B0407

Improvement in Fatigue With Mirikizumab Therapy Is Associated With Improvements in Patient-Reported Outcomes in Patients With Moderately to Severely Active Crohn's Disease

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BACKGROUND

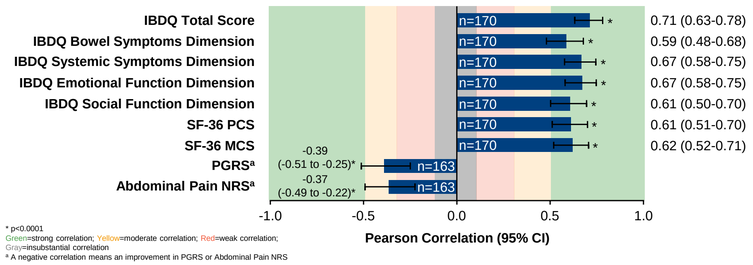
- Fatigue is a debilitating, under-recognized, multi-factorial symptom experienced by many patients with Crohn's disease (CD)[1]
- Mirikizumab is a humanized immunoglobulin G4 monoclonal antibody directed against the p19 subunit of interleukin-23[2]
- Mirikizumab was efficacious and well tolerated in patients with CD in a Phase 2 randomized clinical trial (NCT02891226)[2]
  - Fatigue was significantly improved in patients with CD who received mirikizumab[3]

OBJECTIVE

- To assess the association between changes in selected patient-reported outcomes (PROs) and changes in fatigue

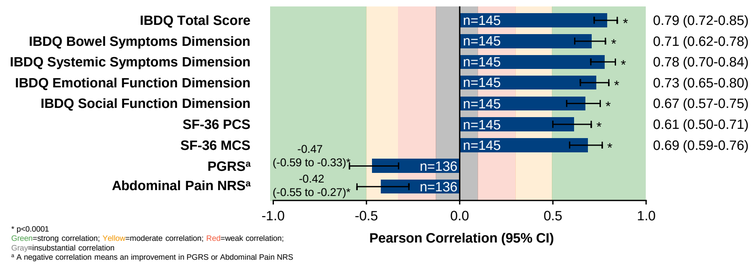
KEY RESULTS

Correlation of FACIT-F Improvement With Changes in PROs at Week 12 of the Induction Period



* p<0.0001
Green=strong correlation; Yellow=moderate correlation; Red=weak correlation; Gray=insubstantial correlation
[a] A negative correlation means an improvement in PGRS or Abdominal Pain NRS

Correlation of FACIT-F Improvement With Changes in PROs at Week 52 of the Maintenance Period



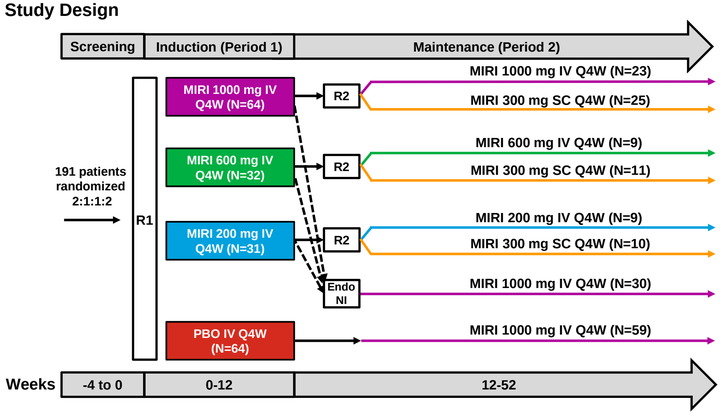
* p<0.0001
Green=strong correlation; Yellow=moderate correlation; Red=weak correlation; Gray=insubstantial correlation
[a] A negative correlation means an improvement in PGRS or Abdominal Pain NRS

