Background: Nonadherence with asthma therapy is common and may contribute to poor clinical outcomes. Objective: To examine the effect of dosing frequency and mode of delivery of therapy on adherence and clinical outcomes. Methods: We examined adherence in patients with mild persistent asthma (15-85 years) enrolled in a randomized study of montelukast (10 mg once daily) or fluticasone (88 µg, 2 puffs twice daily) during a 12-week double-blind treatment period (DB), followed by a 36-week open-label trial (OL). Adherence was monitored using eDEM for montelukast/placebo and MDI Log devices for fluticasone/placebo. Results: Participants used at least 1 puff of inhaled therapy on 83.3% DB/76.8% OL of days (P < .0001). Subjects used inhaled therapy less than prescribed on 49.5%/57.5% of days, compared with 22.5%/28.6% of days for oral therapy (P < .0001). In the DB, a dose-response relationship was observed with fluticasone and asthma rescue-free days (P = .02) and FEV₁ percent predicted (P < .01) only for patients with FEV₁ ≤ 86%. In the OL period, a dose-response relationship was observed with fluticasone and FEV₁ percent predicted (P < .001).

Conclusion: Whereas subjects were more likely to use inhaled fluticasone/placebo at least once a day, subjects were more likely to take once-daily oral montelukast/placebo as prescribed. Clinical outcomes were inconsistently associated with adherence levels.

Clinical implications: Patients were less likely to be fully adherent with twice-daily therapy than with once-daily therapy, but most still achieved adequate asthma control.

Key words: Adherence, compliance, dose-response, mild persistent asthma, leukotriene receptor antagonist, montelukast, inhaled corticosteroids, fluticasone, clinical trial

The clinical effectiveness of any asthma therapy is based on both the pharmacologic properties of the therapy and patient adherence to therapy. Characteristics of the asthma therapy regimen, including mode of delivery and dosing frequency, may influence patient adherence to therapy.1 Simpler therapies are often suggested to offer an adherence advantage; however, the evidence for this recommendation is limited.2-7 In addition, the effect of regimen characteristics on adherence has frequently been limited by inadequate or invalid adherence measurement strategies8 and confounded by patient self-selection of therapy. Evaluating the independent contribution of regimen characteristics to adherence with therapy therefore requires both random assignment to therapies and precise adherence measurement strategies.

A further question is the absolute benefit of regimen characteristics on the therapeutic dose-response relationship between treatment and clinical outcomes. Simpler therapies might enhance overall adherence; however, some researchers have suggested that the clinical consequences of missed doses for once-daily therapy may be greater than that for therapies with twice-daily or greater dosing.9,10 Alternatively, if once-daily therapy enhances adherence with therapy, then the resulting improved effectiveness of such regimens may improve clinical outcomes compared with therapies with higher efficacy but lower patient adherence.

To evaluate the effect of regimen characteristics on patient adherence with asthma therapy and dose-response
relationships, we conducted an ancillary study within the Mild Asthma Montelukast Versus Inhaled Corticosteroid Trial (MIAMI).\textsuperscript{11} MIAMI was a randomized, parallel-group study that was designed to compare the effects of the leukotriene receptor antagonist montelukast and the inhaled corticosteroid fluticasone in patients with mild persistent asthma during a 12-week double-blind, placebo-controlled treatment period (DB) followed by a 36-week open-label period (OL).\textsuperscript{12} MIAMI reported that in patients with mild persistent asthma, rescue-free days (RFDs) and most asthma control measures, except for lung function and nighttime awakenings, improved similarly with fluticasone or montelukast over the short term, but with prolonged open-label treatment, asthma control improved more with fluticasone. Improved asthma control with fluticasone appeared to occur in those with decreased lung function and greater albuterol use at baseline. In the remaining patients, the 2 treatments appeared to be comparable. Patient adherence with both inhaled and oral therapies in MIAMI was measured by using electronic medication monitors. The current study design is unique in that it objectively compares adherence with 2 distinct asthma medication regimens within the same individual.

