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Colonic MicroRNA Profiles, Identified by a Deep Learning Algorithm, That Predict Responses to Therapy of Patients With Acute Severe Ulcerative Colitis

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BACKGROUND & AIMS: **Acute severe ulcerative colitis (ASUC) is a life-threatening condition managed with intravenous steroids followed by infliximab, cyclosporine, or colectomy (for patients with steroid resistance). There are no biomarkers to identify patients most likely to respond to therapy; ineffective medical treatment can delay colectomy and increase morbidity and mortality. We aimed to identify biomarkers of response to medical therapy for patients with ASUC.**

METHODS: **We performed a retrospective analysis of 47 patients with ASUC, well characterized for their responses to steroids, cyclosporine, or infliximab, therapy at 2 centers in France. Fixed colonic biopsies, collected before or within the first 3 days of treatment, were used for microarray analysis of microRNA expression profiles. Deep neural network-based classifiers were used to derive candidate biomarkers for discriminating responders from non-responders to each treatment and to predict which patients would require colectomy. Levels of identified microRNAs were then measured by quantitative PCR analysis in a validation cohort of 29 independent patients—the effectiveness of the classification algorithm was tested on this cohort.**

RESULTS: **A deep neural network-based classifier identified 9 microRNAs plus 5 clinical factors, routinely recorded at time of hospital admission, that associated with responses of patients to treatment. This panel discriminated responders to steroids from non-responders with 93% accuracy (area under the curve, 0.91). We identified 3 algorithms, based on microRNA levels, that identified responders to infliximab vs non-responders (84% accuracy, AUC = 0.82) and responders to cyclosporine vs non-responders (80% accuracy, AUC = 0.79).**

CONCLUSION: **We developed an algorithm that identifies patients with ASUC who respond vs do not respond to first- and second-line treatments, based on microRNA expression profiles in colon tissues.**

Keywords: IBD; Prognostic Factor; Neural Network; Acute Severe Ulcerative Colitis.

Ulcerative colitis (UC) is an idiopathic chronic inflammatory disorder affecting the colorectal mucosa.[1]

Approximately 15%–25% of UC patients have had at least 1 episode of acute severe UC (ASUC). Such an episode is a life-threatening condition, as it exposes patients to serious complications, including sepsis, toxic megacolon, colonic perforation, digestive bleeding, and thromboembolic accidents.[1,2] In patients who do not require emergency colectomy, intravenous (IV)

Abbreviations used in this paper: **ASUC, acute severe ulcerative colitis; AUC, area under the curve; CRP, C-reactive protein; CsA, cyclosporine; FFPE, formaldehyde-fixed, paraffin-embedded; IBD, inflammatory bowel disease; IFX, infliximab; IV, intravenous; miRNA, microRNA; qPCR, quantitative polymerase chain reaction; ROC, receiver-operating characteristic; RT-PCR, real-time polymerase chain reaction; UC, ulcerative colitis.**

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corticosteroids are recommended as the first line of treatment.[3] However, 40% of patients will fail to respond to IV steroids[4,5] and will require a salvage colectomy or second line treatment with cyclosporine (CsA)[6] or infliximab (IFX).[7,8] In patients refractory to medical therapies, an emergency colectomy is recommended, and delayed surgery is associated with an increased mortality rate.[9] Today, physicians' decisions regarding treatment are currently based on patient's evolution and a few clinical or biological parameters, such as the Oxford criteria or Ho index, having low accuracy.[10] New predictors of drug efficacy are required.

MicroRNAs (miRNAs) are short (21–25 nucleotides), noncoding RNA molecules.[11] MiRNAs have recently emerged as important mediators of immune functions, suggesting their potential efficacy as biomarkers for diagnosis, determining prognosis, or predicting treatment response in various diseases.[12,13]

In inflammatory bowel disease (IBD), several studies have identified mucosal miRNA signatures in both active and inactive patients.[14] Thus, we hypothesized that miRNA biomarkers could help predict the therapeutic response in patients with ASUC.

What You Need to Know

Background

Acute severe ulcerative colitis is a severe condition without early predictors of response to medical treatments. Abnormal microRNA expression patterns in several human diseases, including ulcerative colitis, suggest a potential for use as a predictive biomarker of drug response.

Findings

A deep learning algorithm combining 9 mucosal microRNAs plus 5 routine biological parameters predicted the response to steroids, and among steroid nonresponders, infliximab or cyclosporine response profiles.

Implications for patient care

New biomarkers identified by machine learning analysis of mucosal microRNAs signatures will be developed and validated for precision medicine in ulcerative colitis.

Methods

Patients

Patients were selected from 2 French tertiary centers: Beaujon and Haut-Lévêque Hospitals. The institutional review boards of both centers approved this study, and all patients were informed. The selection of patients was retrospectively performed from clinical files and pathological databases. The inclusion criteria were the following: older than 18 years of age, well-established UC diagnosis according to European Crohn's and Colitis Organisation criteria,[15] admission for an ASUC episode based on a Lichtiger index above 10 points at admission,[16] and flexible rectosigmoidoscopy with colonic biopsies performed within 3 days following admission. Colonic biopsies were taken from inflamed mucosa at admission or during the first days of IV steroid treatment before the assessment of the clinical response to this treatment at days 3–5. The exclusion criteria were the following: Crohn's disease, absence of colonic biopsies at admission or insufficient RNA amount (<5 ng/μL), previous exposure to anti–tumor necrosis factor or CsA, and short follow-up duration <3 months after admission. Pathology grading was retrospectively performed using the Nancy score.[17]

Patients recruited in the discovery cohort were admitted from January 2007 to October 2014, including 11 patients previously included in the Ciclosporin versus infliximab in patients with severe ulcerative colitis trial (CYSIF) study.[8] The validation cohort, established after the analysis of the results obtained from the inception cohort, included additional patients from the same centers admitted from March 2010 to June 2016.

