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Longitudinal study of the gut microbiota in ulcerative colitis patients on anti-integrin biologic therapy

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Abstract

Disruptions of the gut microbiome are known to play a role in the pathophysiology of inflammatory bowel disease (IBD) and may influence response to biologic therapies. However, defining microbial signatures associated with treatment outcomes remains challenging. In this prospective longitudinal study, we analyzed changes in the intestinal microbiome of patients with active ulcerative colitis starting anti-integrin therapy with vedolizumab. Stool samples and clinical data were obtained at baseline and at weeks 12, 30, and 52 following treatment initiation. Microbial taxonomic composition and functional capacity were assessed using shotgun metagenomic sequencing.

Patients who did not achieve clinical remission exhibited substantial interindividual heterogeneity in microbial composition and metabolic pathways throughout follow-up. In contrast, responders showed a more uniform and temporally stable microbiome, particularly during the induction phase. Importantly, none of the patients with markedly reduced baseline alpha diversity reached remission. Long-term responders demonstrated a gradual increase in commensal bacteria with reported anti-inflammatory effects, including Bacteroides uniformis, multiple Roseburia species (R. intestinalis, R. inulinivorans, R. faecis), and members of the Lachnospiraceae family. These microbial shifts were absent in non-responders and in patients who subsequently lost response.

Taken together, these results indicate that baseline microbial diversity and longitudinal ecosystem stability may be associated with favorable response to anti-integrin therapy. Gut microbiome features could therefore complement clinical parameters in understanding treatment response and may contribute to future patient stratification strategies in ulcerative colitis.

Introduction

Crohn´s disease (CD) and Ulcerative colitis (UC) are chronic inflammatory disorders of growing prevalence worldwide. The precise aetiology of the diseases is unknown, but the pathophysiology of the intestinal lesions involves a complex and altered interplay between mucosal immunity and microbial factors that trigger and perpetuate inflammation in individuals with genetic susceptibility(1). Cumulative evidence demonstrates several imbalances of the gut microbial ecosystem at taxonomic and functional level in patients with active mucosal inflammation, characterized by decreased microbial diversity and clade-specific enrichments and depletions(2, 3). In ulcerative colitis, a decrease in species richness, an underrepresentation of butyrate producers and a gain of potentially harmful bacteria have been consistently found in samples from patients during disease exacerbation or shortly after remission(4, 5).

Abundance of health-promoting bacteria including butyrate producers (*Faecalibacterium prausnitzii* and *Roseburia* species) and other short-chain fatty acid-producers (*Akkermansia muciniphila* and *Lachnospiraceae* species) is usually lower in patients as compared to controls. The depleted species induce regulatory cells and cytokines on the human gut mucosa and have a physiological role in mucosal homeostasis(6). Interestingly, those patients who recover normal counts of butyrate producing species are prone to maintain long-time remission(7). On the other hand, some other species such as

Bilophila wadsworthia, *Escherichia coli*(8), and *Fusobacterium* species (9, 10), which are known to generate pro-inflammatory stimuli, have been found in higher abundance in patients with UC. Thus, the influence of the intestinal microbiome in the response to immunosuppressors in IBD is plausible but remains largely unexplored. An observational study with Crohn's disease patients suggested that reduced abundance of *F. prausnitzii* in the intestinal microbiome may predict an early relapse after infliximab discontinuation(11). The study by Ananthakrishnan and coworkers explored whether the gut microbiome may predict responses to vedolizumab biologic therapy. The authors conducted a prospective study both in CD and UC patients initiating anti-integrin therapy (vedolizumab). The study identified an interesting network algorithm integrating microbiome and clinical data with predictive value(12).

Longitudinal studies have shown that the microbiomes of IBD subjects fluctuate more than those of healthy individuals, with some correlations between fluctuations and medication intensification due to a flare(13). Temporal microbiome instability has also been demonstrated during periods of remission(14). In this longitudinal study, we followed UC patients who experienced a flare and were eligible for vedoluzimab treatment for induction of remission and subsequent remission maintenance. We used a shotgun metagenomic approach to explore gut microbiome fluctuations associated with response to vedolizumab therapy (29).

Methods

Study design, participants, intervention

The EPIMUC study was a prospective, observational study of adult patients with left-sided or extensive UC requiring vedolizumab therapy. Vedolizumab is an integrin receptor antagonist indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response or intolerance to one or more standard therapies (corticosteroids, immunomodulators or tumour necrosis factor-α inhibitor) or demonstrated dependence on corticosteroids. We recruited adult patients (18-75 years) diagnosed with active ulcerative colitis requiring vedolizumab treatment according to the approved indications. Patients with UC diagnosed by standard criteria at least 6 months before inclusion and moderate to severe activity (Simple Colitis Activity Index, SCAI, ^{3} 6) were eligible(15). Previous anti-TNF therapy with a wash-out period of at least one month was allowed. The exclusion criteria included disease limited to rectum, antibiotics on the previous two months or during the study, pregnancy and breastfeeding. The protocol was approved by the Institutional Review Board of University Hospital Vall de Hebron, study protocol code: IISR-2015-101160 (FGA-VED-2016-01).

Twenty-five patients entered the study. There were four dropouts due to clinical criteria (bacterial gastroenteritis, antibiotic treatment, worsening of psoriasis, and COVID infection), and 21 patients completed the study. Eligible patients were treated with vedolizumab, 300 mg on weeks 0, and 2 and 6. After induction, response to vedolizumab was evaluated at week 14 by clinical and endoscopic scoring. Remission was defined by SCAI < 4, faecal calprotectin < 150 µg/g, C-reactive protein < 0.5 mg/L, and

Mayo index £ 1. Accordingly, patients were then allocated into two groups, i.e, responders (n=9) and non-responders (n=12). Non-responders at week 14 left the study. These patients were offered intensified treatment with vedolizumab or other alternative therapy and were not suitable for the aim of this study. Responders were kept on vedolizumab every 8 weeks until week 52 for maintenance of remission. Three patients lost response during the follow-up while the remainder 6 patients maintained remission until week 52.

Patients provided two faecal samples during the run-in period prior to starting vedolizumab treatment and subsequently at week 12 of vedolizumab treatment. Additional samples were obtained at weeks 30 and 52 from patients who completed the protocol.

