Biomarkers as potential treatment targets in inflammatory bowel disease: A systematic review

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There is increasing interest in the concept of 'treat-to-target' in inflammatory bowel disease as a mechanism to standardize management and prevent complications. While clinical, radiographic and endoscopic treatment end points will figure prominently in this promising management paradigm, the role that noninvasive biomarkers will play is currently undefined. The goal of the present systematic review was to investigate the potential value of biomarkers as treatment targets in inflammatory bowel disease, with particular focus on those best studied: serum C-reactive protein (CRP) and fecal calprotectin. In Crohn disease, elevated CRP levels at baseline predict response to anti-tumour necrosis factor agents, and normalization is usually associated with clinical and endoscopic remission. CRP and hemoglobin levels can be used to help predict clinical relapse in the context of withdrawal of therapy. Ultimately, the authors conclude that currently available biomarkers should not be used as treatment targets in inflammatory bowel disease because they have inadequate operational characteristics to make them safe surrogates for clinical, endoscopic and radiographic evaluation. However, CRP and fecal calprotectin are important adjunctive measures that help alert the clinician to pursue further investigation.

Key Words: *Anti-tumour necrosis factor therapy; Biomarker; C-reactive protein; Crohn disease; Fecal calprotectin; Ulcerative colitis*

Les biomarqueurs comme cibles thérapeutiques potentielles en cas de maladies inflammatoire de l'intestin : une analyse systématique

On constate un intérêt croissant pour le concept de « traitement ciblé » (*treat-to-target*) en cas de maladies inflammatoires de l'intestin, utilisé comme mécanisme pour standardiser la prise en charge et prévenir les complications. Les indicateurs de traitement clinique, radiographique et endoscopique occupent une place de choix dans ce paradigme de prise en charge prometteur, mais le rôle des biomarqueurs non invasifs n'est toujours pas défini. La présente analyse systématique visait à examiner la valeur potentielle des biomarqueurs comme cibles thérapeutiques en cas de maladies inflammatoires de l'intestin, notamment celles qui sont les mieux étudiées, soit la protéine C réactive (PCR) sérique et la calpropectine fécale. Dans le cas de la maladie de Crohn, des taux de PCR élevés en début d'étude sont indicateurs d'une réponse aux agents des inhibiteurs du facteur de nécrose tumorale, et leur normalisation s'associe généralement à une rémission clinique et endoscopique. La PCR et les taux d'hémoglobine peuvent contribuer à prédire les récidives cliniques lors du sevrage thérapeutique. En définitive, les auteurs concluent que les biomarqueurs actuellement offerts ne devraient pas être utilisés comme cibles thérapeutiques en cas de maladies inflammatoires de l'intestin parce qu'en raison de leurs caractéristiques opérationnelles, ils ne peuvent pas se substituer en toute sécurité à l'évaluation clinique, endoscopique et radiographique. Cependant, la PCR et la calpropectine fécale sont des mesures complémentaires importantes qui indiquent au clinicien d'approfondir les examens.

The inflammatory bowel diseases (IBD), encompassing Crohn disease (CD) and ulcerative colitis (UC), remain a challenging group of conditions to treat. Despite many therapeutic modalities, there is uncertainty in terms of proper treatment end points. Endoscopic evaluation, combined with diagnostic imaging modalities, remain important methods to quantify the severity of disease and, by corollary, to determine response and remission following initiation of medical treatment. There is increasing recognition and uptake of the 'treat-to-target' paradigm – a concept borrowed from the rheumatology literature (1) – in guiding the management of IBD.