Nonconsecutive patients retrospectively included into the discovery and the validation cohorts were enrolled according to their response to first- and second-line medical therapy to obtain similar proportion of responders and nonresponders to each drug (steroids, CsA, and IFX).

In both centers, patients received intravenous steroids (at least 0.8 mg/kg/d of methylprednisolone) as first-line therapy. In patients having an insufficient response after 3–5 days according the Oxford criteria,[18] second-line treatment with CsA or IFX was started in patients not requiring an emergent colectomy according to clinical need and experienced physician advice. CsA was started at 2 mg/kg/d and was subsequently adapted according to blood concentrations to obtain levels of 150–250 ng/mL. IFX was infused at the usual dose of 5 mg/kg at weeks 0, 2, and 6 and was continued as maintenance therapy. In responders to second-line medical therapy, thiopurine was offered and steroids switched orally.

For each treatment, the treatment response definitions used were those from the CYSIF trial.[8] Treatment failure was defined by 1 or more of the following conditions: absence of a clinical response at day 7, defined by a Lichtiger index above 10 points; relapse before month 3, defined by a Lichtiger index of >10 or of more than 3 points on 3 consecutive days; need for a new systemic UC therapy; or colectomy or death within 3 months of starting treatment. Conversely, treatment success was defined by a Lichtiger index of <10 points without any failure criteria on at least 2 consecutive days within the first week of treatment.

RNA Extraction

Biopsies were all taken from inflamed mucosa of the sigmoid colon. Total RNA was extracted from

formaldehyde-fixed, paraffin-embedded (FFPE) tissue using a RecoverAll Total Nucleic Acid kit (Ambion; Thermo Fisher Scientific, Waltham, MA). The FFPE samples were deparaffinized using a series of xylene and ethanol washes and then subjected to a protease digestion. Nucleic acids were purified using a rapid glass-fiber filter methodology. The purity and amount of total RNA extracted were assessed with a spectrophotometer (NanoDrop, Thermo Fisher Scientific). All samples had a 260/280 ratio above 1.7.

MicroRNA Assessment

Microarray Analysis (Discovery Cohort). The expression level of human miRNAs was assessed using GeneChip miRNA4.0 Arrays (Affymetrix, Santa Clara, CA). An amount of 70 ng of total RNA was biotin labelled using the FlashTag Biotin HSR RNA labelling kit (Affymetrix). The normalized array data was analyzed by an unpaired *t* test.

To identify discriminant miRNA signatures between steroid and CsA or IFX responders and nonresponders, we modeled data using unsupervised general linear models adopted from the R package "Limma" (R package version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria). The first set of miRNA candidates was chosen from the top-ranking candidates based on the false discovery rate (false discovery rate $<.05$).

MiRNA Real-Time Polymerase Chain Reaction Analysis (Validation Cohort). Individual miRNAs identified in the discovery cohort were analyzed using TaqMan MicroRNA assays (Thermo Fisher Scientific) (see Supplemental Material). Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ methods and normalized to the geometric average of 2 endogenous miRNAs, hsa-miR-16-5p and hsa-miR-191-5p TaqMan MicroRNA assays (Thermo Fisher Scientific), which had a stable expression in our cohort and across most human tissues.[19]

Unsupervised Feature Selection. We made use of hierarchical clustering and integrative data analysis based on nonsupervised matching of particular miRNAs to preexisting biological knowledge. Thus we identified a set of promising miRNAs (top false discovery rate ($<.05$) by means of *F* test statistics) to be tested by our mathematical models in the classification task of patients responses.

Prediction Algorithms

Classification Algorithms. To classify samples into responders or nonresponders, a set of methods including linear discriminant analysis, topological data analysis, neural networks (deep learning [DL]), or the random forest algorithm was evaluated (see Supplemental Material).

The DL model displayed the best performance for the discovery cohort and has been applied in the validation cohort. In particular, we run our model in tandem taking as inputs the normalized expression of the Affymetrix candidate (those derived from the unsupervised clustering) samples first and their validation by real-time polymerase chain reaction (RT-PCR) later.

Additionally, we integrated in the model 48 patient routine clinical and biological parameters (including leukocytes, erythrocytes, basophil and lymphocyte counts, hematocrit, hemoglobin, ferritin, albumin, iron, C-reactive protein (CRP) and transferrin levels, deep ulcers). Among these 48 values, the most discriminating ones were determined according to a linear program described in the Supplementary Methods.

Analysis of Prediction Accuracy. The performance of classifiers was analyzed by means of its receiver-operating characteristic (ROC) curve. Thus we constructed ROC curves for each set of candidate miRNAs in each cohort (discovery and validation) taking their profiles of expression across patients as inputs in our DL models and evaluating their values as outputs of DL classifier. The leave-one-out and K-fold cross-validation approaches were used on each sample to validate the final accuracy of our method.