Metagenomic approach

Total DNA was isolated from fecal samples according to standardized procedures aligned with the International Human Microbiome Standards (30). Briefly, approximately 250 mg of frozen stool material was processed using a combination of chemical lysis and mechanical disruption with bead beating to ensure efficient microbial cell breakage. Following clarification of lysates, nucleic acids were recovered by alcohol precipitation. DNA concentration and purity were assessed spectrophotometrically, and DNA integrity was evaluated by microcapillary electrophoresis to confirm suitability for sequencing.

Shotgun metagenomic sequencing was performed by an external service provider using an Illumina NovaSeq platform, generating paired-end reads (2 × 150 bp) with a target depth of at least 25 million reads per sample. Raw sequencing data were demultiplexed and adapter sequences were removed. Quality filtering and trimming were applied to exclude low-quality reads and short fragments. To eliminate host-derived sequences, reads were aligned against the human reference genome and matching reads were discarded.

High-quality, non-host reads were subsequently used for downstream taxonomic and functional profiling. Taxonomic composition was inferred using an assembly-free approach based on clade-specific marker genes, while functional characterization was performed by mapping reads to reference gene family and metabolic pathway databases (30,31). Gene family and pathway abundances were normalized and expressed as copies per million to allow comparison across samples.

All raw metagenomic sequencing data have been deposited in the Sequence Read Archive (SRA) of the National Center for Biotechnology Information under BioProject accession number PRJNA1198595. The dataset is currently under controlled access during peer review and is available to editors and reviewers through a secure NCBI reviewer link: https://dataview.ncbi.nlm.nih.gov/object/PRJNA1198595?reviewer=kkbjgcq15d2lf8qtsdikc2t15n

Statistical analysis

Statistical analysis compared either two groups, namely, non-responders (No response, NoR, n=12) versus responders (Response, R, n=9), or three groups, namely, non-responders (NoR, n=12), patients on

remission until week 52 (Sustained response, SusR, n=6), and patients who lost response after initial clinical remission (Loss of response, LossR, n=3).

All statistical analyses were performed using R software (version 4.2.3). Microbiome data were analysed by comparing patients according to treatment outcome, including responders and non-responders at week 14, as well as three outcome-based groups: non-responders, patients with sustained remission up to week 52, and patients who experienced loss of response during follow-up.

Within-sample microbial diversity was assessed using alpha diversity indices, while between-sample compositional differences were evaluated using beta diversity metrics based on dissimilarity matrices. Ordination analyses were conducted to visualize differences in microbial community structure across groups. Statistical significance of group-level differences was assessed using permutation-based methods.

Differential abundance analyses of microbial taxa and metabolic pathways were conducted using established statistical frameworks appropriate for metagenomic data. Microbial features identified as significantly different between groups by any analytical approach were selected for downstream interpretation. To control for multiple comparisons, p-values were adjusted and predefined significance thresholds were applied. Prior to differential analyses, metagenomic data were normalized to account for differences in sequencing depth across samples.

Results

Table 1 shows patient demographics comparing Response (R) and No Response (NoR) groups at baseline and Table 2 shows clinical findings at week 12 on treatment. There were no differences in baseline demographic and clinical data between patients who attained remission and those who did not.

Table 1
Baseline epidemiologic data in responders and no responders

	Responders (n = 9)	No responders (n = 12)	p
Female, n (%)	3 (33)	5 (42)	ns
Smoking habit, n (%)			ns
nonsmoker	5 (55)	5 (41)	
ex-smoker	3 (33)	7 (58)	
current smoker	1 (11)	0	
Age, y	48 (32–65)	55 (28–73)	ns
BMI, Kg/m2	24.4 (27.5–32.0)	25.3 (18.6–28.3)	ns
Montreal classification, n (%)			ns
E2	3 (33)	4 (33)	
E3	6 (66)	8 (66)	
Disease duration, y	14 (2–30)	9 (4–16)	ns
Calprotectin, µg/g	1024 (531–4874)	479 (223–3435)	ns
SCCAI	4 (1–8)	5 (2–11)	ns
Previous treatment, n (%)			ns
conventional	1 (11)	3 (25)	
anti-TNF once	6 (66)	5 (41)	
anti-TNF twice	2 (22)	4 (33)	

Qualitative data are n (%); quantitative values are median (range)

Table 2
Response to vedolizumab at week 12

	Responders (n = 9)	No responders (n = 12)	p
SCCAI	2 (1–7)	10 (8–12)	< 0.05
Calprotectin, µg/g	40 (16–302)	383 (349–3032)	< 0.05
Mayo endoscopic subscore, n (%)			< 0.05
0	7 (77)	0	
1	2 (22)	0	
2	0	8 (66)	
3	0	4 (33)	
C-reactive protein, mg/L	0.07 (0.04–0.71)	0.4 (0.07–11.8)	< 0.05

Qualitative data are n (%); quantitative values are median (range)

Metagenomic paired-end sequence reads (2x150bp) showing an average minimum of 25 million reads per sample were generated. The number of clean reads after trimming and contamination removal ranged from 2297384 to 86839985. A total 66 metagenome samples passed the quality control corresponding to the following groups of participants: i) No Response, NoR (n = 30), ii) Sustained Response, SusR (n = 26), iii) Loss of Response, LossR (n = 10).

Baseline gut microbiome

Baseline alpha diversity indices are shown in Fig. 1. Chao1 and Shannon index data showed a widespread dispersion in patients who did not achieve remission at week 12 compared to responders. No significant differences were found between groups, but it is notable that none of the patients with a low Chao1 index at baseline responded to the biologic treatment. Non-redundant gene count is a straightforward marker of microbial richness in faecal samples, and we observed higher richness in responders (44967 ± 10912 non-redundant genes) than in non-responders (41382 ± 11152 non-redundant genes), although the difference is not significant.

Beta diversity is a measure of the dissimilarity between samples from different individuals. Beta diversity within a given group is low when individual samples are similar and cluster together in a graphical representation, whereas beta diversity is high when individual samples show a large difference in composition and are distant in the graphical representation. We found higher beta diversity of metabolic pathways in patients who did not respond to treatment compared to those who did (Fig. 2A), suggesting greater heterogeneity among microbiomes from patients who did not respond to treatment. Analysis of the principal coordinates of the samples identified statistically different clusters ($p < 0.05$), showing a

higher dispersion of samples in the group of patients who did not respond to treatment than in the others (Fig. 2B and 2C).