Biomarkers are defined as measureable substances derived from a biofluid or tissue specimens. This broad definition can include common laboratory work, such as hemoglobin concentration, or even molecular systems biology techniques, such as gene-expression profiling (eg, on peripheral blood cells). They are becoming especially important as less-invasive, cost-effective and resource-saving modalities to determine therapeutic response in IBD are developed. The aim of the present systematic review was to investigate the potential value of biomarkers as treatment targets in IBD, with discussion of their role in monitoring response to therapy and predicting relapse. We focus on assays that are widely available and used in current practice, especially serum C-reactive protein (CRP) and fecal calprotectin (fcalpro), with briefer mention of other assays (see Table 1 for summary of evidence).

METHODS

The present systematic review was performed under the aegis of the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program, sponsored by the International Organization for the Study of Inflammatory Bowel Diseases. The systematic search strategy aimed to answer the question regarding the role of biomarkers as potential treatment targets in IBD. The initial search revealed 228 references that were manually screened by two of the study authors (SOD and TM). The search strategy used is presented in Appendix 1, and 50 relevant publications were found. Reference lists of studies and relevant review articles were reviewed. The search was limited to studies published before January 1, 2014.

SERUM BIOMARKERS

Summary

In CD and UC, CRP should not be used alone as a treatment target because it has inadequate operational characteristics to act as a surrogate for endoscopic, radiographic or clinical end points. CRP is a noninvasive adjunctive measure that can be used in both CD and UC to guide the need for further endoscopic or radiographic evaluation. Failure of CRP normalization following therapy initiation should prompt further endoscopic and/or radiographic evaluation, irrespective of symptoms. Other biomarkers, such as erythrocyte sedimentation rate (ESR), have inadequate evidence to support their use.

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TABLE 1
Summary and evidence level of inflammatory bowel disease biomarkers

Blood biomarkers	Evidence level
Crohn disease	
There is a correlation between endoscopic but not histological disease activity and CRP levels in Crohn disease (6)	3b
A decrease in CRP is seen in anti-TNF therapy concomitant with increased response/remission to therapy in children and adults (10-14)	1b
Maintenance therapy with an anti-TNF agent is associated with continued normalization of CRP (12)	1b
Baseline elevation in CRP predicts anti-TNF responsiveness (8,9,17)	2b
Among responders to anti-TNF induction, normalization of CRP at week 14 is associated with maintenance of response (17)	3b
Elevation in CRP >5 mg/L, hemoglobin level ≤145 g/L, and leukocyte count >6x10^9/L predict relapse in patients on combination therapy in whom anti-TNF therapy is discontinued (25)	2b
Elevation of CRP >20 mg/L and hemoglobin level <120 g/L are predictors of relapse in whom azathioprine is withdrawn (22,24)	2b
Ulcerative colitis	
CRP is associated with active disease on endoscopy (7,37)	2b
Elevated CRP, low albumin and low hemoglobin levels are predictive of colectomy in acute severe ulcerative colitis (31-36)	2b
Few randomized controlled trials in ulcerative colitis have biomarkers as end points. Small studies have found that clinical response to therapy correlates with a reduction in CRP level (26,28,29)	1b
Fecal biomarkers	
Crohn disease	
Fcalpro is positively associated with endoscopic activity and Crohn disease activity index (6,43)	3b
Change in level correlates with change in endoscopic activity (47,48)	3b
Elevated fcalpro is associated with a higher one-year risk of relapse in Crohn disease (51,64)	2b
Ulcerative colitis	
Fcalpro correlates with endoscopic disease and healing (46,52,53)	2b
In trials of vedolizumab, changes in fcalpro correlate with Mayo score (22)	1b
Normalization of fcalpro predicts clinical response to therapy and sustained remission (51,53,54)	2a
In patients on maintenance infliximab, fcalpro was better than CRP at predicting relapse.	1b

CRP C-reactive protein; Fcalpro Fecal calprotectin; TNF Tumour necrosis factor

In CD, elevated CRP levels at baseline predict response to anti-tumour necrosis factor (TNF) agents, and normalization of CRP is modestly associated with clinical and endoscopic remission. CRP and hemoglobin levels can be used to help predict clinical relapse in the context of withdrawal of therapy.