METHODS

Recruitment and eligibility

Institutional review boards at each study site (n = 39) approved the study protocol. Patients or guardians gave written informed consent before enrollment, and adolescents gave their assent. Patients age 15 to 85 years with symptoms and albuterol use consistent with mild persistent asthma for at least 4 months on the basis of the National Asthma Education Prevention Program\textsuperscript{13} and Global Initiative for Asthma\textsuperscript{14} definitions were recruited as detailed elsewhere.\textsuperscript{12} Participants were excluded if they had used other asthma controller medications or systemic corticosteroids within the past month or required recent hospital or urgent care for asthma.

Study design

MIAMI was a randomized, 2-part, parallel-group multicenter study that compared the effects of oral montelukast and inhaled fluticasone in patients with mild persistent asthma.\textsuperscript{12} During the DB, patients received either oral montelukast (10 mg once daily at night) and placebo for inhaled fluticasone or inhaled fluticasone (88 \textmu g twice daily by metered dose inhaler [MDI]) and placebo for oral montelukast (Fig 1). During the 36-week OL, 90% of patients remained on the same active therapy received in the DB, and 10% of patients (determined at randomization) switched therapies to preserve the masking in the preceding period. Placebos were not used during the OL. The primary endpoint of the main study was percentage of RFD, defined as a day in which there was no inhaled albuterol or oral corticosteroid use and no rescue clinical care, including unscheduled asthma care in the office, urgent care center, emergency department, or hospital.

Electronic adherence measures

Adherence with study medications and \( \beta_2 \)-agonist use were monitored by using an electronic Drug Exposure Monitor (eDEM) (APREX, Union City, Calif) for oral montelukast and MDILog devices (Medtrac Technologies, Lakewood, Colo) for inhaled fluticasone and albuterol. The MDILog compliance monitor records the date and time of each inhalation as well as the patient technique for inhaling. These units can record up to 1320 events, enough for several months of use at a time. The eDEM is a pill bottle equipped with a special cap that includes an electronic microchip that stores the date and time of each opening of the bottle. Both the MDILog device and the eDEM have demonstrated reliability and validity and have been widely used in clinical trial research.\textsuperscript{15}

Data analysis

All randomized patients who received at least 1 dose of therapy and had a minimum of 21 days of data available were included in the adherence analysis. Adherence with therapy was calculated as a percentage of all available days in the period (there was no imputation of missing data or weighting of available data); therefore, adherence data reflect individual values rather than person-days. Mean percent prescribed adherence was calculated by averaging across days for each subject, and then the average adherence per subject was averaged across subjects, over all days of the relevant time period (week 0-12 or week 13-48). Less than prescribed adherence for fluticasone/placebo (inhaled) was defined as fewer than 2 sets of use (2 or more puffs with 3 or more hours between sets) in 24 hours. Less than prescribed adherence for montelukast/placebo (oral) was defined as 0 pill bottle openings in 24 hours. Comparisons for less than prescribed use between drugs were assessed using the Wilcoxon signed-rank test.

Only participants with both valid oral and inhaled data during the DB were included in the analyses of daytime and evening use. Daytime (AM) use was defined as \( \geq 2 \) puffs (inhaled) or \( \geq 1 \) bottle opening (oral) between 3 AM and 2:59 PM, and evening (PM) use was defined similarly as occurring between 3 PM and 2:59 AM. Associations for AM/PM use between drugs were assessed using the Wilcoxon signed-rank test. To determine the overall mean patterns of use, the percentage of days of each pattern were calculated per participant and then averaged across participants.

The relations between the change in outcomes from baseline to the end of the DB and the mean percent prescribed adherence (amount taken/amount prescribed) were examined using simple linear regression. Subgroup analyses were not specified post hoc, and all \( P \) values are presented uncorrected for multiple comparisons. Analyses were performed using statistical software (STATA version 9.1; Stata Corp, College Station, Tex). Significance was set at \( P < .05 \), 2-tailed.

RESULTS

Patient demographics

Three hundred eighty patients were randomized to masked treatment with montelukast (\( N = 191 \)) or fluticasone (\( N = 189 \)). Patient accounting, presented elsewhere,\textsuperscript{12} noted the groups were well balanced for all baseline parameters. Patients were predominately female (69.5\%), white (80.8\%), young (mean age, 35.2 \( \pm \) 14.3 years), and atopic (79.6\%). Mean baseline asthma severity characteristics were consistent with asthma treatment guideline definitions.
of mild persistent disease and have been previously described in detail.\textsuperscript{11,12} Three hundred fifty participants (92\%) completed the DB and continued into the OL, and 289 (83\%) of these patients completed the study.