As shown in Tables 3 and 4, most characteristic metabolic pathways of the SusR group correspond to *Bacteroides caccae* and *B. ovatus* and are involved in nucleotide and amino acid metabolism. In the LossR group, most characteristic metabolic pathways correspond to *Faecalibacterium prausnitzii*, *Bifidobacterium longum* and *Eubacterium eligens* and are involved in nucleotide, amino acid and carbohydrate metabolism.

Table 3
Number of microbial metabolic pathways showing the highest abundance ($p < 0.05$ and $p_{adj} < 0.25$) in each group of patients. Metabolic pathways are allocated to microbial taxa. NoR: No Response, LossR: Loss of Response, SusR: Sustained Response.

Group	Taxa	Frequency
NoR	*Bifidobacterium longum*	3
NoR	*Faecalibacterium prausnitzii*	2
LossR	*Faecalibacterium prausnitzii*	55
LossR	*Bifidobacterium longum*	50
LossR	*Eubacterium eligens*	49
LossR	*Fusicatenibacter saccharivorans*	1
LossR	*Ruthenibacterium lactatiformans*	1
SusR	*Bacteroides caccae*	59
SusR	*Bacteroides ovatus*	38
SusR	*Parabacteroides merdae*	14

Table 4
Number of microbial metabolic pathways showing the highest abundance ($p < 0.05$ and $p_{adj} < 0.25$) in each group of patients (metabolic pathways are defined by function). NoR: No Response, LossR: Loss of Response, SusR: Sustained Response.

Group	Function	Frequency
NoR	Carbohydrates	2
NoR	Other	2
NoR	Amino acids	1
LossR	Amino acids	52
LossR	Nucleotides	38
LossR	Carbohydrates	27
LossR	Other	21
LossR	Vitamins	12
LossR	Cell wall	4
LossR	Lipids	2
SusR	Nucleotides	39
SusR	Amino acids	29
SusR	Other	22
SusR	Vitamins	9
SusR	Cell wall	6
SusR	Carbohydrates	4
SusR	Lipids	2

Our analysis also focussed on distinct taxonomic profiles at baseline that could differentiate gut microbiomes in responders from those of no-responders, and eventually serve as predictive markers of clinical response. Figure 3 shows the bacteria species in which statistical differences between groups were detected. Surprisingly, abundance of *Faecalibacterium prausnitzii* and *Eubacterium eligens* at baseline was higher in NoR and LossR than in SusR group.

Patients with a sustained long-term response to vedolizumab (SusR) showed higher abundance of *Bacteroides caccae*, *Bacteroides ovatus*, *Bacteroides uniformis, Fusicatenibacter saccharivorans*, *Ruthenibacterium lactatiformans*, *Parabacteroides merdae*, *Parabacteroides distasonis*, *Odoribacter*

splanchnicus and *Flavonifractor plautii*. Moreover, *Bacteroides uniformis*, was also highly abundant in LossR as compared with NoR group. Studies have demonstrated that the intestinal abundance of *Bacteroides uniformis* is significantly higher in healthy controls than that in UC patients and a strain of this species is being investigated as novel probiotic to treat intestinal inflammation(19).

The species *Fusicatenibacter saccharivorans* belongs to the *Lachnospiraceae* family and is a fermentative short-chain fatty acid producing bacterium. This species has been shown to decrease in colitis patients with active flare and increase during remission. Isolated strains of *F. saccharivorans* suppressed intestinal inflammation in a murine colitis model(20). *Ruthenibacterium lactatiformans* is a lactate-producing member of the Ruminococcaceae family. There were no differences for members of the *Roseburia* genus.

Gut microbiome after starting treatment

Patients provided a stool sample at week 12 of vedolizumab treatment. Figure 4 shows the genus-level microbiome profiles in the three study groups during remission induction. Bands indicate the relative abundance of the dominant genera and changes over the three time points are shown (2 samples at baseline and 1 at week 12). The microbiome composition in patients who achieved sustained remission appears to be more stable than in the other two patient groups. In patients with sustained remission, obvious changes were only detected at week 12 and consisted of the expansion of the genera *Roseburia* and a novel *Lachnospiraceae* genus. In the other two patient groups, changes in microbiome composition are observed at any time point and there is no obvious association with the intervention. Temporal variability appears to be stochastic in these patients.

There were several taxonomic differences between groups at week 12 on vedolizumab, as shown in Fig. 5. First, the abundance of *Bacteroides ovatus* and *Bacteroides uniformis* was higher in patients who responded (SusR and LossR groups) compared with no responders (NoR). Interestingly, patients who progressed to long-term remission (SusR) had a higher abundance of several *Roseburia* species compared with the other two groups. The genus *Roseburia* consists of obligate Gram-positive anaerobic bacteria and includes several species (e.g. *R. intestinalis, R. inulinivorans, R. faecis*) that metabolize dietary components and produce butyrate in the human colon, playing a role in immune cell regulation, cytokine release, and barrier homeostasis(21). In contrast, *Faecalibacterium prausnitzii*, another well-recognised butyrate producing mutualistic bacterium, was lower in abundance in SusR compared to the other two groups.

The patients who maintained remission were followed for one year while on maintenance vedolizumab treatment. A number of taxa changed in abundance over the study period. Figure 6 shows changes in taxa that reached significant difference in this group of patients (SusR). There was a dramatic increase in the abundance of members of the *Lachnospiraceae* family, including the above mentioned *Bacteroides uniformis* and other unclassified species. Likewise, abundance of species of the *Roseburia*

genus progressively increased over time, as well as abundance of *Eubacterium rectale.* There was only little change in the abundance of *Faecalibacterium prausnitzii.*

In contrast, no significant changes in taxonomy were found in patients who lost response to vedolizumab after initial remission at week 14 (LossR).

