapeutic intervals used in nonresponders.

An additional issue partially addressed by our study relates to the concept that anti-integrin therapies such as vedolizumab have a slow onset of action [38]. In our study there were both responders and nonresponders among patients on vedolizumab, irrespective of their previous experience with biologics. Hence, our limited observations suggest that these medications might actually act as fast as any other biologic agent.

Our study has some limitations. First of all, the sample size was relatively small and this might have affected our absolute remission rates and FL cutoff values. Replication of this study by others and on a larger scale would clearly be important. Nevertheless, the basic findings of this study (the high accuracy of early stool marker measures to predict response after induction) are fully consistent with those of others [32–35].

Also, our study is retrospective. In addition, we did not measure TL and ADA, which could have added interesting mechanistic information to our findings. A number of other issues are also worth a mention. First, adopting this fecal marker-based strategy might be challenging when the disease only involves a short small bowel segment and FL levels might [20] or might not [39] be elevated even in the absence of therapy. In general, detectable FL levels at baseline would be the only prerequisite

to apply this strategy. Second, FL should be measured at the same, fixed time after each drug administration since it tends to increase over time [19] – for example, values measured 1 day after drug administration would be lower than those measured 10 days after [19]. Finally, it is important to keep in mind that steroids or any other effective fast-acting medications given before/during induction and the double FL testing could affect the results. In our patients, no concomitant medications were given in such period. If clinically needed (i.e., patient experiencing severe symptoms while waiting for induction), steroids could be initiated and kept on a stable dose well before and after induction – an approach that is classically used in clinical trials. In such case, baseline FL values would be those measured before induction with the patient already on stable steroid therapy.

In conclusion, the timely sensitivity of FL to drug-generated changes in inflammation provides the rationale for an accurate, rapid, and inexpensive stool marker-based strategy to predict PNR in IBD patients undergoing induction with biologic agents. We have recently shown that such fecal marker-based approach might also be applied to patients experiencing a potential LOR to biologic agents [40]. However, larger prospective studies will be needed to evaluate the potential applicability of these strategies to clinical practice and to explore any potential complementary role for TDM [41].

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Statement of Ethics

There was no direct patient involvement. The study conformed to the guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by Carilion Clinic Ethics Committee (“Utilization of stool markers to manage IBD patients losing response to biologics” – approval #IRB-18-259). No patient consent was deemed necessary by the Ethics Committee under 45 CFR 46.116(d).

Conflict of Interest Statement

Dario Sorrentino has received consulting fees from Abbott/AbbVie, Schering-Plough, MSD, Janssen Research & Development, LLC., Centocor Inc., TechLab, Hoffmann-LaRoche, Giuliani, Schering-Plough, and Ferring; research grants from AbbVie, Janssen Research & Development, LLC, Schering-Plough, TechLab, Centocor, Takeda; and serves in the Speakers Bureau of AbbVie and the National Faculty of Janssen. Vu Nguyen has received grant support from AbbVie Inc. Kim Love has no conflicts of interest to declare.

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Author Contributions

Study concept and design: D.S.; acquisition of data: D.S. and V.Q.N.; analysis and interpretation of data: D.S. and K.L.; drafting of the manuscript: D.S. and K.L.; revision of the manuscript for important intellectual content: D.S., V.Q.N., and K.L.; approval of the final manuscript: D.S., V.Q.N., and K.L.; guarantor of the article: D.S.

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