Early Termination of a Trial of Mycophenolate Mofetil for Treatment of Interstitial Cystitis/Painful Bladder Syndrome: Lessons Learned

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Purpose: We evaluated the efficacy and tolerability of mycophenolate mofetil in patients with treatment refractory interstitial cystitis/painful bladder syndrome.

Materials and Methods: A total of 210 patients with interstitial cystitis/painful bladder syndrome were to be randomized into a multicenter, placebo controlled trial using a 2:1 randomization. Participants in whom at least 3 interstitial cystitis/painful bladder syndrome specific treatments had failed and who had at least moderately severe symptoms were enrolled in a 12-week treatment study. The primary study end point was the global response assessment. Secondary end points were general and disease specific symptom questionnaires, and voiding diaries.

Results: Only 58 subjects were randomized before a black box warning regarding mycophenolate mofetil safety was issued by the manufacturer in October 2007. The trial was halted, and interim analysis was performed and presented to an independent data and safety monitoring board. Six of the 39 subjects (15%) randomized at study cessation were considered responders for mycophenolate mofetil compared to 3 of 19 controls (16%, $p = 0.67$). Secondary outcome measures reflected more improvement in controls.

Conclusions: In a randomized, placebo controlled trial that was prematurely halted mycophenolate mofetil showed efficacy similar to that of placebo to treat symptoms of refractory interstitial cystitis/painful bladder syndrome. The results of this limited study cannot be used to confirm or refute the hypothesis that immunosuppressive therapy may be beneficial to at least a subgroup of patients with interstitial cystitis/painful bladder syndrome. Despite study termination lessons can be gleaned to inform future investigations.

Key Words: urinary bladder; cystitis, interstitial; fetus; drug toxicity; mycophenolate mofetil

Abbreviations and Acronyms

CyA = cyclosporine
FSFI = Female Sexual Function Index
GRA = global response assessment
IC = interstitial cystitis
MCS = Mental Component Score
MMF = mycophenolate mofetil
PBS = painful bladder syndrome
PCS = Physical Component Score

Submitted for publication June 21, 2010.

Study received institutional review board approval at all study sites.

Supported by National Institute of Diabetes and Digestive and Kidney Diseases Cooperative Agreements U01 DK65209, U01DK65255, U01DK65213, U01DK65214, U01DK65215, U01DK65178, U01DK65190, U01DK65192, U01DK65255, U01DK65267, U01DK65271 and U01DK65202.

Supplementary material for this article can be obtained at http://depts.washington.edu/uroweb/research/opentrials.html.

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† Financial interest and/or other relationship with Astellas, GlaxoSmithKline and Bayer.

‡ Financial interest and/or other relationship with Bioform, Taris/Lipella, AbbeyMoore, Pfizer and Allergan.

0022-5347/11/1853-0901/0
THE JOURNAL OF UROLOGY®

Vol. 185, 901-906, March 2011
Printed in U.S.A.
DOI:10.1016/j.juro.2010.10.053

§ Financial interest and/or other relationship with Medtronic, Boston Scientific, Uroloplasty, Johnson & Johnson, Celgene, Allergan and Pfizer.
‖ Financial interest and/or other relationship with Merck, GlaxoSmithKline, Pfizer, Ortho Women's Health, Farr Labs, Watson, Medtronic, NeurAxon, Genyous Biomed, Merck, Glaxo-Smith Kline, Allergan, Watson, Pfizer, American Medical Systems, Astellas, Ortho McNeil and Taris.
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‖‖ Financial interest and/or other relationship with Pfizer, Watson, Novartis, Proctor and Gamble, Intuitive Surgical and Elsevier.
¶¶ Financial interest and/or other relationship with deCode Genetics.