Discussion

Diverse interactions between gut microbes, the intestinal epithelium, and gut-associated lymphoid tissues are constantly shaping host immunity and regulate mucosal inflammatory pathways(22). In IBD, mucosal inflammation fluctuates over time and bidirectional interactions between gut microbes and immunocompetent host cells appear to play a key role in the undulating course of these diseases (1, 13, 23). Altered states of the gut microbiome may therefore influence treatment efficacy(24).Our observational study aimed to explore whether pretreatment microbiome signatures could be useful in predicting successful response to anti-integrin biologic therapy in patients with active ulcerative colitis. We also followed-up our patients after clinical and endoscopic remission to further explore whether eventual loss of response was associated with specific microbiome changes.

Twenty-five patients with active ulcerative colitis who were candidates for anti-integrin therapy due to previous therapeutic failures were recruited, and twenty-one of them completed the protocol. At the end of the remission induction phase, nine patients had achieved complete clinical and endoscopic remission, and the remaining twelve patients showed disease activity. There were no demographic or clinical differences at baseline between patients who attained remission and the remaining. When comparing microbiomes from patients who responded to those who did not respond, we did not identify any discriminant microbial marker at baseline capable of predicting a satisfactory response to the biologic drug. Nonetheless, we observed some microbiological features of interest for a better understanding of the interplay between intestinal microbes and mucosal inflammation.

First, none of our patients with very low Chao1 index (Chao1 > 75) went into remission during vedolizumab treatment. Chao1 is an indicator of alpha-diversity based in species richness, i.e. the total number of species in the sample, that is also sensitive to species with low abundance. Second, microbiomes in the group of patients who did not respond were more heterogeneous in taxonomy and functional metabolic pathways than microbiomes in responders. Additionally, responders exhibited a more stable microbiome compositional profile over the 12 weeks of induction than patients who did not respond. Finally, significant increases in well-recognised anti-inflammatory commensals, such as *Bacteroides uniformis*, *Roseburia intestinalis, R. inulinivorans, R. faecis*, *Lachnospiraceae* species, and others, were observed during vedolizumab treatment only in patients with a sustained remission.

Temporal stability and species richness/diversity are important ecological properties of a microbial ecosystem(25). Stability ensures that microbiome functions are maintained over time and relies on its functional attributes to cope with external challenges. High species diversity and functional redundancy are crucial for ecosystem resilience(26). In IBD, periods of disease activity are marked by decreases in

gut microbial diversity and increases in temporal variability, with characteristic taxonomic, functional and biochemical shifts(3). Patients may not recover a fully balanced gut microbiota during periods of remission and studies have shown low diversity and temporal variability in patients during remission(5, 14, 27). Variability has been associated with a higher risk of a subsequent flare (27). In our study, we did not detect significantly lower alpha-diversity or higher temporal variability in the baseline microbiome samples of non-responders compared to those who responded. However, there was an obvious trend, and it can be speculated that our sample size was insufficient to show differences at the statistical level. Interestingly, the heterogeneity observed at baseline in the microbiomes of patients who did not respond to treatment (beta diversity data) is also consistent with instability and temporal variability in that patient group. Temporal variability leads to heterogeneity within the group.

The study by Ananthakrishnan et al. (12) detected lower alpha-diversity in baseline microbiome samples from Crohn's disease patients who did not achieve vedolizumab-induced remission at week 14. As in our study, this indicator did not reach statistical significance in the UC patient cohort. Likewise, beta diversity was higher at baseline in the non-remission group compared to the remission group, but again this finding was only significant for Crohn's disease and not for UC patients. The divergence between Crohn's disease and UC may be explained by the fact that dysbiotic changes are typically more pronounced in Crohn's disease microbiomes than in UC ones (3). In any case, our findings on core gut microbiome indicators are in line with those previously reported by Ananthakrishnan et al (12).

Our analysis was able to differentiate patients who responded to treatment from those

who did not based on microbiome taxonomy at baseline. We identified increased

abundance of Bacteroides uniformis, Fusicatenibacter saccharivorans, and others, in

patients who would achieve remission. Additionally, Bacteroides uniformis,

Lachnospiraceae ssp., and several Roseburia species increased in abundance along with vedolizumab treatment. Ananthakrishnan et al (12) reported that Roseburia inulinivorans and a Burkholderiales species were significantly more abundant at baseline among Chron's disease patients who achieved remission compared to those who did not. However, these species did not increase in abundance during vedolizumab treatment.

As limitations and future perspectives, several aspects of this study should be considered. The present work is a proof-of-concept study involving a moderate sample size but still allows to demonstrate that some descriptive data could preclude response to vedolizumab. The study design includes participants of both genders and covers a broad range of ages and BMI values. Moreover, this is a longitudinal and prospective study with five different timepoints, allowing an assessment of microbiota stability over time. This work contributes to personalized medicine by exploring the role of each participant's baseline microbiota in shaping the individual response to vedolizumab.

On a different note, several microbial biomarkers associated with treatment response were identified in this study; however, further research involving larger cohorts is needed to confirm these findings.

In addition, a more comprehensive characterization of these microbial signatures at the strain level will require deeper metagenomic sequencing, together with validation in independent cohorts.

Nevertheless, given that metagenomic sequencing is complex and costly, the identification of robust microbial markers of vedolizumab response could facilitate the development of simpler diagnostic tools to stratify patients and guide treatment decisions. Ultimately, further studies are needed to elucidate how vedolizumab modulates the intestinal microbiota and to determine whether microbiome-derived markers can reliably predict treatment outcomes.

The ability to predict response to anti-inflammatory treatment in IBD patients using the gut microbiome is an attractive research goal at the hypothesis level. However, a major drawback to the use of microbiome-based biomarkers in diagnosis, prognosis, and precision therapy is that it requires the definition of a healthy microbiome in different populations. Interindividual compositional differences make it difficult to establish normal ranges for taxa that may be present in some healthy individuals but not others, and the abundance of common species is extremely variable between individuals. Furthermore, geography is a surrogate for large-scale variation in the human gut microbiome in terms of ethnicity, culture, diet, lifestyle, etc. (28). In this study, we did not identify predictive markers that would eventually be applicable or reliable for other patient cohorts. However, based on our findings in a small group of patients with active UC, who were refractory to previous therapies, we speculate that the robustness of the gut microbial ecosystem acts as a predictor, among others, for a successful response to anti-integrin therapy. In patients with a sustained response, microbiomes showed high species richness (alpha diversity), lower heterogeneity (beta diversity), consistent stability over time, and capacity to expand the relative abundance of anti-inflammatory species in parallel with the mucosal anti-inflammatory effect of the drug.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Vall d'Hebron Ethical Committee under code IISR-2015-101160 (FGA-VED-2016-01). All participants provided written informed consent before taking part in the study.

