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CLINICAL TRIAL REPORT

A famciclovir + celecoxib combination treatment is safe and efficacious in the treatment of fibromyalgia

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Objective: Infections and other stressors have been implicated in the development of fibromyalgia. We hypothesized that these stressors could result in recurrent reactivations of latent herpes virus infections, which could lead to the development of fibromyalgia. This study evaluated a famciclovir + celecoxib drug combination (IMC-1), active against suspected herpes virus reactivation and infection, for the treatment of fibromyalgia.

Methods: A total of 143 fibromyalgia patients were enrolled at 12 sites in a 16-week, double-blinded, placebo-controlled proof-of-concept trial. Randomized patients received either IMC-1 or placebo in a 1:1 ratio. Outcome measures included a 24-hour recall pain Numerical Rating Scale, the Revised Fibromyalgia Impact Questionnaire (FIQ-R), the Patient's Global Impression of Change (PGIC) questionnaire, the Multidimensional Fatigue Inventory, the NIH Patient-Reported Outcomes Measurement Information System (PROMIS), and the Beck Depression Inventory-II conducted at baseline and weeks 6, 12, and 16 of the study.

Results: A significant decrease in fibromyalgia-related pain was observed for patients on IMC-1 treatment versus placebo. PGIC response rates were significantly improved with IMC-1 treatment. Overall, patient self-reported functioning, as measured by the FIQ-R, was significantly improved. Fatigue was also significantly improved as measured by the PROMIS fatigue inventory. The safety profile was encouraging. Despite the celecoxib component of IMC-1, gastrointestinal and nervous system treatment emergent adverse events were reported less frequently in the IMC-1 group, and study completion rates favored IMC-1 treatment.

Conclusion: IMC-1 was efficacious and safe in treating symptoms of fibromyalgia, supporting the hypothesis that herpes virus infections may contribute to this syndrome. Improved retention rates, decreased adverse event rates, and evidence of efficacy on a broad spectrum of outcome measures are suggestive that IMC-1 may represent an effective, novel treatment for fibromyalgia.

Keywords: fibromyalgia, famciclovir, celecoxib, antiviral, herpes virus

Introduction

Fibromyalgia (FM) is a chronic pain syndrome with symptoms that include widespread pain, fatigue, sleep disruption, and cognitive impairment. FM is estimated to affect 2%–8% of the population[1–3] and is often comorbid with related conditions such as irritable bowel syndrome (IBS) and chronic fatigue syndrome. It is commonly accepted that FM is associated with abnormalities in central pain processing that result in allodynia and hyperalgesia; however, the causal or triggering events leading to these abnormalities have not been fully elucidated, nor is there clarity regarding the factors responsible for the numerous symptoms associated with FM. It is generally believed that central sensitization in FM patients does not occur de novo, but is secondary to

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some combinations of genetic and environmental factors that predispose the patient to this condition.[4] Physical trauma, infection, emotional distress, endocrine disorders, and immune activation have all been hypothesized as potential triggering phenomena in susceptible patients.[4,5]

We hypothesized a persistent viral infection, reactivated by stress and other environmental factors, contributes to the systemic changes and symptoms associated with FM. Members of the herpes virus family are unique among viruses in that they remain in a dormant state, termed latency, until stress and other environmental conditions result in virus reactivation. During latency, viral genomes are maintained as circular episomes in the nuclei of host cells. Upon reactivation, viral proteins are expressed resulting in a productive, lytic infection that can spread within the body and induce an immune response. We hypothesized the recurrent reactivation of a tissue-resident herpes virus in genetically susceptible individuals could lead to abnormalities in the nervous system and hypothalamic–pituitary–adrenal axis. We further hypothesized that in susceptible patients, these abnormalities could lead to central sensitization and other manifestations of FM.

The drugs currently approved for the management of FM, including duloxetine, milnacipran, and pregabalin, are believed to work by modifying central pain processing; duloxetine and milnacipran via serotonin and norepinephrine reuptake inhibition and pregabalin via modulation of voltage-gated calcium channels. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have not been shown to be effective as monotherapies in the treatment of FM pain, but they are nonetheless used by many FM patients, largely to provide an element of analgesia against other peripheral pain generators such as osteoarthritis.[6–8] All of these medications, plus others, have been found to have varying degrees of effectiveness in the management of FM.[9–11] Nonetheless, a significant percentage of FM patients continues to experience pain, fatigue, and other symptoms.

