Effective Initial and Long-Term Prednisone in Doses of Less Than 5 Mg/Day to Treat Rheumatoid Arthritis
Documentation Using a Patient Self-Report Multidimensional Health Assessment Questionnaire (MDHAQ)

Theodore Pincus, M.D., and Isabel Castrejón, M.D.

Abstract
The efficacy of initial and long-term prednisone < 5 mg/day in treatment of rheumatoid arthritis (RA) by one academic rheumatologist over 25 years from 1980 to 2004 is summarized. Patient responses were assessed using a multidimensional health assessment questionnaire (MDHAQ), completed by all patients at all visits in the infrastructure of care. A database was maintained of all visits, which included medications and scores for physical function, pain, patient global estimate of status, and routine assessment of patient index data (RAPID3), an index of these 3 measures. Prednisone doses were higher in patients with more severe MDHAQ/RAPID3 scores, as expected, although formal criteria were not used to determine the initial dose. Similar improvements were seen in clinical status over 12 months in patients treated with < 5 vs ≥ 5 mg/day prednisone and maintained for > 8 years. Adverse effects were primarily bruising and skin-thinning; levels of hypertension, diabetes, and cataracts were not higher than expected, including in 148 patients monitored over > 4 years, 75 over > 8 years. Prednisone at initial and long-term doses of < 5 mg/day appears acceptable and effective for many patients with RA at this time, although further clinical trials and long-term observational studies are needed to optimize treatment of patients with RA with low-dose prednisone. The data also illustrate that MDHAQ scores in usual clinical care can be used to document results of therapy over long periods with no extra work for the physician.

Systemic glucocorticoids have long been recommended in RA primarily as “bridging therapy” while awaiting anticipated benefits of disease modifying anti-rheumatic drugs (DMARDs) or for acute severe disease flares or life-threatening vasculitis, even in recent EULAR guidelines. Nonetheless, prednisone or prednisolone is prescribed for long periods of time by many rheumatologists for RA in usual care clinical settings. For example, in the international database of the Quantitative Clinical Assessment of Patients with Rheumatoid Arthritis (QUEST-RA) study, among 4,363 RA patients seen in usual care at 48 clinical sites (approximately 100 patients per site) in 15 countries, 66% of patients were taking glucocorticoids.2

The efficacy of low-dose prednisone has been documented in 7 double-blind clinical trials since 1995,3-9 defined in the studies as 10 mg/day or less, although it has been suggested that “low-dose” might be defined as 5 mg/day or less.10 A withdrawal clinical trial in RA patients documented clinical efficacy of prednisone in doses of 3 mg/day compared to placebo.10 Disease-modifying properties of 5 to 7.5 mg/day prednisone,3,7,8 confirmed in meta-analyses,11,12 are of particular interest, as long-term doses of 10 mg/day are associated with bone loss13 and higher mortality rates.14,15 Doses of 5 mg/day or less of prednisone do not induce suppression of the hypothalamic-pituitary-adrenal axis in most patients16-19 and are associated with few adverse events.20

In 1949 when glucocorticoids were introduced to clinical medicine by Hench and colleagues in a published report21 as well as dramatic motion pictures, neither clinical trials nor dose-response studies were required for registration of a new therapy to be marketed to physicians for patient care. That may explain in part why prednisone was used in higher than optimal doses for many years. Nonetheless, clinical trials also have many limitations, including patient selection, inflexible dosage schedules, reporting of results in
groups which may not apply to all individual patients, and many others.\textsuperscript{22,23} Perhaps the most important limitation of clinical trials in chronic diseases involves a relatively short time frame to recognize differences as well as adverse events over 5 years or longer. Therefore, the experience of one rheumatologist (TP) over 25 years concerning treatments of RA patients with prednisone (usually in doses < 5 mg/day in recent years with concomitant methotrexate) between 1980 and 2004 at weekly academic clinical setting, appears of interest to the rheumatology community regarding long-term efficacy and safety.

All visits of all patients over this period were entered into a database, which included medications and scores on a multidimensional health assessment questionnaire (MDHAQ) for functional status and pain. RAPID3, an index of three RA core data measures for physical function, pain, and patient global estimate\textsuperscript{24} on the MDHAQ, was calculated at all patients seen after 1995, when patient global estimate was added to the MDHAQ.\textsuperscript{25} RAPID3-EST, a surrogate for RAPID3 that includes only physical function and pain but is correlated with RAPID3 at rho > 0.9, was calculated on all patients as well, as it was the only self-report index available in patients seen prior to 1995. MDHAQ data allowed recognition of clinical improvement, as well as self-report of possible adverse effects, queried at each visit of low-dose < 5 mg initial and long-term prednisone, as summarized below.