In UC, the utility of CRP as an adjunctive measure is greatest in severe disease, in which persistent elevation, in addition to low albumin levels, is associated with the need for colectomy. CRP normalization is modestly correlated with clinical remission and mucosal healing.

Discussion

CRP: CRP is a 224-residue protein synthesized by the liver and named for its ability to precipitate the C-polysaccharide of *Streptococcus pneumoniae* (2). It was the first acute-phase reactant to be described, and is known to be elevated in most acute-phase responses, including infections, inflammatory diseases, trauma and malignancy. It is believed to be more accurate than other acute-phase reactants, such as ESR, which is susceptible to diurnal and nutritional variation (2), and lacks data supporting its use. Given these characteristics, as well as its popularization as a cardiovascular screening tool, CRP has become the acute-phase biomarker of choice for a broad range of diseases. CRP is of limited utility in some individuals because common polymorphisms are known to affect CRP levels and prevent an inflammation-induced rise in CRP (3,4). As such, documenting an elevated CRP level in the context of a flare is an important baseline to instruct the future utility of this assay.

CRP in CD: In CD, there is evidence that extraenteric inflammation according to computed tomography enterography correlates with CRP (5), and CRP is more often elevated in individuals with colonic involvement. There is modest correlation between endoscopic disease activity and CRP levels in CD (6,7).

The majority of randomized clinical trials (RCTs) in the past decade have included serial CRP measurements. Recent trials of biologic and nonbiologic therapy have increasingly used baseline elevated CRP level as an inclusion criterion to insure patients entered into these trials have an objective marker of inflammation. This practice largely stems from results of the phase II induction studies of certolizumab published in the mid-2000s, in which patients with elevated CRP levels were shown to have more robust response rates (8,9). A phase II study by Schreiber et al (9) demonstrated a high placebo response rate in subgroups of patients with low CRP and, in post hoc analysis, a significant effect of therapy only in the subgroup of patients with baseline CRP >10 mg/L. A further certolizumab induction trial by Sandborn et al (8) (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy 1 [PRECISE 1]) stratified randomization of patients according to baseline CRP (≥ or <10 mg/L), and found a significant response among patients with an elevated CRP level. Both studies demonstrated a durable decrease in CRP among patients treated with 400 mg dosing of certolizumab over the study period.

Although these were the some of the first studies to demonstrate the role of CRP as an inclusion criterion, early trials of anti-TNF agents included serial measurement of CRP (10-12). In the original infliximab induction trial published by Targan et al (10), there was a significant decrease in CRP level among patients treated with infliximab (monoclonal cA2) at four weeks (eg, 16 mg/L in those treated with 5 mg/kg infliximab versus 2 mg/kg in placebo). Normal serum CRP levels were maintained among patients who received maintenance therapy with infliximab (12). The pediatric infliximab literature similarly suggests a decrease in CRP in association with infliximab therapy in CD (13). The Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC-1) trial, which explored induction with adalimumab in CD, reproduced the infliximab findings by showing a durable reduction in CRP over four weeks in patients treated with anti-TNF therapy (14).

Clinical trials exploring combination therapy have similarly included CRP as an outcome. The study by van Assche et al (15), which explored the discontinuation of immunosuppressants in CD patients on infliximab at six months, was particularly revealing as to the potential of this biomarker. The study authors demonstrated a significant increase in CRP in patients discontinuing immunosuppressants,

although there was no difference in their primary outcome of patients requiring modification in infliximab dosing. Post hoc analysis demonstrated a correlation between CRP and serum trough levels of infliximab, and low trough levels were associated with higher median CRP levels. Analysis of data from the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial also demonstrated the best therapeutic results among patients with an elevated CRP level (16), as reported in monotherapy trials of anti-TNF agents.