The therapeutic regimen tested in this study was designed to suppress tissue-resident herpes viruses. The famciclovir + celecoxib combination (IMC-1) was intended to provide aggressive antiviral activity against herpes simplex virus 1 (HSV-1), interrupting the cyclical process of virus reactivation and lytic infection hypothesized to trigger and/or perpetuate the symptoms of FM. The mechanism of action of anti-herpes virus nucleoside analogs such as acyclovir, valacyclovir, and famciclovir is well understood. It is perhaps less well known that COX-2 inhibitors also exhibit anti-herpes virus activity. Several herpes viruses, including HSV-1, are known to significantly upregulate COX-2, and virally induced upregulation of COX enzymes is important for efficient HSV-1 replication.[12–17] In addition, researchers have found COX inhibitors are effective in reducing the severity of primary herpes virus lesions and inhibiting reactivation of latent infections.[18–21] Whereas other treatments, such as serotonin/ norepinephrine reuptake inhibitors and antiepileptic agents, are oriented toward the treatment of downstream abnormalities in central pain processing,[22] we hypothesized that the IMC-1 regimen would intervene further upstream in the cascade of events leading to the symptoms of FM.

Patients and methods

Study overview

This 16-week, randomized, double-blinded, placebo-controlled study was conducted at 12 outpatient clinical/ research centers in the USA. All centers, along with the study protocol, were reviewed and approved by a central institutional review board (Quorum Review Institutional Review Board), and all patients provided informed consent. The study was conducted in compliance with the Declaration of Helsinki, consistent with Good Clinical Practice and applicable regulatory requirements. The study was registered with the ClinicalTrials.gov database under the identifier NCT01850420. Data were collected from 14 May 2013 to 10 January 2014.

Entry criteria

Female or male patients, 18–70 years of age, who met the 2010 American College of Rheumatology (ACR) Preliminary Diagnostic Criteria for FM were eligible for inclusion. Patients were required to have a 24-hour recall average pain score between 40 and 90 inclusive on a 100-mm visual analog scale (VAS) at the screening visit and a 24-hour recall average pain score between 4 and 9 inclusive on an 11-point Numerical Rating Scale (NRS) at the baseline visit. Female patients were required to have a negative urine pregnancy test at screening and baseline unless post-menopausal or surgically sterile. Female patients of childbearing age were required to utilize an effective birth control method for the duration of the study. Patients were required to withdraw and refrain from the use of duloxetine, milnacipran, pregabalin, gabapentin, sodium oxybate, and opioids, and the use of NSAIDs other than low-dose aspirin was curtailed at the time of randomization. Acetaminophen was allowed as needed. Candidates were required to have a negative drug screen for opioids and drugs of abuse prior to randomization. Qualified

patients with mild to moderate depression were eligible if clinically stable, without risk of suicidal ideation or behavior, and the dose of allowed antidepressants had been stable for at least 3 months prior to screening.

A partial summary of the exclusion criteria for the study includes use of celecoxib or famciclovir within 30 days of screening; treatment with warfarin, lithium, amiodarone, isoniazid, phenytoin, fluconazole, probenecid, or raloxifene (due to the potential for metabolic interactions with celecoxib or famciclovir); and failed back surgery syndrome, infectious arthritis, rheumatoid arthritis, systemic lupus erythematosus, or other laboratory-confirmed systemic auto-immune disease.

Study design

The PRID-201 study was designed to evaluate the safety and efficacy of a famciclovir + celecoxib combination (IMC-1) in the treatment of FM pain. The study included four phases: screening and washout (5–28 days), baseline assessment and randomization (1 day), acute treatment dose (1 week), and chronic suppressive dose treatment (15 weeks). After providing informed consent and undergoing screening for eligibility, patients completed a washout of prohibited medications, if necessary, for 5–28 days prior to randomization (1:1 ratio) at the baseline visit. To ensure balanced assignment of patients across treatment groups at each site, a centralized by-site randomization scheme was utilized. Enrolled patients received either an acute treatment dosage of famciclovir + celecoxib or placebo for the first week. IMC-1 group patients subsequently received a chronic suppressive dosage of famciclovir + celecoxib for the remaining 15 weeks of the study, whereas placebo-enrolled patients remained on placebo treatment. For blinding purposes, famciclovir and celecoxib were over-encapsulated; the same filler was used for both active and placebo capsules, and active and placebo study drug supplies were identical in appearance. An early termination (ET) visit was performed for patients who discontinued study drug for any reason prior to the completion of the week 16 visit.

Acetaminophen or tramadol was utilized as a rescue for acute exacerbations of pain at the lowest possible dose and for the shortest period of time possible in accordance with the medication-approved product labeling. Tramadol usage was not allowed within 48 hours of the weeks 6 and 12 visits or within 7 days prior to the baseline or week 16 visits to avoid compromised pain assessments.