CONCLUSIONS

- Improvement in fatigue during treatment for CD was correlated with improvement in some aspects of physical symptoms and functioning, including abdominal pain
- Improvement in fatigue was also correlated strongly with improvement in emotional, social, and mental well-being
- Correlations between fatigue and PROs at the end of induction therapy at Week 12 were similar to the Maintenance Period at Week 52
- Investigations into the bi-directional effects of brain-gut interactions could be helpful in understanding the relationship between the subjective perception of well-being and improvement in physical symptoms of CD

METHODS

Study Design



R1=Randomization 1

- Patients were stratified based on previous exposure to biologic therapy for the treatment of CD

R2=Re-randomization after induction

- Patients who received mirikizumab during induction and had endoscopic improvement were re-randomized in a 1:1 ratio at Week 12 to continue their induction regimen or receive mirikizumab 300 mg SC Q4W, with stratification based on endoscopic response. All patients who received placebo in Period 1 received MIRI 1000 mg IV Q4W

Note: Endoscopic improvement defined as ≥1-point improvement in SES-CD. Endoscopic response defined as a ≥50% reduction in SES-CD score vs. baseline

Key Eligibility Criteria

Inclusion Criteria

- Duration of active CD ≥3 months since diagnosis
- Moderately to severely active disease:
  - Stool frequency ≥4 per day (loose and watery stools defined as Bristol Stool Scale Category 6 or 7) and/or abdominal pain ≥2 (on a 4-point scale) at baseline
  - SES-CD score ≥7 for patients with ileal-colonic disease or ≥4 for patients with isolated ileal disease
- Treatment history:
  - Inadequate response or intolerance to ≥1 conventional treatment or prior exposure to ≥1 biologic agent for the treatment of CD

Exclusion Criteria

- Strictures, stenoses, or any other manifestation that might require surgery
- Bowel resection, diversion, or placement of a stoma within 6 months; other intra-abdominal surgery within 3 months
- Previous exposure to any biologic therapy targeting the IL-23 p19 subunit, either licensed or investigational
  - After an amendment, a single prior induction dose of ustekinumab was allowed (USA only)

Assessments

- Fatigue was assessed using the FACIT-F questionnaire[4]
  - 13-item tool that measures an individual's level of fatigue
  - 5-point Likert scale (0=not at all fatigued to 4=very much fatigued), with score reversals
  - Higher score indicates a better outcome
- Additional PROs included:
  - IBDQ
    - Higher score indicates a better outcome
  - SF-36
    - Higher score indicates a better outcome
  - PGRS
    - Lower score indicates a better outcome
  - Abdominal Pain NRS
    - Lower score indicates a better outcome

Statistical Analyses

- Data were pooled for all treatment arms including placebo
- Pearson's correlation coefficients, 95% confidence intervals, and p-values were calculated for patients with baseline and post-baseline measures
- Cohen's conventions were used to assess strength of correlations[5]
  - >0.5 is strong
  - 0.3 to ≤0.5 is moderate
  - 0.1 to <0.3 is weak
  - <0.1 is insubstantial