INTERSTITIAL cystitis/PBS is a syndrome characterized by debilitating pain, pressure or discomfort related to bladder filling, usually accompanied by urinary frequency to relieve pain and the urge to void. Treatments to date have been empirical and inadequate, and there remains a pressing need for an effective oral treatment for IC/PBS. To our knowledge the pathogenesis of the disorder is still undefined and a number of theories based on clinical and experimental observations have been advanced. A case for immune dysregulation in at least a subset of patients with IC/PBS can be made based on epidemiological, histopathological and clinical response criteria.[1–6]

If the etiology of IC/PBS is in part due to an induced autoimmune/inflammatory disorder, immunosuppressant therapy is a reasonable consideration for a treatment trial. Methotrexate used in a small open label study showed no significant effect on voiding patterns[7] but 2 open label trials from Finland showed that CyA produced short-term[8] and long-term[9] pain resolution, decreased frequency and increased voided volume. A subsequent randomized study suggested that CyA was well tolerated and significantly more effective than pentosan polysulfate sodium (active control)[10] for controlling symptoms in patients with severe IC/PBS. MMF is commonly used in transplant recipients as an antirejection agent combined with CyA and corticosteroids. While to our knowledge it has not been used for IC/PBS, there are many published reports of its use for inflammatory and autoimmune disorders, such as inflammatory uveitis,[11] systemic lupus erythematosis[12] and lupus nephritis,[13] and Wegener's granulomatosis.[14]

We performed a randomized, double-blind, placebo controlled clinical trial of MMF in patients with IC/PBS in whom previous therapy for this syndrome failed. The agent was chosen since it was an immunosuppressant drug with a reasonable safety profile. Also, CyA was not available for a randomized trial due to the unavailability of a placebo. Primary trial objectives were to compare 2 gm MMF daily to placebo for effects on overall IC/PBS symptoms and well-being in patients with refractory IC/PBS, and assess the medication safety profile.

METHODS

Participants and Study Design

Men and women older than 18 years were recruited from 11 urology/urogynecology clinics in the United States and Canada. All study sites obtained local institutional review board approval. Eligibility required fulfillment of all of certain criteria, including 1) persistent symptoms of urinary frequency and pain rated at least 4 on a scale of 0 to 10, 2) failure of at least 24 weeks of active treatment with a minimum of 3 standard forms of therapy or combination of therapies for IC/PBS, 3) cystoscopic diagnosis of IC/PBS in the past with findings of glomerulations and/or ulcerations, and 4) screening cystoscopy within the 24 weeks before study entry to evaluate for an unevaluated pathological condition. There were additional exclusion criteria. Except for medications listed in the exclusion criteria subjects were allowed to continue on the current medication regimen.

Eligible participants were randomized to MMF or matching placebo in a 2:1 ratio. For the first 14 days subjects were instructed to ingest 1 gm MMF by mouth daily. Subjects discontinuing the study drug during this introduction/tolerability phase were followed until the primary end point visit at 12 weeks. After successful completion of this phase the full dose phase of 2 gm daily in 2 divided doses was continued for 10 more weeks. Laboratory values, including complete blood count and liver enzymes, and physical symptoms were closely monitored for adverse events at regular intervals throughout the study. All subjects were treated and followed for up to 16 weeks after randomization, including 12 weeks of study treatment and 4 weeks after treatment. Participants who withdrew before completion of the intervention phase were asked to complete all outcome measures.

Outcome Measures

The primary efficacy outcome measure was GRA at 12 weeks. The GRA queries, "As compared to when you started the current study, how would you rate your overall pelvic symptoms now?" with 7 response categories. Participants who indicated that they were moderately or markedly improved were considered intervention responders. Participants with missing GRAs were considered nonresponders and included in the denominator to assess response rates.

Secondary measures obtained at baseline and 12 weeks included a 24-hour voiding diary, ratings of pain and frequency on a 10-point scale, and responses to validated symptom questionnaires, including the McGill Pain Questionnaire,[15] O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes,[16] SF-12® Health Status Questionnaire with separate calculation of PCS and MCS,[17] FSFI[18] or Sexual Health Inventory for Men,[19] as appropriate, and Hospital Anxiety and Depression Scale.[20]

Statistical Methods

The study was powered to detect a difference in GRA response rates between 20% for placebo to 45% for MMF,

a difference of 25%. Based on previous IC/PBS studies the placebo response was estimated at 20%.[21] To achieve 90% power to detect this 25% difference using 2:1 randomization and 2-sided p = 0.05 a minimum of 180 participants was required. Sample size was increased by 15% to account for clinical center variation, that is 210 participants, including 140 on MMF and 70 on placebo. Stratified permuted block randomization with variable block sizes by clinical site was done to ensure balance across treatment groups.