Efficacy assessments included 24-hour recall average pain score recorded on the 11-point NRS, the Revised Fibromyalgia Impact Questionnaire (FIQ-R), the Patient's Global Impression of Change (PGIC) questionnaire, the NIH Patient-Reported Outcomes Measurement Information System fatigue inventory (PROMIS fatigue-SF), the Multidimensional Fatigue Inventory (MFI), and the Beck Depression Inventory-II (BDI-II). Assessments were completed at the baseline and weeks 6, 12, and 16 clinic visits.

Outcome measures

The primary efficacy outcome was response to treatment as assessed by the change from baseline in FM pain. To assess change in FM pain, both the 24-hour recall NRS score and the 7-day recall pain score from the FIQ-R were analyzed. The methodology selected to analyze all available pain data, which was recorded at baseline and weeks 6, 12, and 16/ET, was a Mixed Model Repeated Measures (MMRM) approach with and without imputation for missing data. MMRM methodology allows analysis of all collected data and can be used with and without imputation strategies to handle missing data. The imputation method utilized for this study was a hybrid baseline observation carried forward (BOCF)/last observation carried forward (LOCF) approach to account for missing data and the reason for the data being missing.

Secondary efficacy assessments included the PGIC, FIQ-R, and pain responder analyses. A FM-specific PGIC, in which patients rated their overall change in FM from the start of the study, was implemented as an efficacy assessment at weeks 6, 12, and 16/ET. The PGIC used a scale ranging from 1 to 7 with 1="very much improved" and 7="very much worse". Responders to treatment were calculated based on the proportion of patients who responded with either "1" or "2" on the PGIC assessment. Patients who did not reach the scheduled week 16 visit and then responded "1" or "2" were considered non-responders for this analysis (BOCF analysis). The FIQ-R, a FM-specific instrument designed to assess the impact of FM on various aspects of a patient's well-being, was administered at baseline and weeks 6, 12, and 16/ET. The change from baseline in the total FIQ-R score was determined by comparing the baseline FIQ-R total score to that determined at subsequent visits. Responder analyses of the percentage of patients meeting 30% and 50% reduction in pain scored from baseline was performed utilizing both the 24-hour NRS and the 7-day pain item from the FIQ-R.

Exploratory efficacy variables included the PROMIS fatigue inventory, the MFI, and the BDI-II, all of which were administered at baseline and subsequent clinic visits. Fatigue was measured with the 8-item version of the PROMIS fatigue inventory and the 20-item MFI. Scoring of the BDI-II allowed for the identification of mild, moderate, and severe levels of

depressive symptoms and for the quantification of change in status over time.

Safety assessments

Information concerning any adverse events (AEs) reported by patients or observed by investigators or other staff was collected throughout the study, starting from the time of informed consent. Any AEs that continued at the time of discontinuation or completion of the study were followed until resolution, until the event was no longer considered clinically significant, or for at least 30 days following the patient's completion or discontinuation from the study. Clinical laboratory tests (hematology, biochemistry, HSV-1 IgG, and urinalysis) were evaluated at screening and weeks 6 and 16/ET and processed via a central laboratory. Physical examination and general safety assessments were conducted prior to randomization, and vital signs were obtained at each study visit.

Sample size

Because this was the first double-blind trial of this famciclovir + celecoxib combination, power calculations to determine sample size could only be estimated. Based on studies of other agents in a similar patient population, the sponsor elected to assume an improvement in pain scores for the combination arm of −2.4 units, compared to −1.3 for placebo. The intra-subject variability was assumed to be 1.5 and between-subject variability 2.3. Under these assumptions, the sample size necessary to reject the null hypothesis of no difference in change in mean pain scores over 16 weeks with 80% power at the 0.05 significance level was 69 subjects per arm (138 subjects total). The PRID-201 trial enrolled 143 total subjects with 102 completing the 16-week study.

Statistical analyses

All patients who received at least one dose of study medication were included in the intent-to-treat analyses. All statistical tests were performed by Premier Research using SAS Software version 9.1.

For the primary efficacy outcome measures, mean changes from baseline in pain intensity scores (24-hour recall pain NRS and 7-day recall pain from FIQ-R) were analyzed using an MMRM approach. The analysis model included the fixed categorical effects of treatment, center, weeks (6, 12, and 16), and treatment-by-week interaction, as well as the continuous fixed covariate of baseline score. Significance tests were based on least-squares mean values using a two-sided p=0.05 (two-sided 95% confidence intervals).