Results

Patients

Forty-seven patients with ASUC have been included in the discovery cohort. All patients presented severe clinical and biological signs of colitis, with a mean Lichtiger index of 13.4 (range, 11–18) points and a mean CRP level of 60.3 mg/L. All patients had a Mayo endoscopic subscore of 3, 11 with deep ulcerations. Pathological assessment showed active UC lesions with Nancy scores at 3 and 4 in 65% and 35% of patients, respectively. Briefly, 14 patients responded to the first line of IV steroids, and most were further treated with thiopurines. Among the 33 patients refractory to IV steroids, 24 received IFX and 15 received CsA, including 6 patients who received a third-line medical therapy and were exposed to both drugs. Thus, 12 patients responded and 12 failed to respond to IFX. Additionally, 9 patients responded and 6 patients failed to respond to CsA. In steroid nonresponders, 10 patients underwent a colectomy during follow-up.

Twenty-nine patients with similar ASUC characteristics (including Nancy scores at 3 and 4 in 70% and 30%, respectively) were enrolled in the validation cohort. Eight patients responded to the first line of IV steroids. Among the 21 patients refractory to IV steroids, 15 received IFX and 13 received CsA, including 7 patients who received a third-line medical therapy and were exposed to both drugs. Thus, 5 patients responded and 10 failed to respond to IFX. Additionally, 8 patients responded and 5 patients failed to respond to CsA. In steroid nonresponders, 7 patients underwent a

colectomy during follow-up. Clinical characteristics and treatment response profiles of both cohorts are reported in Table 1, Figure 1, and Supplementary Tables 1 and 2.

MicroRNA Expression Profile

Discovery Cohort. We measured the expression of 3391 human miRNAs in colonic biopsies from 47 patients with ASUC. The FFPE colonic biopsies were obtained from the inflamed mucosa before the IV steroid treatment, and in 12 patients within the first 3 days of the IV steroid course.

Unsupervised clustering analysis identified 24 miRNAs, separating steroid responders from nonresponders (Supplementary Figure 2). Applying an integrative method for feature selection (see Supplemental Methods), a set of 15 miRNAs was selected as statistically significant: *hp_hsa-mir-3934*, *hp_hsa-mir-3667*, *hp_hsa-mir-100*, *hsa-miR-603*, *hsa-miR-718*, *hsa-miR-4259*, *hp_hsa-mir-193b*, *hsa-miR-3150a-5p*, *hp_hsa-mir-1260b*, *hsa-miR-938*, *hsa-miR-3128*, *hsa-miR-4423-3p*, *hsa-miR-518b*, *hsa-miR-1468*, and *hsa-miR-3152-3p* (Figure 2*A*). This signature was not affected, depending on whether the biopsies had been done before, or during, the treatment with steroids (data not shown).

Table 1. Baseline Characteristics of Patients With ASUC at the Time of Colonic Biopsy

	Discovery Cohort	Validation Cohort
	47	29
Female	28 (59.6)	16 (55.2)
Age at diagnosis, y	30.6 ± 17.8	29.7 ± 13.9
UC duration, y	7.7 ± 16.4	2.6 ± 4.3
Pancolitis (E3)	39 (82.9)	22 (75.9)
Extradigestive manifestations	8 (17)	MD
Smoking status		
Active	5 (10.6)	MD
Stopped before UC diagnosis	11 (23.4)	MD
Early ASUC	10 (21.3)	8 (27.6)
Lichtiger index	13.4 ± 2.4	13.6 ± 2.4
Deep ulcers	11 (23.4)	8 (27.6)
Treatment at inclusion		
5-ASA	11	9
Thiopurine	4	3
Methotrexate	0	0
IV steroids at biopsy (<4 d)	12	18
Biological values		
C-reactive protein, mg/L	60.3 ± 64.4	60.5 ± 56.4
Albumin, g/L	29.4 ± 7.4	29.2 ± 7.8
Ferritin, μg/L	163.7 ± 142.9	158.3 ± 112.6
Hemoglobin, g/L	11.4 ± 2.1	11.2 ± 2.2
Leucocytes, Giga/L	10.3 ± 4.8	11.8 ± 3.4
Transferrin, g/L	2.1 ± 0.7	1.9 ± 0.7
Hematocrit, %	33.7 ± 5.9	34.2 ± 5.9

NOTE. Values are n (%) or mean ± SD, unless otherwise indicated.
ASUC, acute severe ulcerative colitis; IV, intravenous; UC, ulcerative colitis; 5-ASA, 5-acetylsalicylic acid.

In the steroid nonresponders group, we identified 6 and 4 miRNAs associated with response to IFX and CsA, respectively (Figures 2*B*, *C*). See the Supplemental Material for further details on chromosome localization and linear or nonlinear association of the miRNA signature obtained.