Standard descriptive statistics were used to summarize baseline characteristics and study outcome measures at each followup visit overall and in each treatment group. The balance of baseline measures across the 3 treatment groups was compared using appropriate k-sample tests, including the Kruskal-Wallis and Fisher exact tests. Primary analysis compared GRA response rates using the exact conditional test version of the Mantel-Haenszel test to control for clustering by clinical center.[22] The pooled rate difference and 95% CI across clinical centers were calculated using the metan routine in Stata®, version 10.[23] For secondary efficacy outcomes changes from baseline to 12 weeks were calculated in subjects with data at each time point, not representing intent to treat analysis. Comparisons of these changes between treatment groups are also shown as the 95% CI, which was calculated using standard normal based methods, not adjusting for clustering by clinical center.

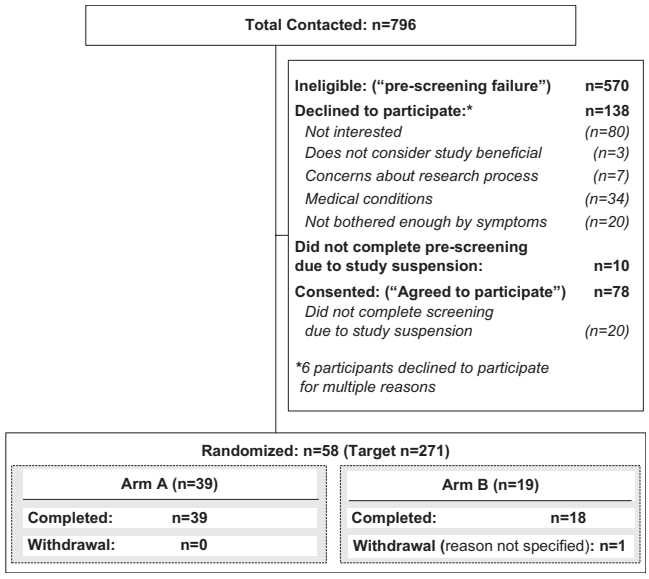
RESULTS

Study recruitment began in April 2007. A black box warning for MMF was issued by Roche Pharmaceuticals on October 31, 2007.[24] The warning addressed the change of the drug classification by the United States Food and Drug Administration from a pregnancy category C (risk of fetal harm cannot be ruled out) to category D (positive evidence of fetal risk). The manufacturer recommendation was for female subjects of child bearing potential to be contacted immediately and for all subjects to be recounseled and reconsented with specific attention to the requirements for 2 methods of effective contraceptive use beginning 4 weeks before the study, use throughout the study and for 6 weeks after stopping MMF. The black box warning also addressed the risk of susceptibility to infection and the possible development of lymphoma. As a result of these warnings, study drug delivery and all subject enrollment were suspended on November 15, 2007, to remain in place until an amended protocol and consent form were approved by the institutional review board at each study site.

Slow recruitment of study participants up to this point prompted the study data and safety monitoring board to request interim analysis in January 2008, which identified observed decreased efficacy of MMF compared to placebo. Due to a lack of treatment efficacy, increased safety concerns due to the black box warning and difficulty recruiting eligible study participants the data and safety monitoring recommended to the study sponsor (National Institute of Diabetes and Digestive and Kidney Diseases) early termination of the study. This recommendation was accepted and the study was terminated on February 4, 2008. The final analysis that we report was performed in April 2008.

The figure shows the Consolidated Standards of Reporting Trials. Table 1 lists baseline demographic data by treatment arm on all 58 randomized subjects. There were no differences in the distribution of demographic characteristics between the 2 treatment arms. Table 1 also shows select baseline symptom scores. Overall baseline symptoms were moderate to severe, that is 72% of subjects presented with severe pain (7 to 10) and 79% presented with severe frequency. Treatment groups were comparable across all baseline measures evaluated.