Secondary efficacy outcome measures were analyzed as follows:

- The PGIC responder analysis used a logistic regression model in which patients with results of "very much improved" or "much improved" at endpoint were compared to those with all other results. In this model, any patients with missing data at week 16 were considered non-responders.
- The total FIQ-R score change from baseline was analyzed by the primary MMRM analysis method.
- Pain responder analyses, used to determine the number of patients meeting 30%–50% reduction in pain, were calculated using a generalized linear regression curve fit comparing each patient's change in pain from baseline to end using the 24-hour recall NRS and 7-day recall FIQ-R pain scores.

The exploratory endpoints of PROMIS fatigue, BDI-II, FIQ-R domains, and MFI domains were also analyzed with the same MMRM approach that was applied to the primary analysis.

Results

Patient disposition

Of the 191 patients screened, 143 entered the study with random assignment to either placebo (n=74) or the IMC-1 treatment (n=69; Figure 1). Completion rates for the 16-week study were 60.8% (45 of 74) for placebo and 82.6% (57 of 69) for the IMC-1 treatment.

Patient demographics and baseline characteristics

Patient demographics and baseline clinical characteristics were comparable across both treatment groups (Table 1). The majority of patients were Caucasian (95.8%) and female (93.7%) with a mean age of ~49 years. The mean 24-hour recall NRS scores at baseline were 7.1 and 6.5 for patients randomized to placebo or IMC-1 treatment, respectively. The mean FIQ-R 7-day recall pain scores at baseline were 6.8 and 6.5 for patients randomized to placebo or IMC-1, respectively. Duration of FM symptoms ranged from <1 year to ~30 years, with a mean duration of 10 years.

Efficacy

The primary efficacy endpoint was reduction in pain from baseline and was evaluated at week 16 using the 24-hour recall NRS and 7-day recall FIQ-R pain measures (Table 2). Analysis of the 24-hour recall NRS with imputation, as well

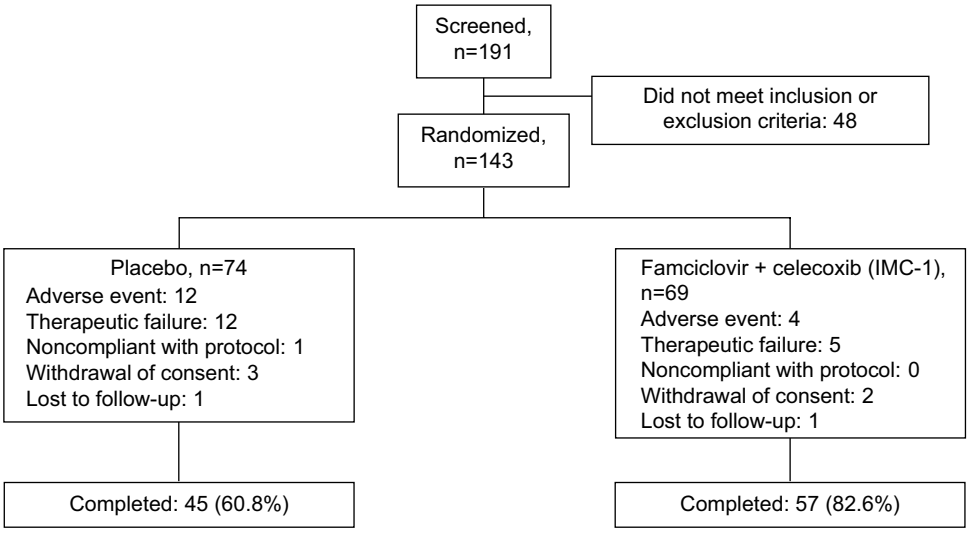

Figure 1 Distribution of patients screened and randomized to placebo or IMC-1 for the 16-week trial.

Table 1 Baseline characteristics of patients

Characteristics	Placebo (n=73)	IMC-1 (n=69)
Sex		
Female	68 (93.2%)	65 (94.2%)
Male	5 (6.8%)	4 (5.8%)
Age, mean ± SD (years)	50.5±11.68	48.1±13.71
Weight, mean ± SD (kg)	84.4±25.2	86.1±24.4
BMI, mean ± SD (kg/m^2)	31.0±9.6	31.4±8.5
ACR WPI, mean ± SD	12.9±3.31	13.5±3.36
ACR SS score, mean ± SD	8.8±1.84	8.8±1.72
ACR WPI + SS score, mean ± SD	21.7±4.20	22.4±3.96
24-hour recall NRS pain, mean ± SD	7.1±1.12	6.5±1.11
7-day recall FIQ-R pain, mean ± SD	6.8±1.43	6.5±1.57

Abbreviations: ACR, American College of Rheumatology; BMI, body mass index; FIQ-R, Revised Fibromyalgia Impact Questionnaire, NRS, Numerical Rating Scale; SD, standard deviation; SS score, symptom severity score; WPI, widespread pain index.

as the 7-day recall pain item with and without imputation showed that patients on the IMC-1 treatment experienced a statistically significant greater reduction in pain when compared with placebo. The 24-hour recall pain item, when analyzed without imputation, did not separate from placebo.