### Decline of Mean Initial Prednisone Dose from 1980 to 1985 to 3.6 mg/day in 2000 to 2004

The mean initial prednisone dose in 308 patients with RA treated between 1980 and 2004 in 5-year periods was 10.3, 6.5, 5.1, 4.1, and 3.6 mg/day in 1980 to 1984, 1985 to 1989, 1990 to 1994, 1995 to 1999, and 2000 to 2004, respectively (Table 1). The proportion of patients whose initial dose was < 5 mg/day was 0, 4%, 23%, 67%, and 86%, compared to 5 mg/day of 51%, 80%, 70%, 26%, and 10%, and > 5 mg/day of 49%, 16%, 7%, 7%, and 3%, in the 5-year periods, respectively (Table 1). The proportion of patients who took methotrexate rose from 10.2% to 25.9% to 56.7% to 71.0% to 77.7% in the 5-year periods.\textsuperscript{26}

#### Table 1  Initial Prednisone Dose in 308 Patients with Rheumatoid Arthritis (RA) Seen from 1980 Through 2004

<table>
<thead>
<tr>
<th>Year First Seen</th>
<th>N</th>
<th>Mean (median) initial dose: mg/d</th>
<th>Percentage of Patients Taking Initial Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 5 mg/d</td>
<td>= 5 mg/d</td>
</tr>
<tr>
<td>1980-1984</td>
<td>37</td>
<td>10.3 (5)</td>
<td></td>
</tr>
<tr>
<td>1985-1989</td>
<td>74</td>
<td>6.5 (5)</td>
<td></td>
</tr>
<tr>
<td>1990-1994</td>
<td>77</td>
<td>5.1 (5)</td>
<td></td>
</tr>
<tr>
<td>1995-1999</td>
<td>61</td>
<td>4.1 (3)</td>
<td></td>
</tr>
<tr>
<td>2000-2004</td>
<td>59</td>
<td>3.6 (3)</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2  Baseline and Endpoint (12-month) Scores on Multidimensional Health Assessment Questionnaire (MDHAQ) for Physical Function (FN) and Pain in 308 Patients with Rheumatoid Arthritis, According to Initial Prednisone Dose < 5 Versus ≥ 5 mg/day

<table>
<thead>
<tr>
<th>Year First Seen</th>
<th>Initial Dose</th>
<th>MDHAQ-FN</th>
<th>MDHAQ-Pain</th>
<th>MDHAQ-FN</th>
<th>MDHAQ-Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1984</td>
<td>10.3 (5)</td>
<td>0</td>
<td>1.4</td>
<td>1.5</td>
<td>5.3</td>
</tr>
<tr>
<td>1985-1989</td>
<td>6.5 (5)</td>
<td>3</td>
<td>1.4</td>
<td>1.5</td>
<td>5.3</td>
</tr>
<tr>
<td>1990-1994</td>
<td>5.1 (5)</td>
<td>18</td>
<td>1.7</td>
<td>1.3</td>
<td>4.7</td>
</tr>
<tr>
<td>1995-1999</td>
<td>4.1 (3)</td>
<td>41</td>
<td>2.7</td>
<td>1.8</td>
<td>4.6</td>
</tr>
<tr>
<td>2000-2004</td>
<td>3.6 (3)</td>
<td>51</td>
<td>2.6</td>
<td>1.6</td>
<td>5.9</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5.6 (5)</td>
<td>113</td>
<td>2.4</td>
<td>1.6</td>
<td>5.2</td>
</tr>
</tbody>
</table>
appear to add clinically important efficacy, while increasing adverse effects.

**Similar Improvement in Clinical Status Over 12 Months Was Seen in Patients Treated with < 5 mg/day versus ≥ 5 mg/day of Prednisone**

Scores for function, pain, and RAPID3-EST fell by 34%, 37%, and 37% in patients treated with < 5 mg/day versus 40%, 37%, and 38% in patients treated with ≥ 5 mg/day (Table 3). Substantially better results were seen after 1990, possibly associated with early concomitant methotrexate in most patients. Improvement was similar in most patients, with little difference according to dosage in different 5-year periods (Table 3).

**Improved Long-term Outcomes in Patients Treated with Low-Dose (< 5 mg/day) Prednisone were Maintained Over Long Periods**

All 290 patients treated between 1980 and 2005 with longitudinal data whose prednisone was begun between 1980 and 2005 and had available at least two visits were analyzed in quartiles according to duration of prednisone therapy of 1 year or less, 1.1 to 4 years, 4.1 to 8 years, and more than 8 years (Table 4). Clinical improvement was maintained for up to 8 years in most patients (Table 4), although some worsening was seen in patients with longest follow-up. These findings differ considerably from those in the 1980s and 1990s, when severe declines began after 2 to 3 years in most patients.