RESULTS

Baseline Demographics and Disease Characteristics by Induction Treatment Group

	Induction Treatment Groups			
	PBO IV (N=64)	MIRI 200 mg IV (N=31)	MIRI 600 mg IV (N=32)	MIRI 1000 mg IV (N=64)
Age, years	39.0 (13.0)	38.1 (11.8)	40.4 (13.3)	37.7 (13.1)
Male, n (%)	28 (43.8)	17 (54.8)	14 (43.8)	34 (53.1)
Disease duration, years	10.2 (9.8)	8.9 (7.4)	10.8 (9.7)	8.6 (6.7)
Disease location, n (%)				
Ileal	11 (17.2)	6 (19.4)	5 (15.6)	11 (17.2)
Colonic	25 (39.1)	14 (45.2)	10 (31.3)	26 (40.6)
Ileal-colonic	28 (43.8)	11 (35.5)	17 (53.1)	27 (42.2)
CRP, mg/L, median (range)	6.8 (0-92)	7.4 (0-94)	6.8 (0-78)	4.5 (0-108)
SES-CD	11.9 (5.6)	14.4 (7.9)	15.2 (7.4)	13.1 (6.8)
PROs				
Stool frequency	6.4 (3.1)	7.4 (3.0)	6.4 (3.8)	6.6 (5.5)
Abdominal pain	1.9 (0.6)	2.0 (0.6)	1.7 (0.7)	1.9 (0.6)
CDAI (0-600)	304.7 (93.1)	348.3 (92.1)	298.2 (103.7)	304.5 (94.4)
FACIT-F (13 items, 0-52)	21.9 (12.7)	19.3 (10.4)	28.2 (12.5)	24.1 (12.1)
IBDQ	113.9 (37.1)	104.8 (34.3)	127.0 (35.5)	120.3 (32.4)

Data are presented as mean (SD) unless stated otherwise

Correlation of FACIT-F Improvement With Changes in PROs

	Week 12 (N=170)			Week 52 (N=145)		
PRO	**Pearson Correlation**	**95% CI**	**p-Value**	**Pearson Correlation**	**95% CI**	**p-Value**
IBDQ Total Score	0.714	0.632-0.781	<0.0001	0.791	0.721-0.845	<0.0001
IBDQ Bowel Symptoms Dimension	0.588	0.480-0.678	<0.0001	0.709	0.617-0.782	<0.0001
IBDQ Systemic Symptoms Dimension	0.669	0.577-0.745	<0.0001	0.777	0.703-0.835	<0.0001
IBDQ Emotional Function Dimension	0.672	0.580-0.747	<0.0001	0.733	0.647-0.800	<0.0001
IBDQ Social Function Dimension	0.608	0.503-0.695	<0.0001	0.674	0.574-0.754	<0.0001
SF-36 PCS	0.614	0.511-0.700	<0.0001	0.613	0.500-0.705	<0.0001
SF-36 MCS	0.621	0.519-0.706	<0.0001	0.687	0.590-0.764	<0.0001
PGRS	-0.389	-0.512 to -0.250	<0.0001	-0.469	-0.591 to -0.327	<0.0001
Abdominal Pain NRS	-0.365	-0.491 to -0.224	<0.0001	-0.421	-0.550 to -0.272	<0.0001

Green=strong correlation; Yellow=moderate correlation

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ABBREVIATIONS

CD=Crohn's disease; CDAI=Crohn's Disease Activity Index; CI=confidence interval; CRP=C-reactive protein; Endo NI=endoscopic non-improver; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ=Inflammatory Bowel Disease Questionnaire; IL=interleukin; IV=intravenous; MCS=Mental Component Summary; MIRI=mirikizumab; N=number of patients in the analysis, including patients with non-missing change scores; NRS=Numeric Rating Scale; PBO=placebo; PCS=Physical Component Summary; PGRS=Patient's Global Rating of Severity; PRO=patient-reported outcome; Q4W=every 4 weeks; R1=randomization 1; R2=re-randomization after induction; SC=subcutaneous; SD=standard deviation; SES-CD=Simplified Endoscopic Activity Score for Crohn's Disease; SF-36=36-Item Short Form Health Survey