Secondary efficacy assessments included the PGIC, FIQ-R, and 30% and 50% pain responder analyses (Table 3). The PGIC can be viewed as a patient's assessment of overall benefit of therapy. Using this measure, the IMC-1 treatment group showed significant improvement over placebo with responder rates of 37.7% and 33.3% at weeks 12 and 16, respectively, versus responder rates of 17.8% and 19.2% at the same visits for the placebo group (p=0.005 and 0.040,

Table 2 Summary of analyses of primary efficacy outcomes[a]

Data analysis group	Placebo (n=73)	IMC-1 (n=69)	p-value
7-day recall FIQ-R, LOCF/BOCF imputation			
Week 16 change from baseline, mean ± SEM	−0.92±0.30	−2.2±0.30	0.001
Treatment difference, mean ± SEM		−1.25±0.38	
7-day recall FIQ-R, no imputation			
Week 16 change from baseline, mean ± SEM	−1.4±0.38	−2.5±0.34	0.016
Treatment difference, mean ± SEM		−1.1±0.47	
24-hour recall NRS, LOCF/BOCF imputation			
Week 16 change from baseline, mean ± SEM	−1.1±0.28	−1.9±0.28	0.031
Treatment difference, mean ± SEM		−0.8±0.37	
24-hour recall NRS, no imputation			
Week 16 change from baseline, mean ± SEM	−1.7±0.34	−2.0±0.31	0.379
Treatment difference, mean ± SEM		−0.4±0.43	

Notes: [a]All values for treatment difference are versus placebo.
Abbreviations: BOCF, baseline observation carried forward; FIQ-R, Revised Fibromyalgia Impact Questionnaire; LOCF, last observation carried forward; NRS, Numerical Rating Scale; SEM, standard error of the mean.

Table 3 Summary of analyses of secondary efficacy measures[a]

PGIC	Placebo		IMC-1		*p*-value
	Responders	Non-responders	Responders	Non-responders	
Week 6 (%)	14 (19.2)	59 (80.8)	26 (37.7)	43 (62.3)	0.015
Week 12 (%)	13 (17.8)	60 (82.2)	26 (37.7)	43 (62.3)	0.005
Week 16 (%)	14 (19.2)	59 (80.8)	23 (33.3)	46 (66.6)	0.040
FIQ-R total score, BOCF/LOCF imputation					
Number of patients	73		69		
Baseline, mean	56.81		54.28		
Week 6 change from baseline, mean ± SEM	−11.29±2.28		−17.74±2.39		0.033
Week 12 change from baseline, mean ± SEM	−9.53±2.35		−15.25±2.46		0.069[b]
Week 16 change from baseline, mean ± SEM	−7.87±2.33		−17.54±2.40		0.002
FIQ-R domain analysis, BOCF/LOCF imputation					
Number of patients	73		69		
Functional domain					
Baseline, mean	43.68		40.71		
Week 16 change from baseline, mean ± SEM	−5.44±2.32		−14.29±2.40		
Treatment difference, mean ± SEM			−8.85±3.03		0.004
Overall impact domain					
Baseline, mean	11.99		11.06		
Week 16 change from baseline, mean ± SEM	−1.89±0.61		−4.29±0.63		
Treatment difference, mean ± SEM			−2.40±0.79		0.003
Symptoms domain					
Baseline, mean	60.52		59.29		
Week 16 change from baseline, mean ± SEM	−7.90±2.33		−16.77±2.40		
Treatment difference, mean ± SEM			−8.88±3.06		0.004
Pain responder analysis, 30% pain reduction					
Week 6, 24-hour recall NRS (%)	31 (44.3)	39 (55.7)	32 (50.8)	31 (49.2)	0.190[b]
Week 12, 24-hour recall NRS (%)	27 (37.5)	45 (62.5)	29 (45.3)	35 (54.7)	0.190[b]
Week 16, 24-hour recall NRS (%)	23 (31.5)	50 (68.5)	28 (42.4)	38 (57.6)	0.052[b]
Week 6, 7-day recall FIQ-R pain (%)	34 (48.6)	36 (51.4)	32 (50.8)	31 (49.2)	0.652[b]
Week 12, 7-day recall FIQ-R pain (%)	25 (34.7)	47 (65.3)	34 (53.1)	30 (46.9)	0.010
Week 16, 7-day recall FIQ-R pain (%)	20 (28.2)	51 (71.8)	29 (43.9)	37 (56.1)	0.012
Pain responder analysis, 50% pain reduction					
Week 6, 24-hour recall NRS pain (%)	20 (28.6)	50 (71.4)	22 (34.9)	41 (65.1)	0.223[b]
Week 12, 24-hour recall NRS (%)	11 (15.3)	61 (84.7)	20 (31.3)	44 (68.8)	0.018
Week 16, 24-hour recall NRS (%)	11 (15.1)	62 (84.9)	20 (30.3)	46 (69.7)	0.009
Week 6, 7-day recall FIQ-R pain (%)	18 (25.7)	52 (74.3)	22 (34.9)	41 (65.1)	0.294[b]
Week 12, 7-day recall FIQ-R pain (%)	12 (16.7)	60 (83.3)	23 (35.9)	41 (64.1)	0.006
Week 16, 7-day recall FIQ-R pain (%)	12 (16.9)	59 (83.1)	25 (37.9)	41 (62.1)	0.001