Collectively, these trials raise several important questions. First, a majority of anti-TNF trials have included CRP measurement, and show significant decreases in CRP in the trial arm with higher rates of response and remission. However, little post hoc analysis has been performed to explore correlations between clinical and endoscopic end points of remission and CRP. Some of the best evidence comes from analysis of A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment regimen (ACCENT I) data by Reinisch et al (17). The central hypothesis was that CRP levels at baseline and 14 weeks are predictive of durable response/remission, in this case between 14 weeks to one year after induction with infliximab. As shown in other trials, their results suggested an association between high baseline CRP and maintenance of remission in CD treated with infliximab. They also demonstrated that in responders, CRP <5 mg/L at week 14 was associated with maintenance of response (56.6% of patients versus 37% of patients with a CRP ≥5 mg/L) and, furthermore, that a CRP level drop from >5 mg/L to <5 mg/L (ie, normalization) was associated with significant probability of remaining in remission (55% versus 36%). Nonetheless, the ROC curve of baseline CRP as a predictor of response after 14 weeks suggests no optimal cut-off point and, thus, it is difficult to make firm clinical suggestions about the role of CRP in effecting a therapeutic change at 14 weeks.

A second question that arises about CRP from CD trials of anti-TNF agents is whether CRP is a general measure of systemic inflammation, versus a specific predictor of a disease phenotype that is responsive to anti-TNF agents. Recent investigation of novel biologic agents that target different inflammatory pathways, including the interleukin 23/Th17 axis and leukocyte adhesion, sheds further light on this question. A study assessing the use of ustekinumab for induction and maintenance therapy in refractory Crohn's disease explored use of ustekinumab, an anti-interleukin 12/23 p40 agent, in induction and maintenance of CD resistant to anti-TNF treatment (18). There was a significant reduction in mean CRP levels in patients receiving 6 mg/kg of ustekinumab induction versus placebo; reductions were sustained only in those receiving ustekinumab maintenance therapy. One reason for choosing anti-TNF-experienced patients in this trial was the demonstration of greater effect on CRP reduction in this subgroup (19). Further consistent with the hypothesis that CRP is a therapy-independent biomarker of response to therapy is the demonstration of changes in CRP in response to anti-integrin therapy. Studies suggest a significant decrease in CRP level in patients treated with natalizumab, among those with an elevated baseline CRP (20,21). This finding was not reproduced in the recent trial of vedolizumab (22).

In addition to biologic trials, thiopurine trials have confirmed CRP as a key biomarker predictive of relapse. Two studies exploring thiopurine withdrawal (23,24) demonstrated an elevated CRP level to be an independent predictor of relapse after withdrawal of azathioprine, in addition to a low hemoglobin level. Among patients treated with combination therapy, in whom infliximab is discontinued, CRP is also a predictor of relapse (25). However, the CRP cut-off used in these trials varied, between 5 mg/mL and 20 mg/L.

CRP in UC: Few RCTs assessing medical therapy in active UC have used CRP as an end point. An early multicentre prospective RCT designed to assess the efficacy, safety and tolerability of infliximab used CRP as a secondary end point (26). Eleven UC patients with severe, steroid-refractory disease were treated with a single dose of infliximab at 5 mg/kg, 10 mg/kg or 20 mg/kg, and the authors reported a decrease in CRP associated with clinical response. While >50% of patients enrolled to the Active Ulcerative Colitis (ACT) 1 and ACT 2 trials had an elevated CRP at enrollment, changes were not reported as a marker of response to treatment (27).

Other, smaller studies have included CRP measurement. A head-to-head trial of intravenous heparin and steroid therapy for moderate and severe UC in hospitalized patients included a secondary analysis focusing on changes in serological inflammatory indexes (28). In the first 10 days of treatment, a significant decrease in the CRP levels was observed in the steroid group, with no change in the heparin group. None of the heparin-treated patients showed an improvement in disease activity. An open-label randomized study involving 30 pediatric patients, comparing oral beclomethasone for eight weeks followed by oral mesalazine with oral mesalazine alone (29), demonstrated decreased ESR in both treatments arms by week 12; CRP level only dropped significantly in the beclomethasone group. There was concomitant reduction in clinical activity in the beclomethasone group.