DISCLOSURES

- **M. Reguiero** has received consulting fees from: AbbVie, Allergan, Amgen, Celgene, Eli Lilly and Company, Genentech, Gilead Sciences, Janssen, Miraca Life Sciences, Pfizer, Prometheus Therapeutics and Diagnostics, Salix Pharmaceuticals, Seres Therapeutics, Takeda, Target RWE, and UCB Pharma; and has received research support from: AbbVie, Janssen, Pfizer, and Takeda; **M. Fischer** has received consulting fees from: AbbVie, Bristol Myers Squibb, Eli Lilly and Company, Janssen, and Takeda; **D. T. Rubin** has been a consultant for: AbbVie, AbGenomics, Allergan, Biomica, Boehringer Ingelheim, Bristol Myers Squibb, Celgene/Syneos Health, Check-Cap, Dizal Pharma, Eli Lilly and Company, Galen/Atlantica, Genentech/Roche, Gilead Sciences, GlaxoSmithKline, Ichnos Sciences, InDex Pharmaceuticals, Janssen, Narrow River Management, Pfizer, Prometheus Therapeutics and Diagnostics, Reistone Biopharma, Shire, Takeda, and TECHLAB; received grant research support from: AbbVie, Genentech/Roche, Janssen, Prometheus Therapeutics and Diagnostics, Shire, and Takeda; has stock options at: AbGenomics and Biomica; has been on the board of trustees at: American College of Gastroenterology; is co-founder and CFO of: Cornerstones Health (non-profit); and is co-founder of: GoDuRn; **T. Hibi** has received lecture fees from: AbbVie, Aspen Japan K.K., Ferring Pharmaceuticals, Gilead Sciences, Janssen, JIMRO, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Pfizer, and Takeda; has received consulting fees from: AbbVie, Apo Plus Station, Bristol Myers Squib, Celltrion, EA Pharma, Eli Lilly and Company, Gilead Sciences, Janssen, Kyorin, Mitsubishi Tanabe Pharma, Nichi-Iko Pharmaceutical, Pfizer, Takeda, and Zeria Pharmaceutical; has received research grants from: AbbVie, ActivAid, Alfresa Pharma, Bristol Myers Squibb, Eli Lilly Japan K.K., Ferring Pharmaceuticals, Gilead Sciences, Janssen Pharmaceutical K.K., JMDC, Mochida Pharmaceutical, Nippon Kayaku, Pfizer Japan, and Takeda; has received scholarship contributions from: Mitsubishi Tanabe Pharma, Nippon Kayaku, and Zeria Pharmaceutical; and has belonged to study groups sponsored by: AbbVie, Alfresa Pharma, EA Pharma, JIMRO, Kyorin, MIYARISAN Pharmaceutical, Mochida Pharmaceutical, Otsuka, and Zeria Pharmaceutical; **P. Bossuyt** has received research support from: AbbVie, Amgen, Celltrion, Mylan, Pfizer, and Takeda; has received lecture fees from: AbbVie, Celltrion, Eli Lilly and Company, Janssen, and Takeda; and has received advisory board fees from: AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Celltrion, Dr. Falk Pharma, Eli Lilly and Company, Galapagos NV, Janssen, Pentax, PSI CRO, Roche, Takeda, and Tetrameros; **P. Juillerat** has received research support from: Vifor Pharma; has received consulting and/or advisory board and/or speaker fees from: AbbVie, Amgen, Arena Pharmaceuticals, Bristol Myers Squibb, Eli Lilly and Company, Ferring Pharmaceuticals, Gilead Sciences, Janssen, Merck Sharp & Dohme, Pfizer, Pierre Fabre, Roche, Sandoz, Takeda, Tillots Pharma AG, and UCB Pharma; **P. Pollack, M. Protic, T. Hunter Gibble, L. Shan Chan**, and **Hilde Carlier** are employees and shareholders of: Eli Lilly and Company; **X. Zhou** was an employee of: Syneos Health under contract with Eli Lilly and Company; **Pieter Hindryckx** has received consulting fees from: AbbVie, Eli Lilly and Company, Janssen, and Takeda; has received speaker fees from: AbbVie, Chiesi, Dr. Falk Pharma, Ferring Pharmaceuticals, Takeda, Tillotts Pharma AG, and Vifor Pharma; and has received research support from: Eli Lilly and Company
- Medical writing assistance was provided by Joanna Best, PhD, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company. This study was previously presented at the United European Gastroenterology Week (UEGW) 2022.