Consent for publication

Not applicable.

Availability of data and materials

Raw metagenomic sequencing data have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject accession number PRJNA1198595. During peer review, the dataset is available to editors and reviewers through the following private reviewer link:
https://dataview.ncbi.nlm.nih.gov/object/PRJNA1198595?reviewer=kkbjgcq15d2lf8qtsdikc2t15n
The data will be made publicly available upon acceptance of the manuscript.

Competing interests

VR, LM, CH: Sponsorship for congress attendance: Pfizer, Janssen, Takeda, Ferring, Lilly, Falk, Abbvie.
FG received research grants from Abbvie, Takeda, and AB-Biotics and is a member of the Biocodex Microbiota Institute's scientific advisory board.
EV, FG, CS: no disclosures.
AM is Scientific Founder and Member of the Scientific Advisory Board of MicroViable Therapeutics S.L.
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Authors' contributions

VR, NB: Conceptualization and study design, Methodology, Data curation, Supervision, Data collection, Writing – original draft, Writing – review & editing.
CH, LM, FC, MDMA: Data collection, formal analysis.
CS, AM, EV: Analysis, Writing – review & editing, Formal analysis.
FG: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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Figures

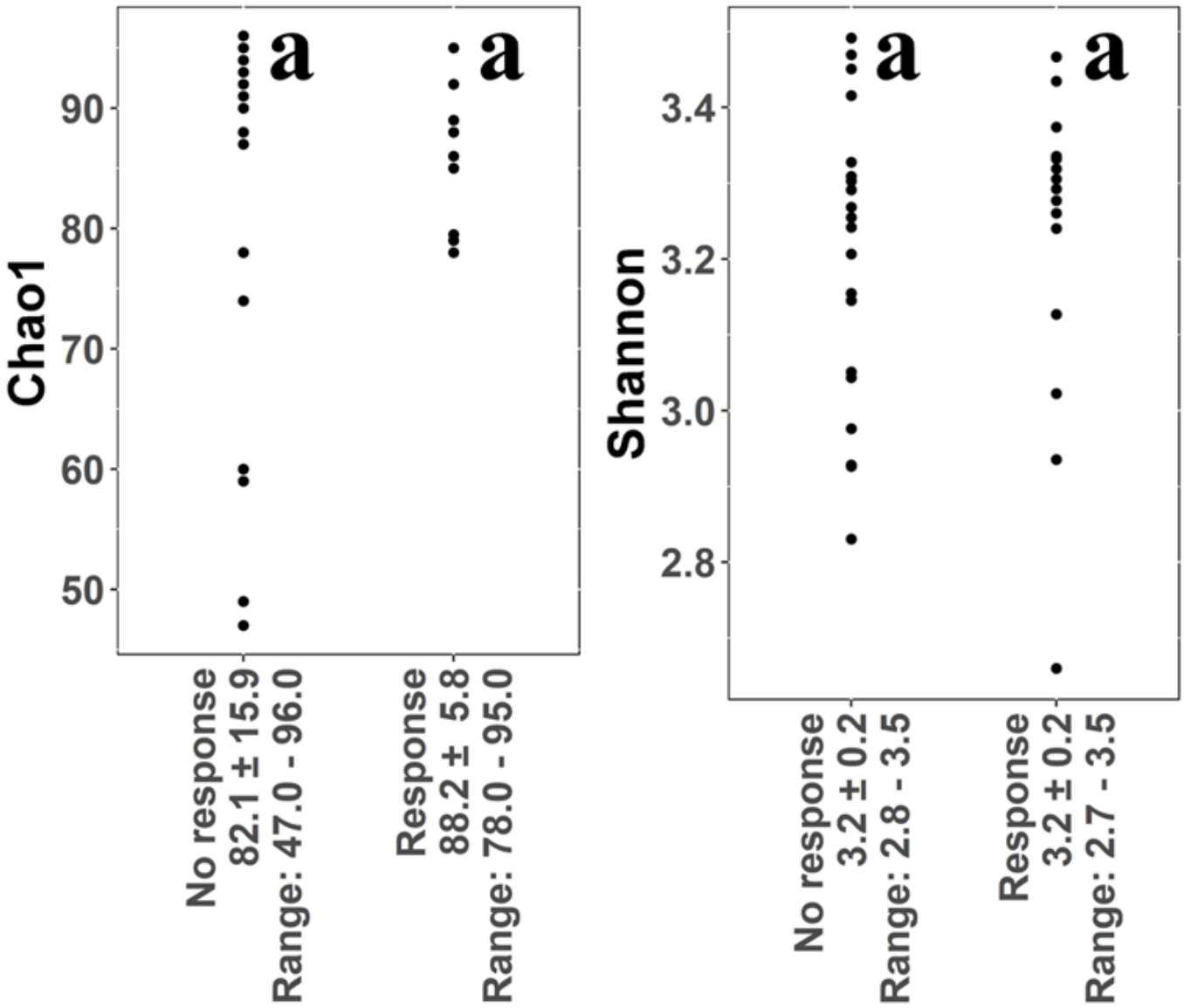


Figure 1

Chao1 and Shannon alpha-diversity indexes of the microbial communities in samples at baseline. [a]No statistically significant ($p > 0.05$) difference was found between groups.