The role of CRP in UC patients receiving anti-integrin therapy remains unclear. In patients receiving a single infusion of natalizumab, there was reduction in median CRP level two weeks postinfusion (30). However, the more recent induction and maintenance trials of vedolizumab did not include CRP level as an outcome (22).

In severe UC, baseline CRP elevation is a predictor of failure of medical therapy (31-33). A study involving 72 patients with steroid-refractory UC patients treated with oral or intravenous cyclosporin demonstrated a significant association of colectomy at three months with baseline CRP (11.8 mg/L in the colectomy group versus 5.5 mg/L) (34). However, a multivariate analysis found only the Ho index to be an independent predictor of colectomy, or treatment failure. Another retrospective chart review involving 135 patients with steroid-refractory UC treated with cyclosporine (35) found a CRP >45 mg/L to be predictive for colectomy. The Oxford score, designed following a prospective study involving hospitalized patients with acute severe UC, also includes a CRP >45 mg/L in patients with four to eight bowel movements per day as a predictor of colectomy (36). Elevated CRP level has been associated specifically with severe clinical activity, anemia and hypoalbuminemia, in addition to active disease on endoscopy (7,37).

Clinical disease activity scores have generally been used as primary end points in UC RCTs. Some of these clinical measures, such as the Truelove & Witts' criteria, Seo and Ho indexes, integrate biomarkers such as albumin, hemoglobin, ESR and CRP into their scoring. However, associations between biomarkers and response to therapy are generally not reported in RCTs.

Other peripheral blood biomarkers: Several other common laboratory tests have potential applicability in monitoring IBD, although they are not as well studied as CRP. Simple values derived from the complete blood count, including hemoglobin level and leukocyte counts, have demonstrated some utility in this context (23,25). In the aforementioned study by Louis et al (25), a hemoglobin level ≤145 g/L and a leukocyte count of $>6\times10^9$/L were both associated with decreased time-to-relapse in CD patients in whom infliximab therapy was stopped (HR 6.0 and 2.4, respectively). Interestingly, the HR was greater for hemoglobin than any other measured factor. Similarly, a study of azathioprine withdrawal found an association between a hemoglobin level <120 g/L and risk of relapse (23). Hypoalbuminemia and anemia are both associated with failure of medical therapy in severe ulcerative colitis (31). Nonetheless, there remains concern as to the sensitivity and specificity of these tests as biomarkers in IBD, given their variability in many disease states.

FECAL BIOMARKERS

Summary

In CD and UC, fcalpro should not be used alone as a treatment target because it has inadequate operational characteristics to act as a surrogate for endoscopic, radiographic or clinical end points. Fcalpro is a noninvasive adjunctive measure that can be used in both CD and UC to guide need for further endoscopic or radiographic evaluation.

In CD, fcalpro may especially useful in Crohn's colitis as a biomarker of response to therapy and to predict relapse. In UC, fcalpro likely has greater utility than CRP as an adjunctive measure to guide need for further investigation. Fcalpro has been shown to correlate with mucosal healing and response to induction therapy, and is predictive of loss of response to maintenance therapy in UC.

Discussion

Fcalpro: While blood-based biomarkers offer insight into systemic inflammation occurring as part of active IBD, fecal assays have the potential advantage of better reflecting inflammation at the mucosal level. Several different assays have been developed, most prominently those using calprotectin and lactoferrin as biomarkers. Both of these tests leverage the fact that actively inflamed bowel contains a large number of neutrophils and, furthermore, that the mucosal defects that occur during active inflammation result in spillover of neutrophils into stool. Calprotectin has become a more widely used assay, both because of better operational characteristics and the increasing availability of a rapid test.