Notes: [a]Except where indicated otherwise, values are the number of patients. All values for treatment difference are versus placebo. [b]Not statistically significant using the predefined testing strategy.

Abbreviations: BOCF, baseline observation carried forward; FIQ-R, Revised Fibromyalgia Impact Questionnaire; LOCF, last observation carried forward; NRS, Numerical Rating Scale; PGIC, Patient's Global Impression of Change; SEM, standard error of the mean.

respectively). The FIQ-R was designed to be a disease-specific measure of change in several domains important to FM patients. At week 16, the IMC-1 group showed a statistically significant improvement in their FM as measured by the FIQ-R total score (p=0.002), FIQ-R functional domain (p=0.004), FIQ-R overall impact domain (p=0.003), and FIQ-R symptoms domain (p=0.004). Responder analyses, used to estimate whether each patient's pain scores met/exceeded a 30% or 50% reduction from baseline, were performed using the 24-hour recall NRS and the 7-day recall FIQ-R pain scores from weeks 6, 12, and 16. A statistically significant separation between treatment groups was not observed for the 30% responder analysis using the 24-hour recall NRS pain scores. However, the higher hurdle of 50% pain reduction from baseline showed a significant separation between treatment groups with response rates of 31.3% and 30.3% for IMC-1 treatment at weeks 12 and 16, respectively, and rates of 15.3% and 15.1% for placebo at the same visits (p=0.018 and 0.009, respectively). Using the 7-day recall FIQ-R pain measure, the IMC-1 treatment group showed significantly improved 30% and 50% responder rates at weeks 12 and 16, respectively.

Table 4 Summary of analyses of exploratory efficacy outcomes[a]

Data analysis group	Placebo (n=73)	IMC-1 (n=69)	*p*-value
PROMIS fatigue			
Baseline, mean	65.83	65.55	
Week 16 change from baseline, mean ± SEM	−2.68±0.93	−6.65±0.96	
Treatment difference, mean ± SEM		−3.96±1.22	0.001
MFI total score			
Baseline, mean	70.26	71.01	
Week 16 change from baseline, mean ± SEM	−3.69±1.57	−6.90±1.45	
Treatment difference, mean ± SEM		−3.22±1.98	0.107[b]
MFI general fatigue			
Baseline, mean	16.99	17.25	
Week 16 change from baseline, mean ± SEM	−1.57±0.45	−2.31±0.41	
Treatment difference, mean ± SEM		−0.73±0.56	0.191[b]
MFI physical fatigue			
Baseline, mean	15.73	15.32	
Week 16 change from baseline, mean ± SEM	−1.07±0.45	−2.01±0.41	
Treatment difference, mean ± SEM		−1.02±0.56	0.070[b]
MFI reduced activity			
Baseline, mean	13.77	14.12	
Week 16 change from baseline, mean ± SEM	−0.77±0.54	−1.58±0.50	
Treatment difference, mean ± SEM		−0.81±0.56	0.234[b]
MFI reduced motivation			
Baseline, mean	11.78	11.46	
Week 16 change from baseline, mean ± SEM	0.36±0.33	0.22 ± 0.30	
Treatment difference, mean ± SEM		−0.14±0.42	0.746[b]
BDI-II			
Baseline, mean	12.1	13.3	
Week 6 change from baseline, mean ± SEM	−1.7±0.82	−3.3±0.87	
Week 6 treatment difference, mean ± SEM		−1.6±1.07	0.133[b]
Week 12 change from baseline, mean ± SEM	−1.2±1.02	−3.7±1.02	
Week 12 treatment difference, mean ± SEM		−2.5±1.34	0.062[b]
Week 16 change from baseline, mean ± SEM	−1.9±0.94	−4.0±0.90	
Week 16 treatment difference, mean ± SEM		−2.1±1.18	0.077[b]