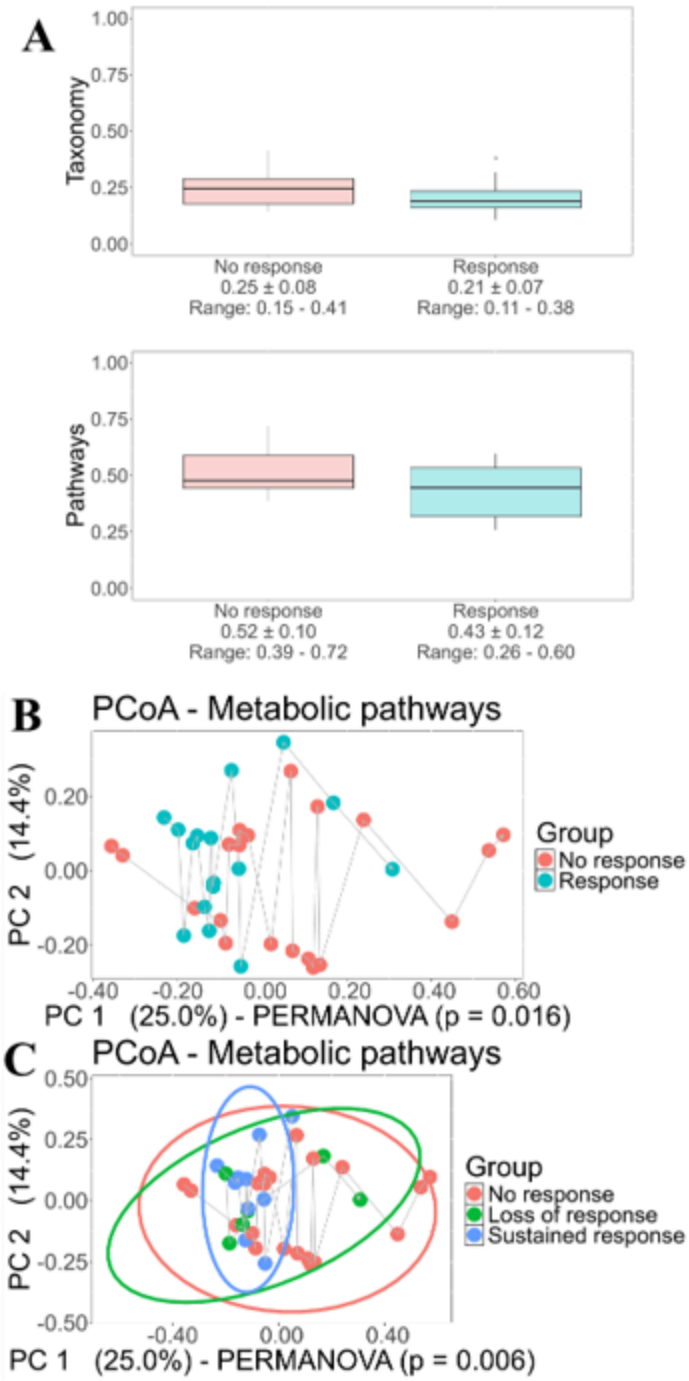


Figure 2

A:Beta-diversity was higher in no responders than in responders, indicating greater heterogeneity of microbiomes within NoR as compared with R patients. Bray-Curtis method was selected for the calculation. **B and C:** Graphical representation of Bray-Curtis distances as principal coordinates analysis (PCoA). The percentage (%) of variance explained by each PC is indicated in the axis. Differences between groups are statistically significant ($p < 0.05$).

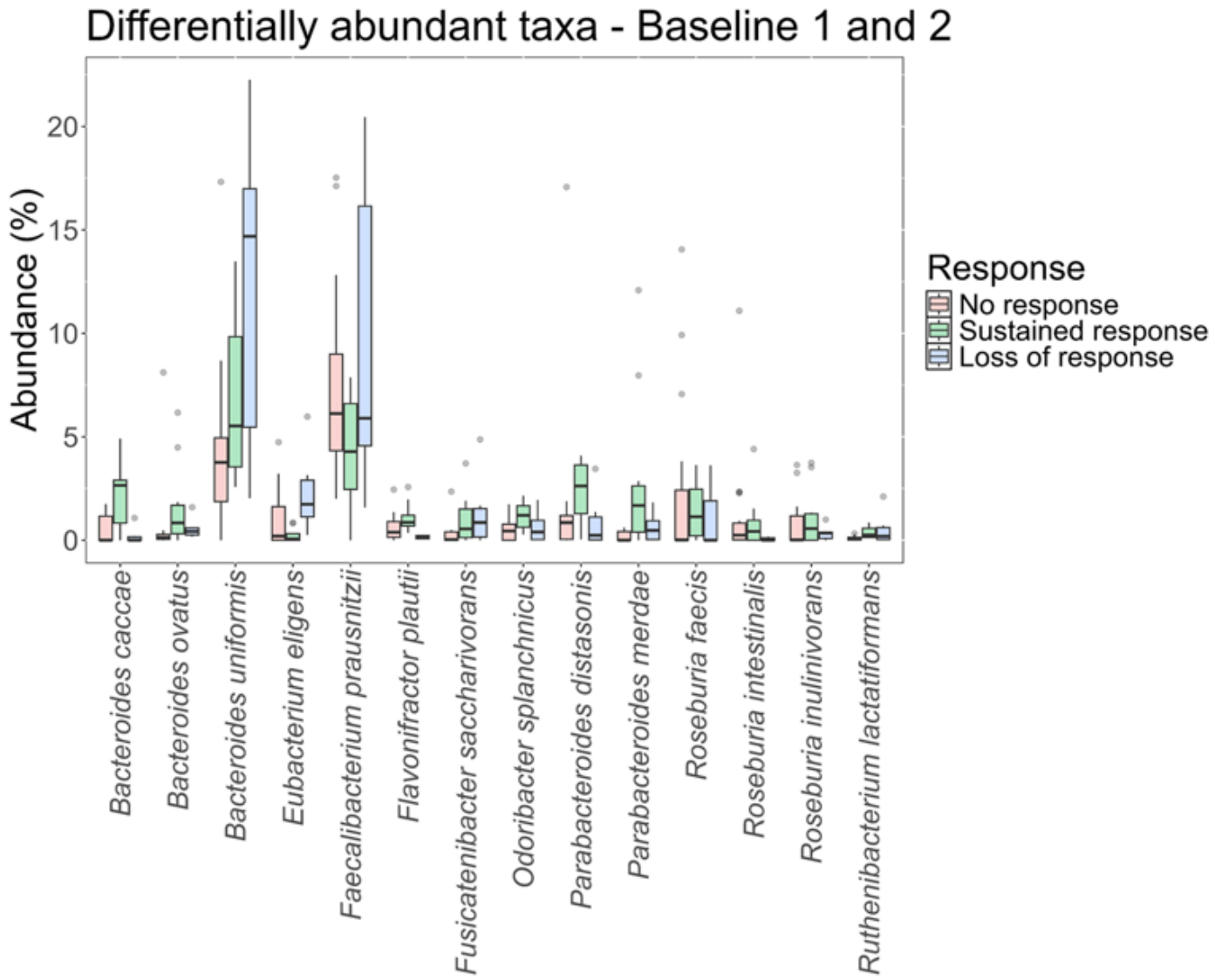


Figure 3

Differentially abundant bacteria species in patient samples at baseline. Data are expressed as abundance percentages (%).