Calprotectin is a calcium- and zinc-binding neutrophilic cystolic protein. It is an appropriate marker for mucosal inflammation, given that it is evenly distributed and stable in stool for up to one week (38,39). This protein can be measured using commercially available ELISA or more recently developed quantitative rapid tests (40), although there are data suggesting that quantitation is less accurate with a rapid test (PreventID Caldetect, Preventis GmbH, Germany) at values >15 µg/g (40). A major interest lies in the use of fcalpro to distinguish IBD from non-IBD (41), with studies reporting a sensitivity between 63% and 100%, and specificity of 48% to 100%, depending on trial design and fcalpro cut-off value (41). Several studies have demonstrated correlation between endoscopic/histological disease activity and fcalpro (42-45). This was first studied by Røseth et al (44) in patients with UC, who demonstrated increased correlation between endoscopic and histological grading of inflammation and fcalpro levels.

Fcalpro in CD: Recent work has suggested a correlation between fcalpro concentration and endoscopic disease activity in CD, and weaker associations with the CD activity index (6,46). Correlation between elevated fcalpro and active disease is strongest in Crohn's colitis (Spearman coefficient 0.80 versus 0.45 for all CD) (6). This finding has been reproduced in the pediatric population (43). There is evidence that supports use of fcalpro for monitoring response to anti-TNF therapy. Sipponen et al (47) demonstrated a drop in mean fcalpro levels after therapy with anti-TNF agents (from 1173 µg/g to 130 µg/g) (47); there was moderate correlation between change in fcalpro level and change in endoscopic activity using the CD Endoscopic Index of Severity (Spearman's rank-order correlation = 0.561), but not with ileal or colonic histological scores. Another study failed to demonstrate a significant change in fcalpro levels in patients who responded to medical therapy (48); however, both of these studies were limited by sample size (n=15 and n=11 CD patients, respectively). Although similar to CRP, fcalpro is now used as an objective measure of inflammation for inclusion in clinical trials of novel agents (49,50), few biologics trials report data regarding fcalpro in response to therapy.

There are data supporting the use of fcalpro to predict relapse in CD. In a prospective multicentre study, Gisbert et al (51) demonstrated that CD patients who relapsed within one year had significantly higher fcalpro levels at baseline. In this clinical context, fcalpro had a low sensitivity (28%) but was highly specific (93%). Collectively, it is difficult to suggest that fcalpro could replace endoscopic and clinical evaluation as a treatment target.

Fcalpro in UC: Fcalpro has been shown to correlate well with mucosal healing in ulcerative colitis (46,52,53). D'Haens et al (46) further reported that a fcalpro level >250 µg/g predicted active mucosal disease (sensitivity of 71% and specificity of 100%). Several studies have demonstrated that normalization of fcalpro predicts clinical response to medical therapies and sustained remission (51,53,54). One study (52) assessed the use of fcalpro as a marker of sustained remission in UC patients receiving maintenance infliximab. Of 87 patients included in the study, 30 (34.4%) were considered to be in sustained deep remission (defined as a partial Mayo score of 3 at all points and a Mayo endoscopic subscore 0 at week 52) and 13 (14.9%) to have relapsed. Fcalpro levels remained low (median 40 µg/g) throughout the study in those with sustained deep remission. Two consecutive fcalpro measurements of 300 µg/g at monthly intervals were identified as the best predictor of flare (61.5% sensitive and 100% specific). In that study, fcalpro level at time of relapse was significantly better than serum CRP concentration at predicting relapse. In a pediatric hospitalized severe UC population, clinical scores were most predictive of steroid nonresponse; CRP and fcalpro levels could predict steroid response, although neither were found to be predictive of infliximab response (33).