DL Algorithms to Predict Treatment Responses

Several classification methods were applied (see Supplementary Table 1) to develop a miRNA classifier for steroid, IFX, and CsA responders vs nonresponders. Among them, we selected the DL method, whose performance was the best (Figure 3; Supplemental Figure 1). In turn, DL performing multiclassification with 2 categorical features, 14 numerical levels, and expecting to have 33 input neurons (see Supplemental Material) yielded the best results (Supplementary Table 3). Upon the use of the unsupervised feature selection, the classifiers for the discovery cohort processed in the DL algorithm were the normalized expression levels of the 15-miRNA steroid responses, 6-miRNA IFX response, and 4-miRNA CsA response. We included in the DL model 5 routine biological parameters (hemoglobin, hematocrit, albumin, CRP, and transferrin levels) identified, by linear programming among the 48 tested values, as discriminating between responders and nonresponders and collected at the same time as the biopsy. Importantly, prognostic values for the steroid response were improved by combining the selected miRNAs and a nonlinear transformation of 5 biological parameters. The models achieved classification success levels of ~97%, ~90%, and ~83% between responders and nonresponders to steroids, IFX, and CsA, respectively (Figure 4). However, no combination of biological routine parameters could improve the IFX and CsA response classifiers.

Validation Cohort. We measured by quantitative PCR (qPCR) analysis the expression of the 15 selected miRNAs in FFPE colonic biopsies from 29 additional patients with similar inclusion criteria recruited secondarily. The analysis resulted in 9 miRNAs: *hp_hsa-mir-3934*, *hp_hsa-mir-100*, *hsa-miR-718*, *hp_hsa-mir-193b*, *hsa-miR-3150a-5p*, *hp_hsa-mir-1260b*, *hsa-miR-938*, *hsa-miR-518b*, and *hsa-miR-1468*. Next, we evaluated these 9 miRNA candidates in the discrimination between steroids responders and nonresponders (Figure 5*A*; Supplemental Figure 7). Three miRNAs were associated with a response to IFX and CsA (Figures 5*B*, *C*). Within this signature, only 2 miRNAs were significantly expressed differently between responders and nonresponders: miR3934 ($P < .001$) for steroids, and miR938 ($P < .01$) for the second line of treatments. The same DL method was applied on the qPCR expression level of 9-miRNA steroid response, 3-miRNA IFX response, and 3-miRNA CsA response. The models achieved classification success levels of ~90% (93% with 5

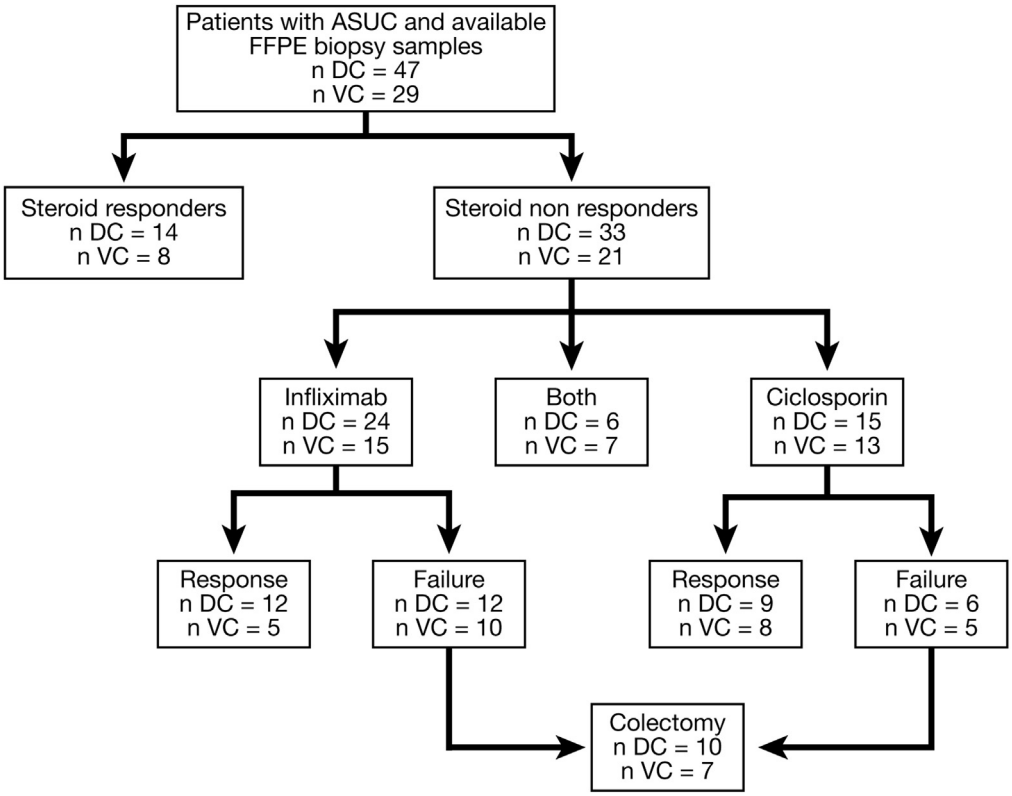

Figure 1. Flow chart of patients with acute severe ulcerative colitis (ASUC) included in the discovery cohort (DC) and in the validation cohort (VC) regarding their responses to intravenous (IV) steroids and second line treatments. FFPE, formaldehyde-fixed, paraffin-embedded.

routine biological parameters), ~84%, and ~80% between responders and nonresponders to steroids, IFX, and CsA in the validation cohort, respectively (Figure 5*D*, *F*).