GRA response rates in the MMF and placebo groups were 15.4% and 15.8%, respectively (p = 0.67). Table 2 shows the CI for the difference in response rates, adjusted for center variability. The primary end point was the 12-week response rate and the secondary end point was the change from baseline to 12 weeks. Responders were considered those reporting markedly or moderately improved on GRA. Consistent with intent to treat analytic strategies participants who did not provide data at 12 weeks (only 1, who was on placebo) were considered treatment nonresponders. Given the single subject who did not complete the study, additional noncompleter analysis would not have changed the conclusions. Eight subjects on placebo and 14 on MMF were not on drug at the primary end point due to study suspension, as



Consolidated Standards of Reporting Trials diagram shows flow of subjects through study phases by treatment arm.

Table 1. *Baseline characteristics by treatment group*

	No. Subjects	MMF*	No. Subjects	Placebo*
No. female (%)		33 (85)		15 (79)
Mean ± SD age		51.3 ± 10.3		51.8 ± 11.6
No. race (%):				
White		35 (90)		17 (89)
Black		1 (3)		1 (5)
Multirace, Asian, other		3 (8)		1 (5)
No. ever diagnosed with IC/PBS (%)		38 (97)		19 (100)
Mean ± SD yrs:				
Since diagnosis, if applicable		6.4 ± 4.1		6.3 ± 5.9
Since initial symptom onset†		13.8 ± 12.0		14.4 ± 14.4
Mean ± SD Score (range 0–10):				
Pain		6.9 ± 1.5		7.2 ± 1.2
Urgency		7.1 ± 1.8		7.1 ± 1.7
Frequency‡		7.7 ± 1.4		7.4 ± 1.8
Mean ± SD IC index:				
Symptom		15.7 ± 3		15.1 ± 3
Problem		12.9 ± 3		12.8 ± 3
Mean ± SD SF-12:	38		18	
PCS		34.9 ± 10		34.8 ± 11
MCS		42.6 ± 11		38.3 ± 13
Mean ± SD total FSFI	30	14.0 ± 10	12	11.5 ± 9
Mean ± SD total McGill Pain Questionnaire	37	21.5 ± 10.4	16	21.5 ± 11.3

* Baseline symptom scores represent average of measurements made at 2 baseline visits with data missing on at most 1 subject per arm for all measures except initial symptom onset and voiding frequency.
† Data missing on 8 subjects per arm.
‡ Data missing on approximately 9 subjects per arm.

described. When these subjects were excluded from analysis, ie removed from the intent to treat process, the responder rates were 2 of 25 on MMF (8%) and 3 of 11 (27.3%) on placebo.

Table 2 also lists changes in select symptom outcomes from baseline to 12 weeks by treatment arm and provides the CI for these differences. This analysis does not strictly represent intent to treat analysis since it was based only on subjects with complete data. No comparisons for these secondary end points were statistically significant at the more stringent $p = 0.01$ typically used for statistical comparisons of secondary end points. At the primary end point 19 subjects (50%) in the treatment arm were not receiving study drug due to study suspension (14) or drug tolerability (5).

Table 3. *Significant cumulative adverse events by body system and treatment group*

	No. MMF (%)*	No. Placebo (%)*
At least 1 adverse event	34 (87)	13 (68)
Blood/bone marrow	2 (5)	1 (5)
Constitutional symptoms (primarily fatigue, malaise)	14 (36)	6 (32)
Dermatology/skin	7 (18)	3 (16)
Gastrointestinal (primarily nausea, constipation, diarrhea)	27 (69)	8 (42)
Hemorrhage	2 (5)	0
Infectious/febrile	7 (18)	2 (11)
Lymphatics	0	1 (5)
Metabolic/laboratory	4 (10)	0
Musculoskeletal	1 (3)	2 (11)
Neurological (primarily dizziness, anxiety)	8 (21)	4 (21)
Ocular, visual	2 (5)	1 (5)
Pain, primarily headache	21 (54)	11 (58)
Pulmonary	2 (5)	2 (11)
Renal/genitourinary	9 (23)	2 (11)
Sexual/reproductive function	1 (3)	1 (5)
Benign viral syndromes	2 (5)	1 (5)
Vascular	0	1 (5)

* Subject may be in more than 1 category.