**Electronic medication data completion**

The completeness of electronic medication monitoring can be influenced by device failure and lost or missing devices. Three hundred forty-six participants had both MDILog and eDEM data available for the DB, and 336 participants had MDILog and eDEM data during the OL. The percentage of participants who were excluded because of fewer than 21 days electronic data were as follows: MDILog DB, 7.8\%; eDEM DB, 5.2\%; MDILog OL, 2.3\%; eDEM OL, 5.6\%. Overall rates of device failure were 14.7\% for MDILog devices and 2.2\% for eDEM devices. Overall rates of missing devices were 1.6\% for MDILog devices and 1.3\% for eDEM devices. Consistent with the mean differences in missing data, MDILog data reflected a wider range of missingness than did eDEM data (days of available adherence data: eDEM DB, n = 346; median (interquartile range [IQR]), 82 (80, 87) days; MDILog DB, n = 346; median (IQR), 82 (50, 84) days; P < .0001; eDEM OL, n = 167; median (IQR), 245 (213, 255) days; MDILog OL, n = 169; median (IQR), 235 (144, 250) days; P = .01). These rates are consistent with previous studies examining the respective reliability and failure rates of MDILog and eDEM devices.\textsuperscript{16-19} When electronic data were missing, adherence rates were calculated on the basis of available data. Participants with complete MDILog electronic data had significantly higher adherence than those with partially missing MDILog data (n = 20) in the DB (77.9\% any use vs 62.9\% any use; P = .04). Likewise, during the OL, participants with complete eDEM data had significantly higher adherence than those with partially missing eDEM data (N = 17; 74.0\% prescribed use vs 48.9\% prescribed use; P = .002).

**Subject adherence with inhaled and oral therapy: DB**

Among subjects with both inhaled and oral adherence data, mean percent prescribed adherence during the 12-week DB of the study was 70.2\% (SD = 22.8\%) for inhaled therapy and 77.5\% (SD = 21.4\%) for oral therapy (P < .0001). Subjects used at least 1 puff of inhaled therapy on 83.3\% of days during the DB and at least 1 dose of oral therapy on 77.5\% of days (P < .0001). However, during the same period, participants used twice-daily inhaled therapy less than prescribed on 49.5\% (SD = 26.4\%) of the days compared with less than prescribed use of once-daily oral therapy on 22.5\% (SD = 21.4\%) of days (P < .0001). Participants used their inhaled therapy 3 sets or more on 1.2\% (SD = 1.9\%) of days and took more than 1 dose of oral therapy on 6.5\% (SD = 6.9\%) of days (P < .0001). Participants were less likely to have a no-use day for twice-daily inhaled therapy than for once-daily oral therapy (16.7\% inhaled vs 22.5\% oral; P < .0001; Table 1).

**Subject adherence with inhaled and oral therapy: OL**

Mean percent prescribed adherence during the 36-week OL of the study was 63.9\% (SD = 25.9\%) for inhaled therapy and 71.4\% (SD = 25.6\%) for oral therapy (P = .001). During the OL, subjects receiving inhaled therapy used at least 1 puff on 76.8\% of days, and those receiving oral therapy recorded at least 1 opening on 71.4\% of days (P = .0002). Participants used inhaled therapy less than prescribed on 57.5\% (SD = 28.0\%) of days compared


Health care education, delivery, and quality
TABLE I. Patterns of use of inhaled therapy and oral therapy during the DB and OL (day starts at 03:00:00; day ends at 02:59:59; sets are at least 3 hours apart)

<table>
<thead>
<tr>
<th>Use</th>
<th>Inhaled therapy (fluticasone/placebo)</th>
<th>Oral therapy (montelukast/placebo)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean % of days (SD%)</td>
<td>Mean % of days (SD%)</td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>16.7 (22.9)</td>
<td>22.5 (21.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Any use</td>
<td>83.3 (22.9)</td>
<td>77.5 (21.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Underuse</td>
<td>32.8 (16.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As prescribed use</td>
<td>49.3 (26.0)</td>
<td>71.0 (22.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Overuse</td>
<td>1.2 (1.9)</td>
<td>6.5 (6.5)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Open-label trial (n = 336)