Until recently, most therapeutics trials investigating UC have not included fecal biomarkers as secondary end points. Two recent studies assessing vedolizumab in UC included fcalpro measurement (22,55). In the phase 3 trial in UC by Feagan et al (22), significant decreases in fcalpro were seen in the group receiving vedolizumab for induction and maintenance. An earlier vedolizumab dose-ranging study found decreases in the fcalpro corresponding with decrease in Mayo score; however, the sample size was inadequate to allow statistical analysis (55).

Lactoferrin: Lactoferrin is an iron-binding glycoprotein found in many body fluids, and is a major component of secondary granules of neutrophils (56). Similar to fcalpro, lactoferrin is very stable in feces over extended periods of time. However, some studies have suggested that fcalpro has better operational characteristics to distinguish IBD from non-IBD, and this, in part, has led to fcalpro becoming a more universally used and available biomarker (57,58).

A prospective study of UC patients in remission on mesalamine found fcalpro to be more sensitive and specific than fecal lactoferrin for predicting UC relapse (54). A cut-off value of 170 µg/g for fcalpro had a sensitivity of 76% and a specificity of 76% to predict relapse, while a cut-off value of 140 µg/g for lactoferrin had a sensitivity of 67% and a specificity of 68%. Others have shown similar results (51). There are data supporting the utility of lactoferrin for monitoring response to therapy (59); however, a major challenge remains significant overlap in fecal lactoferrin concentrations in patients with active and quiescent IBD (56).

FUTURE BIOMARKERS

With the advent of high-throughput systems and biology approaches, such as genomics, metagenomics and transcriptomics, it is likely that future biomarkers will result from integration of multiple metrics derived using these techniques. Gene expression profiling has found some utility in IBD; transcriptional profiles from biopsies of pediatric patients with severe UC predicts responsiveness to steroids (60). Polymorphisms in *FOXO3* have been associated with more severe CD, despite not being associated with disease development (61).

In other immune-mediated diseases, systems biology approaches have directly impacted clinical care. For instance, gene expression profiling of peripheral blood in heart transplant patients has great potential in monitoring for rejection (62). Proteomic profiling of blood plasmacytoid dendritic cells in systemic sclerosis patients demonstrated an association between CXCL4 levels and severity as well as pulmonary involvement (63). In the case of IBD, future studies should expand on the potential use of bioinformatics platforms to develop biomarkers for use as surrogates of endoscopic outcomes.

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CONCLUSION

As was suggested by consensus of the STRIDE program, currently available serum and fecal biomarkers do not possess adequate operational characteristics to make them stand-alone treatment targets in IBD; however, they should be considered important adjunctive measures to clinical, endoscopic and radiographic assessment. The present review demonstrated the continued value that biomarkers provide in alerting the clinician to a need for further investigation. As the strategy of 'treat-to-target' becomes more widespread in IBD management, it becomes crucial to define noninvasive measures that reliably reflect clinical and endoscopic disease activity. The development of more accurate biomarkers in IBD remains an important goal.

APPENDIX 1

The following search strategy was used on PubMed, with filters for only human studies, and only English results.
("calprotectin"[Title/Abstract] OR "lactoferrin"[Title/Abstract] OR "c-reactive protein"[Title/Abstract] OR "CRP"[Title/Abstract] OR "erythrocyte sedimentation rate"[Title/Abstract] OR "ESR"[Title/Abstract]OR "hemoglobin"[Title/Abstract] OR "bone mineral density"[Title/Abstract] OR "ferritin"[Title/Abstract] OR "erythrocyte sedimentation rate"[Title/Abstract] OR "ESR"[Title/Abstract]) AND ("ulcerative colitis"[Title/Abstract] OR "crohn disease"[Title/Abstract] OR "crohn's disease"[Title/Abstract] OR "crohns disease"[Title/Abstract] OR "inflammatory bowel disease"[Title/Abstract] OR "IBD"[Title/Abstract]) AND ("response"[Title/Abstract] OR "remission"[Title/Abstract] OR "Flare"[Title/Abstract]) AND (Clinical Trial[ptyp] OR Review[ptyp])

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