Table 3 shows the cumulative numbers of participants with at least 1 adverse event subdivided by the primary body system or specific itemized categories for each treatment arm. Overall at least 1 mild, at least 1 moderate and at least 1 severe adverse event was reported by 16 (28%), 15 (26%) and 16 (28%) of the 58 study participants, respectively.

Table 2. *Primary and select secondary symptom outcomes*

	No. Subjects	MMF	No. Subjects	Placebo	% Difference (95% CI)*
No. subjects randomized/analyzed		39/39		19/18	58/57
No. primary end point (%)†		6 (15)		3 (16)	−0.5 (−32, 22)
Mean ± SD secondary end points:					
Pain score		−0.5 ± 2.0		−1.9 ± 2.1	1.4 (0.2, 2.5)
Urgency		−0.7 ± 2.0		−1.8 ± 1.9	1.1 (0.02, 2.2)
Frequency		−1.0 ± 2.1		−1.9 ± 2.1	0.9 (−0.3, 2.1)
IC Symptom Index		−0.8 ± 3		−1.8 ± 4	1.0 (−0.7, 2.6)
IC Problem Index		−0.7 ± 3		−1.7 ± 4	0.9 (−0.9, 2.7)
SF-12 PCS	37	−2.5 ± 8	17	0.6 ± 10	−3.1 (−8.2, 2.1)
SF-12 MCS	37	0.0 ± 10	17	−4.6 ± 10	4.6 (−1.3, 10.5)
Total FSFI	26	−0.9 ± 6	10	2.9 ± 6	−3.8 (−8.5, 0.9)
Total McGill Pain Questionnaire	34	−1.4 ± 8.8	14	−6.7 ± 11.4	5.4 (−0.8, 11.5)
Hospital Anxiety + Depression Scale	39	0.0 ± 6	18	−4.9 ± 7	4.9 (1.5, 8.3)

* Positive secondary end point values indicate greater improvement in placebo group.
† Patients with missing GRA were considered nonresponders and included in denominator to assess response rate using intent to treat analysis.

Thus, 47 of 58 participants (81%) reported at least 1 adverse event. There was no statistically significant difference in overall adverse event rates between the MMF and control treatment arms (87% vs 68%, $p = 0.09$). There were 2 reported serious adverse events in the treatment arm. Neither event required unmasking of treatment and each subject continued on study. One event was determined to be unrelated to treatment (narcotic withdrawal) and 1 was determined to be possibly related to treatment (asthma exacerbation).

DISCUSSION

The etiology and pathophysiology of IC/PBS remain obscure. The rationale for selecting MMF for this trial was based on evidence that immune system dysregulation/autoimmunity has a role in the perpetuation of IC/PBS symptoms. The evidence includes the age and sex distribution of patients with IC/PBS, which is similar to those of known autoimmune diseases,[25] the clinical concordance of IC/PBS with other established autoimmune diseases[26] and the efficacy of immunosuppressive drugs for IC/PBS,[7,10,27] mostly in small case series. However, scientific investigation of bladder tissue has failed to produce any strong indication that autoimmune complexes are consistently associated with IC/PBS.

Sairanen et al performed a randomized, controlled trial showing that 75% of patients responded to CyA compared to only 19% on pentosan polysulfate.[10] These compelling data led to our interest in assessing immunotherapy in a well designed, placebo controlled study. We believed that the risks of immunosuppressive therapy were outweighed by the morbidity experienced by patients with a severe albeit benign disease. We tried to perform such an investigation with CyA but were unable to have placebo pills made. Ultimately MMF was chosen based on strongly positive data presented as an abstract at a 2003 National Institutes of Health Interstitial Cystitis research meeting (unpublished data).

Unfortunately, as described, the study was interrupted by unforeseeable events and then appropriately halted due to futility analysis. It should be emphasized that 19 of the 39 subjects randomized to the study drug were not receiving it at the primary end point, including 14 due to study suspension, strongly biasing the study toward a negative result and limiting the interpretation of tolerability and other data related to drug ingestion. However, results in aggregate do not indicate that further investigation of the specific drug MMF would be fruitful.