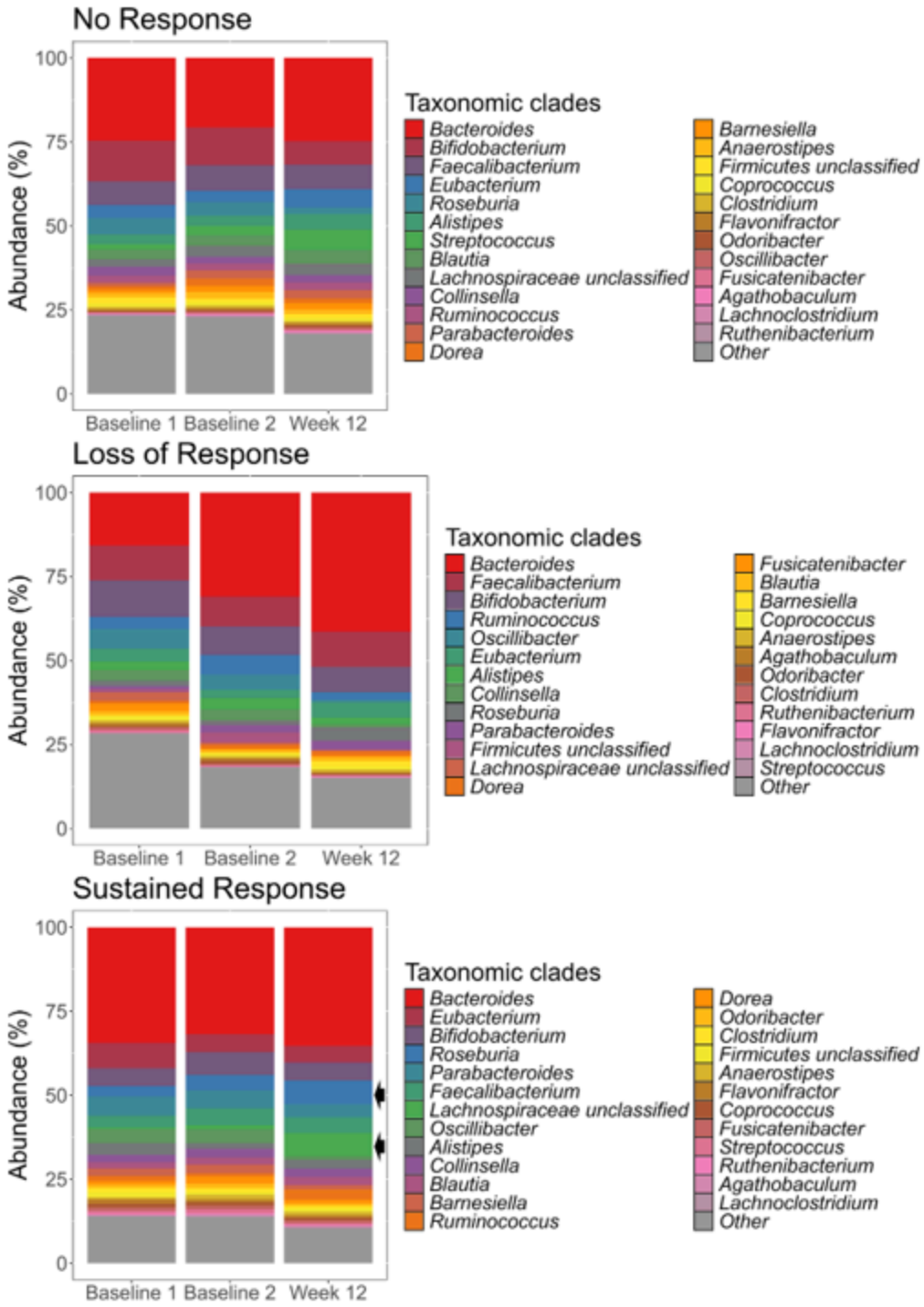


Figure 4

Microbiome profiles at genus level in the three study groups during induction of remission. The microbiome in patients who evolved to a sustained response showed consistent stability in composition over time and expansion of *Roseburia* and a novel *Lachnospiraceae* genus (arrow).