<table>
<thead>
<tr>
<th>Use</th>
<th>Inhaled therapy (fluticasone, n = 169)</th>
<th>Oral therapy (montelukast, n = 167)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean % of days (SD%)</td>
<td>Mean % of days (SD%)</td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>23.2 (26.6)</td>
<td>28.6 (25.6)</td>
<td>.0002</td>
</tr>
<tr>
<td>Any use</td>
<td>76.8 (26.6)</td>
<td>71.4 (25.6)</td>
<td>.0002</td>
</tr>
<tr>
<td>Underuse</td>
<td>34.3 (16.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As prescribed use</td>
<td>41.3 (27.5)</td>
<td>63.8 (25.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Overuse</td>
<td>1.2 (1.8)</td>
<td>7.6 (7.3)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*p values were calculated using the Wilcoxon signed-rank test.

with less than prescribed use of oral therapy on 28.6% (SD = 25.6%) of days (P < .0001). Participants used their inhaled therapy 3 sets or more on 1.2% (SD = 1.8%) of days and took more than 1 dose of oral therapy on 7.6% (SD = 7.3%) of days (P < .0001). Participants were less likely to have a no-use day for twice-daily inhaled therapy than for once-daily oral therapy (23.2% inhaled vs 28.6% oral; P < .0001; Table I).

Dose-response relationship between active treatment and study outcomes: DB

We examined the relationship between adherence with active inhaled or oral study drug (fluticasone or montelukast, respectively) during the DB and the following MIAMI study outcomes: change in FEV1 percent predicted, change in percent asthma RFD, and nighttime symptoms. No significant relationships were observed between mean percent prescribed adherence and change in any of these outcomes for either fluticasone or montelukast. However, among participants with a baseline FEV1 percent predicted ≤86% (lowest quartile), higher adherents to fluticasone had a larger change in FEV1 percent predicted (P < .01; Fig 2, A) and a larger change in %RFD (P = .02; Fig 2, B). Similarly, among participants with baseline β2-agonist use >4 days/wk (highest quartile), higher adherents to fluticasone had a larger change in FEV1 percent predicted (P < .01).

Dose-response relationship between active treatment and study outcomes: OL

Participants’ mean percent prescribed adherence with fluticasone during the OL was positively associated with change in FEV1 percent predicted for all participants (P < .001; Fig 3, A), but not significantly associated with change in %RFD (Fig 3, B) or change in nighttime symptoms (data not shown). As was seen in the DB, among participants with a baseline FEV1 percent predicted ≤86% (lowest quartile), higher adherence to fluticasone was also associated with a larger change in %RFD (P = .02).

Participants’ mean percent prescribed adherence with montelukast during the OL of the trial was not associated with change in FEV1 percent predicted, change in %RFD, or change in nighttime symptoms. However, among participants with higher baseline use of rescue medication, greater adherence to montelukast was associated with a larger change in FEV1 percent predicted (P < .03). Conversely, among those participants with baseline β2-agonist use >4 days/wk, greater adherence with montelukast was associated with a larger change in nighttime symptoms (P = .03).

DISCUSSION

We examined adherence to once-daily oral montelukast/placebo compared with adherence with twice-daily inhaled fluticasone/placebo in the same individuals and found that participants were slightly more likely to take at least 1 daily dose of their twice-daily inhaled medication than to take their once-daily dose of oral medication. However, participants were more likely to take the twice-daily inhaled therapy less than prescribed compared with once-daily oral therapy. In fact, inhaled therapy was used as a once-daily medication approximately 1/3 of the time.