What lessons can we take away from this effort that will inform future investigators? 1) MMF was reasonably well tolerated. Risks of immunosuppressive therapy include general risks of cytopenia, infection and promotion of malignancy as well as specific risks unique to individual drugs. Overall 87% of subjects on the active agent experienced an adverse event compared to 68% on placebo with grade 3 adverse events in 31% vs 21%. There were no grade 3 infectious events and no significant cytopenia. These data suggest that further research in immunosuppressive therapy is reasonably safe with a need for specific precautions related to the drug to be studied. Notably long-term risks, such as malignancy, cannot be assessed in a short-term trial.

2) Recruitment was difficult. A much higher proportion of interested and otherwise eligible patients were excluded from study than in other randomized trials for IC/PBS. This was primarily due to the exclusion criteria mandated for prior malignancies or premalignant conditions, including cervical dysplasia, colon polyps and any skin cancer, including basal cell cancer. Projected risks were largely based on experience with these drugs in the transplant community, in which triple therapy including steroids is standard. There are inadequate data on the risk of immunosuppressive agents as monotherapy. It is conceivable that risks to subjects who receive monotherapy are much less. Our experience suggests that it will continue to be difficult to investigate immunosuppressive therapy until other studies of the drugs used as monotherapy allow for relaxed exclusion criteria.

3) The rationale for selecting MMF was based on less than solid reasoning. Although an immunosuppressant agent (CyA) was effective for IC/PBS symptoms, it does not necessarily follow that another immunosuppressant drug (MMF) would also be effective. CyA and MMF inhibit T-cell function but through different mechanisms.[28] Immunosuppression medications have multiple immune and nonimmune effects, which are not all defined for each agent. There is no compelling evidence that IC is a purely T-cell mediated condition and, thus, the immunosuppressant mechanism(s) of MMF may not be effective for IC/PBS. However, although MMF is not the ideal agent for IC/PBS, this should not preclude future trials of other immunosuppressant medications.

CONCLUSIONS

In a multicenter, randomized, placebo controlled trial that was prematurely halted MMF showed efficacy similar to that of placebo to treat refractory IC/PBS symptoms. The results of this limited study cannot be used to confirm or refute the hypothesis that immunosuppressive therapy may be beneficial to at least a subgroup of patients with IC/PBS. Despite the study termination lessons can be gleaned to inform future investigations.

APPENDIX

Study Group Participants

In addition to the authors, the Interstitial Cystitis Collaborative Research Network Study Group includes the following institutions and individuals: Robert Mayer, Edward Messing, Elizabeth Betty Smith, Kay Rust and Jay Reeder, University of Rochester (8 subjects randomized at center); Eleanor Anton, Cheryl Wolfert and Loni Lampkins, William Beaumont Hospital (8); Alvaro Morales, Laurel Emerson, Lesley Carr, Joseph Downey, Janet Clark-Pereira and Sylvia Robb, Queen's University (7); Rajesh Shinghal, Rodney Anderson, Debra Clay and Anna Ramakrishnan, Stanford University (7); Linda Brubaker, Judy Senka, Lucia Radukanu, Janet Rindels and Grace Bucher, Loyola University Medical Center (6); Diane K. Newman, Sylvia Salazar, Jennifer Milado and Gia Deleon, University of Pennsylvania (6); Susan Keay, Rosanna Dinh, Rupali Sangrampurkar, Judith Murray and Lisa Radebaugh, University of Maryland (4); Michael O'Donnell, Susan Lutgendorf, Mary Eno and Kelly O'Berry, University of Iowa (4); Jane Miller, Jean Kalhoff, Sharon Downing and Robert F. Bale, Jr., University of Washington (3); Charles Nager and Marianne Chenoweth, University of California-San Diego (3); Kandis Rivers, Samina Romero, Michelle Peabody and Jill Sullivan, Henry Ford Hospital (2); Keith Mickelberg, Ted Barrell, Shannon Chuai and Rosemary Madigan, Data Coordinating Center, University of Pennsylvania School of Medicine; Christopher Mullins and Mary Harris, National Institute of Diabetes and Digestive and Kidney Diseases; and Vickie Ratner, Interstitial Cystitis Association.

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