Cross-Validation of DL Models. The last validation of our DL classifier (designed as "DeepCol" for DL colitis classifier) combining 9 colonic miRNAs plus 5 routine biological values was performed as the following. The parameter leveraged to mathematically validate our predictors was the cross-validation, which was used as an exponent of the goodness exhibited by our strategy and a raw score of classification. Then, a thorough analysis of each DL drug classification was performed according to their associated ROC curves (ie, area under the curve [AUC] for steroids, 0.87–0.91 [without or with biological indicators at inclusion]; AUC for IFX, 0.86; and AUC for CsA, 0.81). The cross-validation values for the steroid, IFX, and CsA classifier performances were 0.03–0.01 (without or with routine biological parameters), 0.05, and 0.08, respectively (see Supplementary Table 4).

Discussion

The identification of predictors of therapeutic response is a major challenge in ASUC that is a severe condition requiring a rapid step-by-step management. Several scores have been established to predict clinical outcomes after starting steroid treatment for ASUC with a limited value to predict treatment failure.[18,19] In case of first-line steroid therapy failure, IFX and CsA have got close short- and long-term colectomy rates, with similar safety profiles,[8,20] with a significant percentage of nonresponders for each drug.[21] However, choosing the best second line remains crucial to reduce the risk of colectomy and mortality. Dysregulation of a specific subset of miRNAs has been identified in several studies performed on inflammatory or quiescent colonic mucosa of patients with UC.[22] Interestingly, in other diseases, mostly cancers, some miRNAs have been studied for their potential prognostic values. To our knowledge, miRNA-based prognostic biomarkers have still not been established for IBD management. DeepCol is a neural network–based-algorithm combining colonic miRNAs with the expression of blood parameters, predictive of response to first- and second-line treatments in patients with ASUC. The DeepCol algorithm utilizes a mathematical approach that improves the classification yield of a simple miRNA signature. Thus, for patients tested in the algorithm, one obtains a probability of their response to IV steroids, IFX, and CsA by learning a nonlinear equation composed by 9 miRNAs expression in qPCR and 5 routine blood parameters. So, patients exposed to both IFX and CsA with no response, or a response of one and failed to the other, could be analyzed by DeepCol. Interestingly, the presence of deep ulcerations at baseline endoscopy was not associated with the prediction of drug responses, and this item was not retained in the final DL algorithm.

One of the novelties of our selection approach relies on a combination of unsupervised feature selection by