Notes: [a]All values for treatment difference are versus placebo. [b]Not statistically significant using the predefined testing strategy.
Abbreviations: BDI, Beck Depression Inventory; MFI, Multidimensional Fatigue Inventory; PROMIS, Patient-Reported Outcomes Measurement Information System; SEM, standard error of the mean.

Exploratory efficacy assessments included the PROMIS fatigue inventory, the MFI, and the BDI-II (Table 4). Fatigue was measured with the PROMIS and MFI assessment instruments. The PROMIS fatigue short form, developed by the NIH PROMIS program, focuses on fatigue related to "energy levels" and was designed to assess symptom changes in populations irrespective of the underlying condition. The PROMIS fatigue scale showed a statistically significant separation between treatment groups at week 16 (p=0.001). The older MFI was designed to measure multiple aspects of fatigue including mental fatigue and motivation. None of the MFI domains was statistically significant at week 16.

The BDI-II was used as both a safety and efficacy parameter. Over the 16 weeks of the study, the IMC-1 group exhibited a 3.3–4.4 point reduction in total BDI-II score compared to a 1.2–1.9 point reduction in the placebo group, with the ranges reflecting the results using different imputation methods for missing data. Although the difference between the treatment groups was not statistically significant, the results corroborate the overall improvement observed with IMC-1 treatment.

Tolerability and safety

No deaths were reported during the study. The safety and tolerability profile for IMC-1 in this first multicenter clinical trial was encouraging, with a lower frequency of AEs and a higher completion rate in the IMC-1 group as compared to the placebo group. The difference in completion rates was driven by a nearly three-fold higher discontinuation rate in the placebo group secondary to AEs (16.4% vs. 5.8%, placebo vs. IMC-1) and therapeutic failure (17.2% vs. 6.2%, placebo vs. IMC-1). AEs reported for the IMC-1 group were less severe

than those for the placebo group with 31.9% mild, 33.3% moderate, and 7.2% severe for IMC-1 versus 19.2% mild, 42.5% moderate, and 16.4% severe for placebo.

Placebo group patients reported treatment emergent adverse events (TEAEs) in many of the Medical Dictionary for Regulatory Activities System Organ Classes more frequently than IMC-1 patients (Table 5). Interestingly, gastrointestinal (GI) TEAEs were reported by 42.5% of placebo patients, but by only 29% of IMC-1 patients. The low frequency of vascular and cardiac AEs was also encouraging given the COX-2 inhibitor component of IMC-1. Hypertension was reported in two IMC-1 patients and one placebo patient. One IMC-1 patient experienced a non-ST segment elevation myocardial infarction within a few weeks of randomization; however, this patient was discovered to have significant coronary artery disease that was considered the most important causal factor. Three placebo patients also reported cardiac AEs (angina pectoris, palpitations, and supraventricular extrasystoles).

Consistent with the known safety profile of celecoxib, there was evidence of a slightly higher frequency of TEAEs related to increase in hepatic enzymes (lactate dehydrogenase and gamma-glutamyl transferase) in the IMC-1 treatment group. Other TEAEs reported more frequently in IMC-1-treated patients also appeared consistent with the known safety profiles of celecoxib and famciclovir. Based on the results of this study, there is no evidence for any additional safety signals secondary to the combined use of celecoxib and famciclovir at the doses studied.