**Few Adverse Events in Patients Treated with Low-Dose (< 5 mg/day) Prednisone Over 5 to 15 Years (25% for Longer Than 8 Years)**

Adverse events were ascertained through self-report in usual care on the MDHAQ, which includes queries about hypertension, diabetes, cataracts, weight gain, and other comorbidities. The primary adverse events were bruising and skin-thinning. In 109 patients treated after 1995, the proportion of patients with the prevalence of hypertension was 25%, diabetes 8%, and cataracts 9% (Table 5). It is not possible to identify precise statistics concerning expected levels of comorbidities in RA in the total absence of glucocorticoids over 5 years or longer, and the incidence and prevalence of more feared complications of glucocorticoids therapy were not ascertained systematically as in a randomized trial. However, patients generally report development of hypertension, diabetes, and cataracts on the MDHAQ. Therefore, it is not likely that the incidence of these adverse events was substantially higher than what was found and reported. Development of diabetes, hypertension, and cataracts in fewer than 10% of patients is consistent with findings in a German database of self-report database of RA patients indicating few adverse events, with the comment of Da Silva and colleagues, based on randomized trial data, that “adverse effects associated with [low-dose prednisone] are modest and often not statistically different from those of...”

### Table 3  Percentage Changes in Scores on Multidimensional Health Assessment Questionnaire (MDHAQ) for Physical Function (FN), Pain (PN), and RAPID3-estimate (RAPID3-EST) Over 12 Months in 308 Patients According to Initial Prednisone Dose < 5 versus ≥ 5 mg/day

<table>
<thead>
<tr>
<th>Year First Seen</th>
<th>Mean (Median) Initial Dose (mg/d)</th>
<th>Percent Clinical Change Over 12 Months*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Dose &lt; 5 mg/day</td>
<td>Initial Dose ≥ 5 mg/day</td>
</tr>
<tr>
<td>1980-1984</td>
<td>10.3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>1985-1989</td>
<td>6.5 (5)</td>
<td>3</td>
</tr>
<tr>
<td>1990-1994</td>
<td>5.1 (5)</td>
<td>18</td>
</tr>
<tr>
<td>1995-1999</td>
<td>4.1 (3)</td>
<td>41</td>
</tr>
<tr>
<td>2000-2004</td>
<td>3.6 (3)</td>
<td>51</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5.6 (5)</td>
<td>113</td>
</tr>
</tbody>
</table>

*“+” indicates improvement and “−” worsening in function (FN), pain (PN), and RAPID3-EST scores.*
Table 4  Scores on Multidimensional Health Assessment Questionnaire (MDHAQ) for Physical Function (FN),
Pain, and RAPID3-EST, and New Adverse Events Reported by Patients, According to Length of Prednisone
Treatment in 344 Patients with Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Duration of Prednisone Use</th>
<th>No Follow-up (N = 44)</th>
<th>0.1-1.0 Years (N = 72)</th>
<th>1.1-4.0 Years (N = 70)</th>
<th>4.1-8.0 Years (N = 75)</th>
<th>&gt; 8 Years (N = 73)</th>
<th>TOTAL (N = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical MDHAQ Variable, Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline MDHAQ-FN [0-10 scale]</td>
<td>3.4 (2.0)</td>
<td>3.2 (2.0)</td>
<td>2.8 (1.6)</td>
<td>3.0 (2.1)</td>
<td>3.3 (1.9)</td>
<td>3.1 (2.0)</td>
</tr>
<tr>
<td>Last visit MDHAQ-FN [0-10 scale]</td>
<td>—</td>
<td>2.7 (2.3)</td>
<td>2.3 (1.8)</td>
<td>2.7 (2.3)</td>
<td>3.3 (2.4)</td>
<td>2.8 (2.2)</td>
</tr>
<tr>
<td>Baseline MDHAQ-pain [0-10 scale]</td>
<td>5.8 (2.8)</td>
<td>5.9 (2.5)</td>
<td>5.8 (2.6)</td>
<td>6.1 (2.4)</td>
<td>5.9 (2.6)</td>
<td>5.9 (2.6)</td>
</tr>
<tr>
<td>Last visit MDHAQ-pain [0-10 scale]</td>
<td>—</td>
<td>4.0 (3.0)</td>
<td>4.0 (2.7)</td>
<td>4.1 (3.0)</td>
<td>4.5 (3.2)</td>
<td>4.2 (3.0)</td>
</tr>
<tr>
<td>Baseline RAPID3-EST [0-30 scale]</td>
<td>14.8 (6.7)</td>
<td>15.1 (6.4)</td>
<td>14.4 (5.9)</td>
<td>15.0 (6.6)</td>
<td>14.9 (6.6)</td>
<td>14.8 (6.3)</td>
</tr>
<tr>
<td>Last visit RAPID3-EST [0-30 scale]</td>
<td>—</td>
<td>10.6 (7.8)</td>
<td>10.3 (6.7)</td>
<td>10.9 (7.6)</td>
<td>12.3 (7.9)</td>
<td>11.0 (7.5)</td>
</tr>
</tbody>
</table>