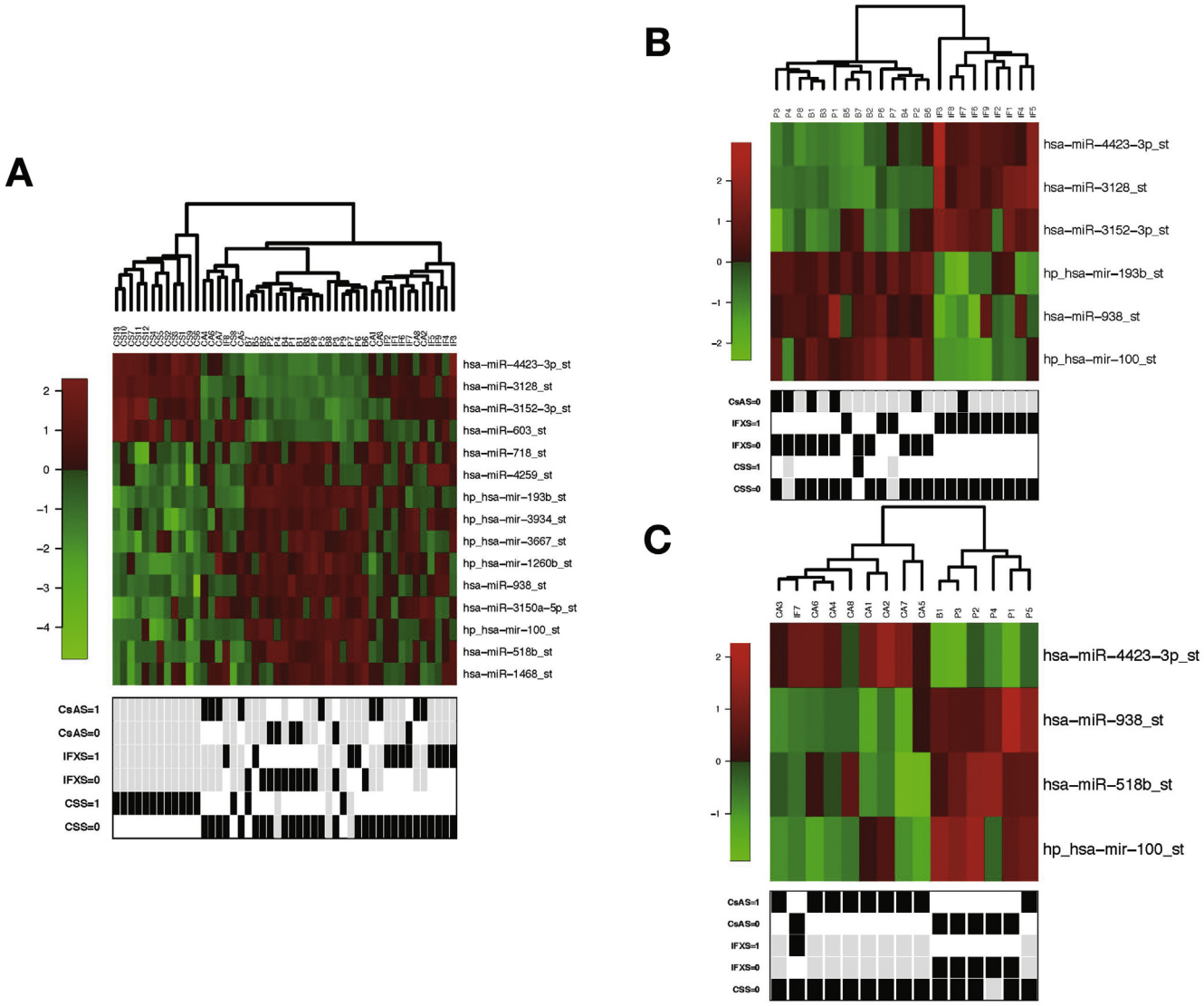

Figure 2. Unsupervised linear model clustering of colonic microRNAs (miRNAs) in 47 patients with acute severe ulcerative colitis (ASUC) (discovery cohort) regarding their responses to intravenous steroids and to infliximab or cyclosporine, in steroid nonresponders. We considered normalized expression data from the 3391 miRNAs (microarray) with a false discovery rate $<.05$, and correlated the data with specific knowledge regarding the disease. For each drug, responders were labeled by 1 and nonresponders labeled by 0 (eg, intravenous corticoids = 1, steroid responder; intravenous corticoids = 0, steroid nonresponder) Patients not exposed to the drug(s) are labeled in gray. (*A*) First-line treatment with intravenous steroids. (*B*) Second-line treatment based with infliximab. (*C*) Second-line treatment with cyclosporine. CsAS, cyclosporine; CSS, corticosteroids (1 = responders, 0 = nonresponders); IFXS, infliximab.

hierarchical clustering and integrative data analysis by matching the identified miRNAs with existing biological knowledge. In a recent study, the response to vedolizumab in patients with UC could be predicted with a neural network-based approach using gut microbial structures.[23]

We acknowledge some limitations of our study, mainly related to its retrospective design. To build this prediction algorithm, we established 2 retrospective, bicentric, well-defined cohorts of patients with UC who were admitted for an episode of ASUC. Despite its retrospective design, the predictive nature of the algorithm results from the fact that the molecular signatures were obtained before or during the first days of initial treatment. Microarray analysis identified a signature of 15 miRNAs in the discovery cohort. Due to the small amount of retrospective biological material, we chose to validate this signature directly by qPCR analysis in a second cohort constituted independently, sharing the same inclusion criteria. In this second cohort, 9 (of the 15) miRNAs allowed to obtain a robust stratification of patients with a minimal decrease of the performances using the DeepCol algorithm. The use of fixed biopsies can also be criticized. However, a preliminary feasibility study (see Supplemental Material) and data support high correlations between matched frozen and FFPE samples enabling the use of FFPE-derived miRNAs for array-based, or qPCR, gene expression profiling.

Validation of DeepCol algorithm will require its testing in a prospective cohort. This validation will be