Discussion

The clinical evidence supporting the drug combination utilized in this study was first derived through care of the lead author's patients with irritable bowel syndrome. A number of chronic GI disorders, including IBS and reflux, are frequently comorbid with FM. IBS patients were initially treated with famciclovir, yet those also placed on celecoxib for arthritis were the patients who demonstrated a dramatic improvement. A number of these patients expressed gratitude that their fibromyalgia symptoms were also reduced with this combination therapy. This clinical experience led to the hypothesis that recurrent reactivation of a tissue-resident herpesvirus in genetically susceptible individuals could contribute to the symptoms of fibromyalgia. At the end of this 16-week trial, famciclovir + celecoxib IMC-1 treatment provided a significant improvement in FM pain as compared to placebo and as measured by the FIQ-R 7-day recall pain item and 24-hour recall pain score. The PGIC has been shown in previous FM studies to be a sensitive measure of clinical benefit. At all study visits, a statistically greater number of the IMC-1-treated patients reported meaningful improvement on the PGIC when compared to placebo-treated patients. The FIQ-R was included in the study as a key secondary endpoint as a measure of disease-specific activity of the therapy. At all follow-up visits, IMC-1-treated patients reported higher rates of improvement in the total score of the FIQ-R with the contrast at weeks 6 and 16 meeting statistical significance. Analysis of the domains that comprises the FIQ total score showed that all three individual domains were statistically

Table 5 Treatment emergent adverse events sorted by MedDRA system organ class[a]

MedDRA system organ class	Placebo, n=73 (%)	IMC-1, n=69 (%)	Total, n=142, (%)
Gastrointestinal disorders	31 (42.5)	20 (29.0)	51 (35.9)
Infections and infestations	18 (24.7)	17 (24.6)	35 (24.6)
Nervous system disorders	17 (23.3)	12 (17.4)	29 (20.4)
Musculoskeletal and connective tissue disorders	14 (19.2)	11 (15.9)	25 (17.6)
Investigations	8 (11.0)	8 (11.6)	16 (11.3)
Injury, poisoning, and procedural complications	2 (2.7)	7 (10.1)	9 (6.3)
Psychiatric disorders	4 (5.5)	7 (10.1)	11 (7.7)
Skin and subcutaneous tissue disorders	9 (12.3)	7 (10.1)	16 (11.3)
General disorders and administration site conditions	10 (13.7)	6 (8.7)	16 (11.3)
Respiratory, thoracic, and mediastinal disorders	9 (12.3)	5 (7.2)	14 (9.9)
Metabolism and nutrition disorders	2 (2.7)	4 (5.8)	6 (4.2)
Reproductive system and breast disorders	1 (1.4)	3 (4.3)	4 (2.8)
Vascular disorders	1 (1.4)	3 (4.3)	4 (2.8)
Cardiac disorders	3 (4.1)	1 (1.4)	4 (2.8)
Ear and labyrinth disorders	1 (1.4)	1 (1.4)	2 (1.4)
Eye disorders	2 (2.7)	1 (1.4)	3 (2.1)
Neoplasms benign, malignant, and unspecified	3 (4.1)	0	3 (2.1)
Renal and urinary disorders	2 (2.7)	0	2 (1.4)

Notes: [a]Values are numbers of patients (%).

significant at the primary endpoint. Strong support for the efficacy of IMC-1 was also found in the lower discontinuation rate of IMC-1 relative to placebo (17% vs. 39%), the lower rates of rescue medication usage among IMC-1-treated patients relative to placebo (25% vs. 41%), a significant reduction in fatigue as measured by the PROMIS fatigue scale, and a trend toward decreased depressive symptomatology as measured by the BDI-II.

One explanation for the promising results of this is the combination effect of the famciclovir and celecoxib components of the IMC-1 both of which act to inhibit herpesvirus infections. Famciclovir is ultimately converted to penciclovir triphosphate in herpesvirus infected cells and acts through competitive inhibition of the viral DNA polymerase and chain termination, reducing viral DNA synthesis and replication.[23] As mentioned above, many herpesviruses significantly up-regulate COX-2 and to a lesser degree COX-1. Virally-induced up-regulation of COX enzymes is important for efficient viral replication and COX inhibitors exhibit antiherpetic properties reducing both virus replication during lytic infections as well as the frequency of reactivation of latent infections.[12–21] The efficacy of this drug combination in treating multiple symptoms of fibromyalgia suggests a persistent nociceptive infection with HSV may contribute to this chronic pain syndrome in some patients. When studied alone as monotherapies in previous investigations, neither an anti-herpesvirus nucleoside analog nor a COX-2 inhibitor was found to be efficacious in the treatment of fibromyalgia,[7,24] suggesting when used in concert these two drug classes may act additively and/or synergistically, thereby increasing efficacy.

Conclusion

Virtually all outcome measures, with the exception of the 24-hour recall NRS pain item when analyzed without imputation for missing data, were statistically significant or strongly trended in favor of IMC-1 over placebo. Given the modest size of the trial, coupled with the fact that this was the first clinical evaluation of IMC-1 in a multicenter trial setting, we conclude that there is evidence of clinical efficacy for the tested famciclovir + celecoxib combination in treating the symptoms of FM.

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