The moderate to fair levels of adherence observed in this trial are noteworthy when one considers that patients enrolled in clinical trials typically represent the best-case scenario for patient adherence. Nonetheless, regardless of form of therapy, average adherence during this study was less than prescribed, with adherence during the first 12 weeks averaging 77.5% for oral therapy and 70.2% for inhaled therapy and decreasing to 71.4% for oral and 63.9% for inhaled therapy in the 36-week OL. The premise that simplified asthma medication regimens and
Dosing schedules should contribute to better adherence has been widely proposed; however, only a few studies have directly examined this question. Several studies based on pharmacy database review have suggested that adherence with once-daily montelukast is significantly better than with twice-daily fluticasone.\textsuperscript{7,20} Pharmacy-based studies such as these, however, have a number of methodologic limitations for assessing the adherence-related properties of adherence-related properties.

![FIG 2. Dose-response relationship between active treatment and study outcomes: DB. Line graphs showing the results of the regression analysis for change in FEV1 percent predicted (A) and change in percentage of asthma RFDs (%RFD) with adherence to fluticasone or montelukast (B) for patients with baseline FEV1 percent predicted <86%, >86%, and for all participants.](image-url)
of therapies. For example, patients may not consume filled prescriptions, and patient/provider preference will influence the selection of therapies. The current randomized study provides a more methodologically rigorous examination of patients’ adherence patterns to once-daily oral montelukast/placebo compared with twice-daily inhaled fluticasone/placebo because adherence to both therapies was electronically monitored within the same

**FIG 3.** Dose-response relationship between active treatment and study outcomes: OL. Line graphs showing the results of the regression analysis for change in FEV₁ percent predicted (A) and change in percentage of asthma RFDs (%RFD) with adherence to fluticasone or montelukast (B) for patients with baseline FEV₁ percent predicted ≤86%, >86%, and for all participants.
patient. Similar to studies by Stoloff et al and Sherman et al, we observed that participants on once-daily oral montelukast/placebo had significantly better mean prescribed adherence with therapy than patients taking twice-daily inhaled fluticasone/placebo therapy. However, participants were less likely to have a no-use day with twice-daily inhaled fluticasone/placebo therapy than with once-daily oral montelukast/placebo (16.7% vs 22.5%, DB; 23.2% vs 28.6%, OL).

A unique feature of the study design was the fact that participants transitioned from the 12-week DB in which they took 2 different forms of therapy into a 36-week OL in which they continued on only 1 randomly assigned active therapy. Thus, for all participants, regardless of treatment assignment, the prescribed regimen was simplified in the 36-week OL compared with the 12-week DB. Less than prescribed patient adherence increased for both therapies in the OL (22.5% oral vs 49.5% inhaled, DB; 28.6% oral vs 57.5% inhaled, OL). Although this increase in nonadherence may be attributable to a number of factors, including less frequent study contacts, it also highlights that regimen simplification alone is not sufficient to improve adherence.

Although once-a-day therapy may offer some advantages in achieving higher overall levels of adherence, our study suggests that once-daily montelukast was also associated with more days of no use. When patients miss the evening window for taking their montelukast, they potentially will have a 24-hour window without therapeutic drug coverage, which Urquhart1,10 has suggested may be more problematic than underdosing. However, we speculated that patients who missed evening doses might take make-up doses in the morning, and further analysis found that 50% of all overuse days for montelukast/placebo occurred the morning after a no-use day (data not shown). Thus, true therapeutic coverage for montelukast was likely greater than indicated by the number of no-use days.

Although the presumed benefit of increased adherence with asthma therapy is improved clinical outcomes, for the majority of subjects in this study, variations in adherence with therapy did not influence most indices of asthma control. Among patients with milder asthma (baseline FEV1 >86%), we observed no dose-response relationship between level of adherence with either fluticasone or montelukast and measures of daytime and nighttime symptoms, FEV1, improved quality of life, and number of symptom-free days during the DB. Only for subjects with less mild disease (baseline FEV1 ≤ 86%) taking fluticasone did we observe any relationship between adherence level and study outcomes. Among these subjects, greater adherence with fluticasone was associated with improved asthma control, as measured by change from baseline %RFD and FEV1 percent predicted. These adherence results are consistent with findings of MIAMI overall, which showed in post hoc analyses that, among subjects with milder asthma, montelukast and fluticasone provided comparable asthma control.12 However, for MIAMI subjects with less mild disease at baseline (FEV1 ≤ 86% or albuterol >4 days per week), taking fluticasone was associated with significantly better symptom control as measured by %RFD and improvement in FEV1 percent predicted compared with those of similar severity taking montelukast.12