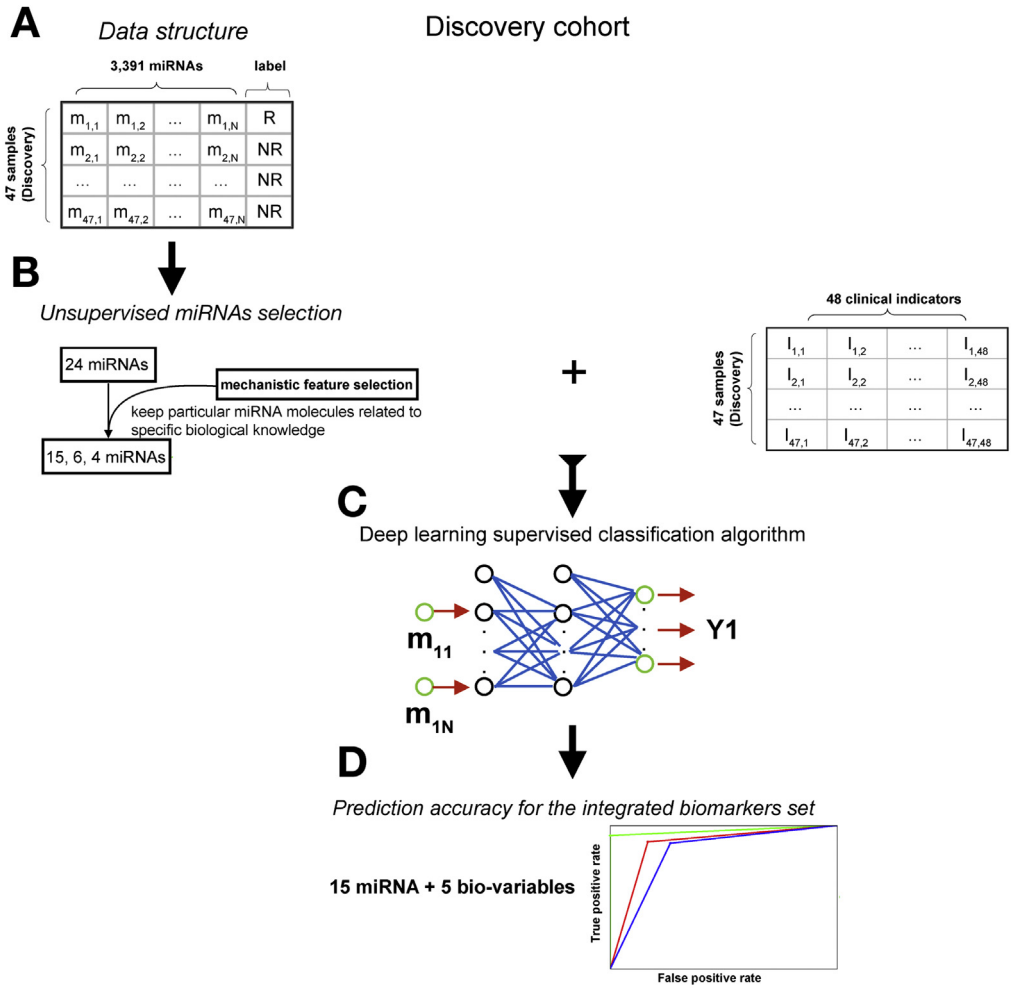

Figure 3. Algorithm method for microRNA (miRNA)–based classifier identification in the discovery cohort. (*A*) Data from the microarray were processed and expressed by a 47 × 3391 matrix with a responder (R) or nonresponder (NR) variable of the response column. (*B*) Unsupervised feature selection by hierarchical clustering and integrative data analysis matching the obtained miRNAs with existing biological knowledge resulting in 15, 6, and 4 miRNAs. Five of the 48 routine biological values were included in the model. (*C*) A deep learning supervised classification algorithm was leveraged to an estimated treatment response a priori. (*D*) The accuracy analysis for the 47 samples were determined (receiver-operating characteristic curves).

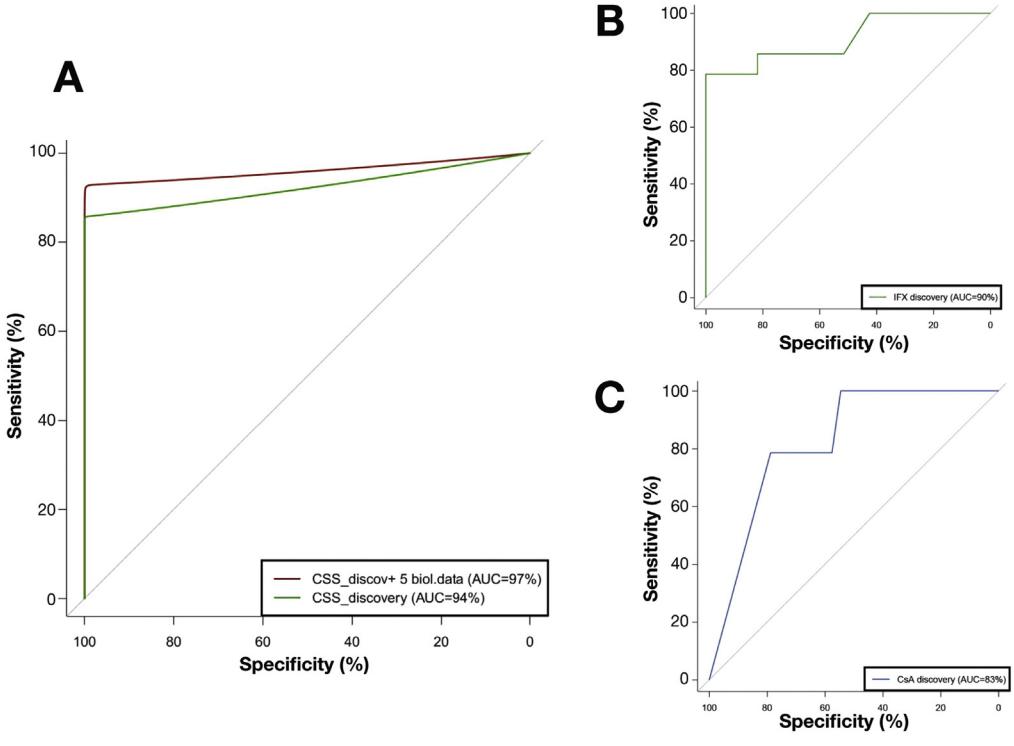

Figure 4. Performance of the DeepCol algorithm to predict treatment response measured by the receiver-operating characteristic curves in the discovery cohort. Prediction value for the red curve: (*A*) first-line treatment with intravenous steroid (deep learning with 15 microRNAs [green curve], deep learning with 15 microRNAs + 5 biological parameters [red curve]), and in steroid NRs, prediction value to respond to a second-line treatment with (*B*) infliximab (IFX) (6 miRNAs) and (*C*) cyclosporine (CsA) (4 miRNAs). AUC, area under the curve; CSS, corticosteroids.