Possible Adverse Events

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>N (%) at Baseline</th>
<th>N (%) Overall</th>
<th>N New Cases (Mean Number of Years)</th>
<th>Patients Years at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>21 (19%)</td>
<td>27 (25%)</td>
<td>6 (5.2 Years)</td>
<td>557</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (4%)</td>
<td>9 (8%)</td>
<td>5 (5.0 Years)</td>
<td>632</td>
</tr>
<tr>
<td>Cataracts</td>
<td>6 (6%)</td>
<td>10 (9%)</td>
<td>4 (2.5 Years)</td>
<td>617</td>
</tr>
</tbody>
</table>

Table 5  Proportion of 109 RA Patients Who Took Long-term Low-Dose Prednisone and Developed Hypertension, Diabetes, and Cataracts

placebo.”20 Even if the level of adverse events were 25% to 50% higher, the prevalence of comorbidities is little or no more than would be expected, and might be acceptable to many doctors and patients to preserve physical function and offset joint damage.

The data concerning long-term efficacy and safety are derived from an MDHAQ, a patient-self-report questionnaire, which allowed long-term data to be collected at low cost, as the patient does most of the work. Self-report RAPID3 scores are as efficient as DAS28 (disease activity score with 28 joint count)31 and CDAI (clinical disease activity index)32 to distinguish active from control treatments in clinical trials involving methotrexate,33 leflunomide,33 anakinra,34 adalimumab,35 abatacept,36 infliximab37 and certolizumab.38 RAPID3 scores are correlated significantly with DAS28 and CDAI scores in clinical trials35,38-40 and usual clinical care,41,42 including categories for high, moderate, low severity, and remission. Physical function scores on MDHAQ and other questionnaires are far more significant than radiographs or laboratory tests in the prognosis of severe outcomes in RA, including functional status,27,43 work disability,24,46 costs,47 joint replacement surgery,48 and premature death.14,27,49-54

It is not feasible to conduct a randomized study over periods of 3 to 5 years or longer. Furthermore, randomized trials are affected by many limitations that often are not articulated, including patient selection due to exclusion and inclusion criteria, relatively short-term periods of observation when long-term data are needed, fixed dosage of medications, limitations on changes in other medications, etc.22,55-62  Long-term observations are required to assess the likelihood of long-term adverse events with any medication, including low-dose glucocorticoids, with effort to try to control possible confounding variables.

A database of consecutive patients may provide data that are not available through randomized controlled clinical trials,63 which may be quite relevant to patient care. The most important consideration involves the need to include all consecutive patients, to avoid patient selection. Indeed, selection of patients in traditional clinical series provides a strong rationale for a randomized clinical trial, to isolate the therapy variable compared to another therapy or a placebo while all other variables are hoped to be similar through randomization. All patients can be included through completion of MDHAQ at all patient visits in the infrastructure of patient care.

The data presented here indicate that long-term prednisone, at doses < 5 mg/day, is effective and well-tolerated for most patients with RA at this time, including initial dose of 3 mg/day and indefinite continuation. Logistic, medical, and ethical considerations would require that multiple therapies
be provided to most RA patients to achieve best outcomes, and it may never be possible to isolate prednisone (or methotrexate or a biological agent or physical therapy or any single variable) for the treatment of RA (or any chronic disease) over 5 years or longer in a long-term clinical trial. However, this limitation should not deter efforts to analyze low-dose risks and benefits of low-dose prednisone in shorter clinical trials and to collect rigorous quantitative data in usual clinical care to analyze results of treatment over long periods. MDHAQ/RAPID3 provides rigorous quantitative data in the infrastructure of clinical care, with minimal cost and extra effort on the part of true rheumatologist. MDHAQ/RAPID3 prepares patients for a visit and improves doctor-patient communication while saving time for the doctor. All rheumatologists can use MDHAQ/RAPID to analyze results of treatments with low does prednisone and all other therapies to achieve optimal outcomes for patients with RA.

Disclosure Statement
Dr. Pincus/Health Report Services, Inc., owns the copyright for the MDHAQ/RAPID3. No license is needed for clinicians who may freely use MDHAQ/RAPID3 to monitor patient status in usual clinical care. Royalties and license fee are received from for-profit pharmaceutical and electronic medical record companies for the use of MDHAQ/RAPID3. The other author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References