During the OL, when overall participant adherence decreased markedly and there was greater variability in adherence, a dose-response relationship for fluticasone and change in FEV1 percent predicted was observed for all participants, not just those with less mild disease. No overall dose-response relationships were observed for montelukast during the OL. The absence of a dose-response relationship between study outcomes and level of adherence among mild patients during the DB of the trial may be attributable to several factors. Overall subject adherence in the first 12 weeks of the study, although imperfect, may have been sufficient to achieve maximum therapeutic benefit in mild patients, resulting in a ceiling effect. In fact, even when mild subjects took only half of the prescribed dosage of fluticasone or montelukast, their study outcomes were not different from more adherent subjects, suggesting that many mild patients may achieve asthma control on lower dosages than standard prescriptions of fluticasone and montelukast. A recent study by Boushey et al concluded that patients with mild intermittent asthma may achieve adequate asthma control with intermittent inhaled corticosteroid therapy. It is therefore reasonable to assume that, for some participants, less than prescribed use of therapy was nonetheless sufficient to meet their asthma control goals.

We considered the possibility that patient adherence during the trial might be mediated by baseline level of asthma severity; however, in subsequent analysis (not shown), we saw no relationship between baseline level of severity or control (as measured by baseline FEV1, β2-agonist use, or symptoms) and subsequent adherence during the trial. The fact that a dose-response relationship was observed between study outcomes and fluticasone (but not montelukast) for patients with less mild disease is consistent with this explanation.

A number of limitations should be considered when evaluating the results of this study. Electronic medication adherence data for inhaled fluticasone/placebo was missing for more than a quarter of the participants, whereas electronic data for oral montelukast/placebo was nearly complete. Although these differential failure rates are consistent with the literature on the relative reliability of the different devices,15-19 the differences in missing data might influence the study findings. Participants with missing MDILog data tended to have lower average adherence; thus, missing data from these participants might have resulted in an overestimation of the true average adherence with inhaled fluticasone/placebo during the DB. However, because no significant difference was observed in average inhaled fluticasone/placebo adherence between those with and without missing data during the OL, it is unlikely that the adherence differences observed during this time were a result of missing data. It is also possible that missing data might have contributed to an underestimation of the true dose-response relationship for fluticasone during the DB. However, because electronic data was virtually
complete for oral montelukast/placebo, the estimations for both average adherence and dose-response relationships for montelukast are not likely to be influenced by missing data. To assess further the effect of missing data on study outcomes, we conducted a sensitivity analysis in which we examined the effect of a range of values (0% to 100% adherence) for missing data. Results of this sensitivity analysis indicated that the relationship between adherence and study outcomes presented in this study were robust across a wide range of imputed values (data not shown). Nonetheless, the absence of complete adherence data for all participants in both treatment groups limits the conclusions of this study. Because adherence estimations in this study are based on participants enrolled in a clinical trial, they may not reflect the typical adherence of patients in the community. In fact, studies suggest that average adherence with both fluticasone and montelukast is considerably lower in clinical practice.7,20 In addition, the characteristics of the study population (ie, predominantly young, white women with mild persistent asthma) and the duration of the study limit the generalizability of the conclusions.

In conclusion, our study found that patients were less likely to be fully adherent with twice-daily therapy than with once-daily therapy. Our results confirm past observations that patient adherence with controller therapy is often much less than prescribed; however, our findings further suggest that many patients with mild persistent asthma may achieve adequate asthma control with adherence levels and/or dosing levels of either fluticasone or montelukast lower than those generally prescribed.

The following are members of the MIAMI Study Research Group Steering Committee: James W. Baker, MD; Steven Bird, MS; John C. Carl, MD; Jonathan Corren, MD; Jonathan Edelman, MD; Kathleen Harden, RN; Michael S. Kaplan, MD; Guillermo R. Mendoza, MD; David S. Pearlman, MD; Cynthia Rand, PhD; Michael Schatz, MD; Robert Zeiger, MD, PhD. We also acknowledge the Medical Program Coordinator, Elizabeth Desrosiers. We thank Dr Bruce Bender for his helpful comments on the data analysis and manuscript.

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