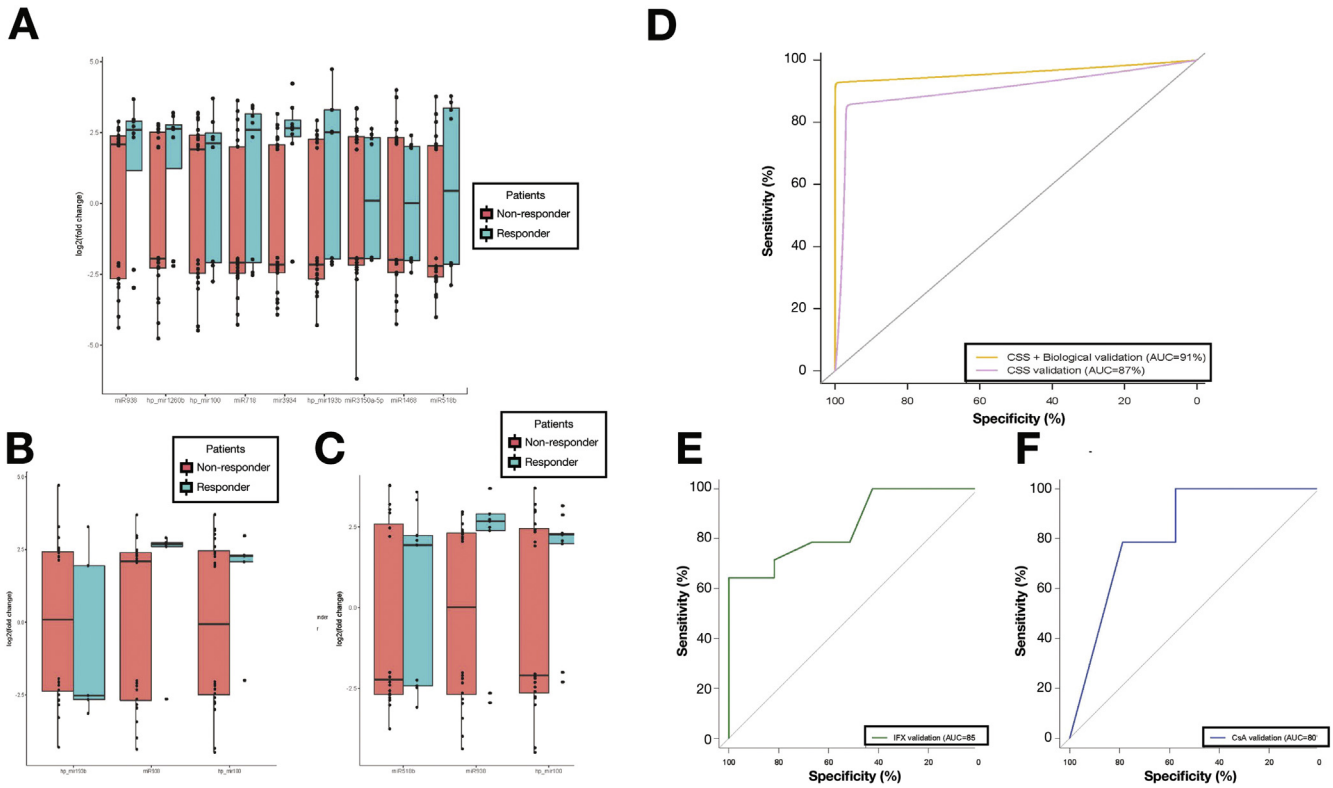

Figure 5. Quantitative polymerase chain reaction of 15 mucosal microRNAs (miRNAs) analysis and DeepCol algorithm values in the 29 patients with acute severe ulcerative colitis included in the validation cohort. The quantitative polymerase chain reaction expression of 9 of 15 expressed miRNAs associated with (*A*) first-line intravenous steroid response, and response to second line of treatments with (*B*) infliximab (IFX) or (*C*) cyclosporine (CsA). The box marks the interquartile range (IQR), the whiskers mark the range between the lower quartile (–1.5 IQR) and upper quartile (+1.5 IQR), and dots mark the outliers. **P* < .01; ***P* < .001. **mir3934 and *mir938. Prediction values of the deep learning–based algorithm expressed by areas under the receiver-operating characteristic curves for response to (*D*) CSS, and to second line of treatments with (*E*) IFX and (*F*) CsA. AUC, area under the curve; CSS, corticosteroids.

feasible because current routine qPCR techniques allow results to be obtained in <48 hours by far, and the DeepCol results will be obtained through a dedicated web application.

In summary, our study provides the first prediction tool for first- and second-line treatments in ASUC. Our results are encouraging for the development of new biomarkers based on biological signatures analyzed by artificial intelligence to predict individual responses to therapies in UC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.08.068.

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Reprint requests
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Conflicts of interest
These authors disclose the following: Xavier Treton: lecture and consulting fees for MSD, Abbvie, Takeda, Ferring, Inception IBD. David Laharie: lecture and consulting fees for MSD, Abbvie, Takeda, Janssen, Ferring, Tillots, HAC-pharma, Pfizer. Yoram Bouhnik: lecture and consulting fees for Abbvie, Biogaran, Boehringer Ingelheim, CTMA, Ferring, Gilead, Hospira, ICON, Inception IBD, Janssen, Lilly, Mayoli Spindler, Merck, MSD, Norgine, Pfizer, Robarts Clinical Trials, Roche, Sanofi, Shire, Takeda, UCB, Vifor Pharma. The remaining authors disclose no conflicts.