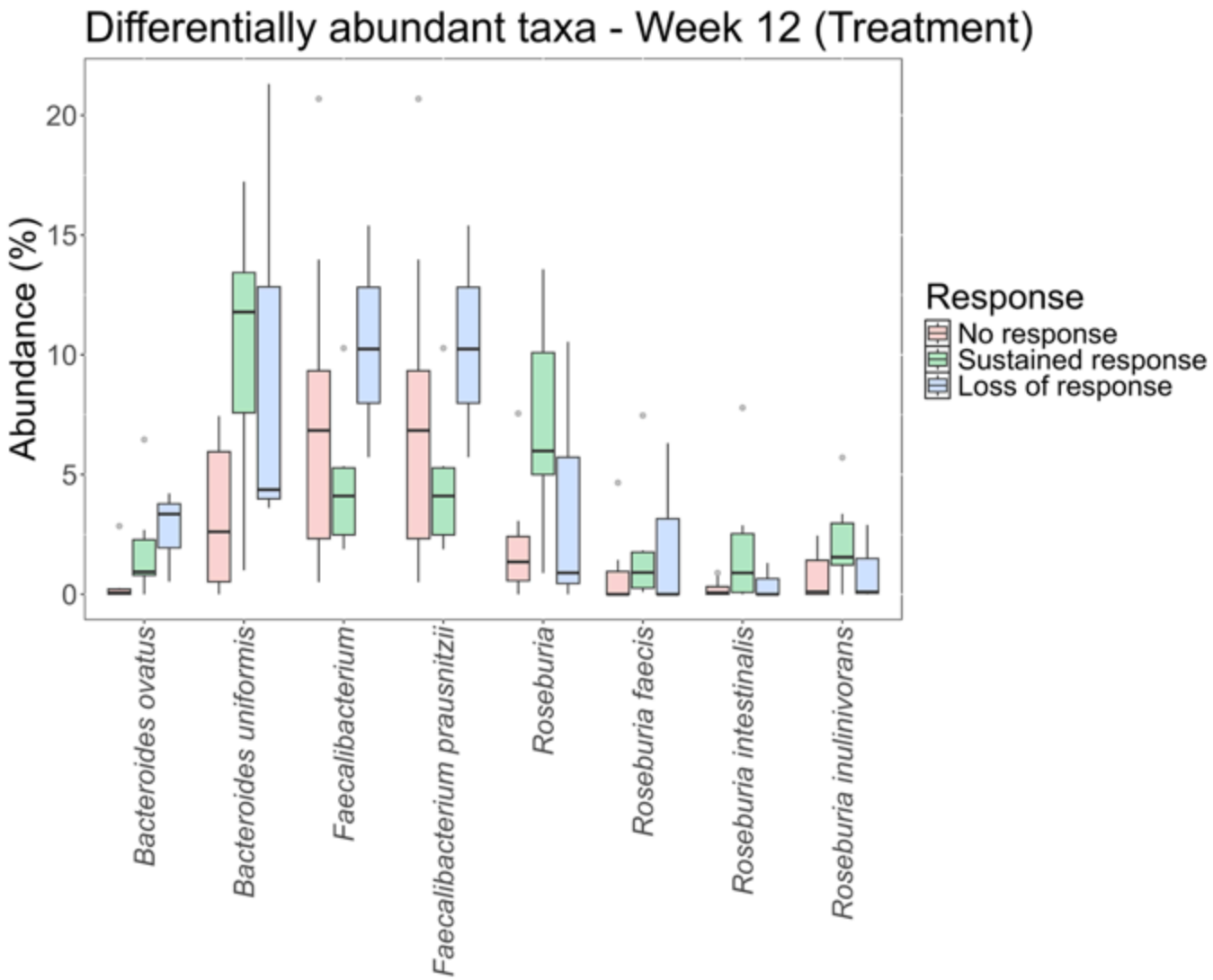


Figure 5

Differentially abundant taxonomic clades in patient samples at week 12 on vedolizumab treatment. Data are expressed as abundance percentages (%).

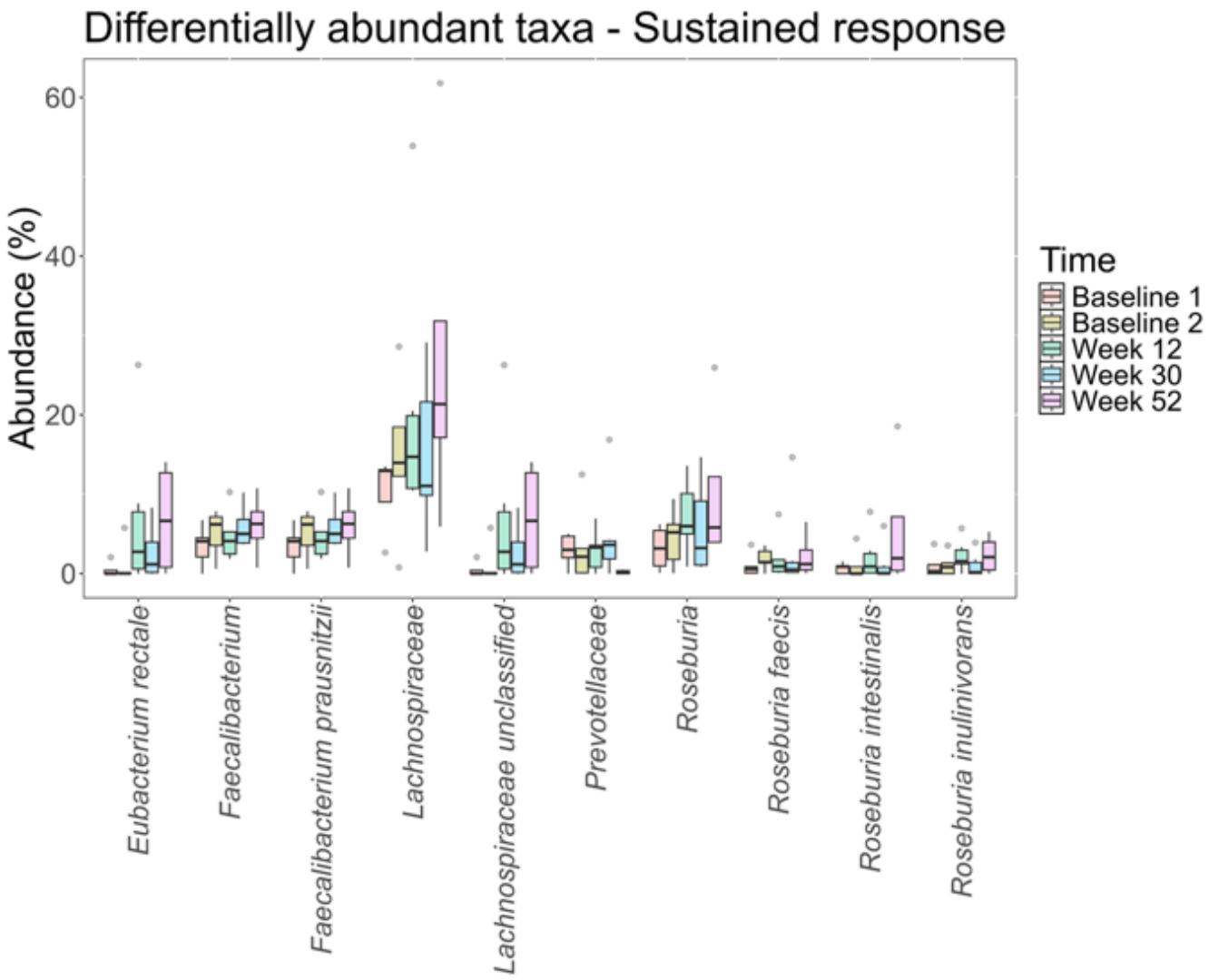


Figure 6

Differentially abundant taxonomic clades found in patients with sustained response over the one-year follow-up period. Data are expressed as abundance percentage (%).