Long-term prednisone in doses of less than 5 mg/day for treatment of rheumatoid arthritis: Personal experience over 25 years

T. Pincus[1], I. Castrejón[1], T. Sokka[2]

[1]*New York University Hospital for Joint Diseases, New York, NY, USA;*
[2]*Jyväskylä Central Hospital, Jyväskylä, Finland.*

Theodore Pincus, MD
Isabel Castrejón, MD
Tuulikki Sokka, MD, PhD

Please address correspondence to:
Theodore Pincus, MD,
Department of Rheumatology, Room 1608,
NYU-Hospital for Joint Diseases,
301 East 17th Street,
New York, NY 10003, USA.
E-mail: tedpincus@gmail.com

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ABSTRACT

This article summarises the experience of one academic rheumatologist in treatment of patients with rheumatoid arthritis (RA) over 25 years from 1980-2004 with low-dose prednisone, most with <5 mg/day over long periods. A database was available which included medications and multidimensional health assessment questionnaire (MDHAQ) scores for physical function, pain, and routine assessment of patient index data (RAPID3), completed by all patients at all visits in the infrastructure of care. Most patients were treated with long-term low-dose prednisone, often from the initial visit and indefinitely, and with methotrexate after 1990. The mean initial prednisone dose declined from 10.3 mg/day in 1980–1984 to 3.6 mg/day in 2000–2004. Although no formal criteria were used to determine the initial dose, prednisone doses were higher in patients who had more severe MDHAQ/RAPID3 scores, as expected, reflecting confounding by indication. 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, with low levels of hypertension, diabetes, and cataracts, although this information was based only on self-report rather than systematic assessment by a health professional. These data reflect limitations of observational data. However, a consecutive patient database may provide long-term information not available from clinical trials. The data document that prednisone at doses <5 mg/day over long periods appears acceptable and effective for many patients with RA at this time. Further clinical trials and long-term observational studies are needed to develop optimal treatment strategies for patients with RA with low-dose prednisone.

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Introduction

Glucocorticoids for treatment of rheumatoid arthritis (RA) have evoked controversy for more than half a century (1-4). The Nobel Prize was awarded to Hench, Kendall and Reichstein in 1950 for discovery of glucocorticoids and documentation of dramatic short-term clinical improvement in patients with RA (5). Disease-modifying activity of moderate doses of glucocorticoids was documented during the 1950s (6). However, adverse effects of long-term glucocorticoids in pharmacologic doses of prednisone or prednisolone of 10 mg/day or more, as was the clinical practice in the 1950s, were inevitable (7). Therefore, since the 1950s, systemic glucocorticoids have 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 (8).

Despite guidelines and teachings over many years to limit or refrain entirely from use of glucocorticoids, prednisone or prednisolone nonetheless are 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 (~100 patients per site) in 15 countries, 66% of patients were taking glucocorticoids, including more than 70% in Argentina, Finland, France, Ireland, Serbia, and USA, more than 50% in Germany, Italy, Poland, Spain, Sweden, Turkey, and UK – fewer than 50% only in Denmark (43%) and the Netherlands (26%) (9) (Table I). Although the data are not from a random sample of practices in these countries, consistent

patterns among 3 practices within each country suggest that the information is at least moderately generalisable.

Extensive use of glucocorticoids in RA at this time appears based in part on a reassessment of glucocorticoid therapy which began during the 1980s (10), with somewhat simultaneous recognition of severe long-term outcomes of RA (11, 12). The efficacy and safety of low doses of glucocorticoids was documented in an open study reported in 1964 (13), and a 24-week non-blinded clinical trial reported in 1982 (10). Doses of 5 mg/day or less of prednisone do not induce significant suppression of the hypothalamic-pituitary-adrenal axis (14-17).

Since 1995, six double-blind clinical trials (18-23) (see articles by Kirwan, Boers, Jacobs, Svensson, Krause *et al*., in this Supplement) have provided strong evidence for efficacy and safety with low doses of glucocorticoids compared to placebo. A withdrawal clinical trial in RA patients documented clinical efficacy of prednisone in doses of 3 mg/day compared to placebo (24), and is discussed in greater detail in another article in this Supplement (Pincus T: *Withdrawal Clinical Trial*). Disease-modifying properties of low-dose prednisone in slowing radiographic progression have been confirmed in meta-analyses (25, 26).

Reports indicating disease modification even with low doses of prednisone or prednisolone of 5–7.5 mg/day (18, 22, 23) are of particular interest, as doses of 10 mg/day are associated with bone loss (27) and higher mortality rates (28, 29). Most adverse effects of glucocorticoids are dose-dependent (30, 31), although it is often difficult to distinguish adverse effects of glucocorticoids from the "side effects" of RA (32). For example, bone loss and premature mortality are seen in RA, independent of glucocorticoids, associated with severity, as is glucocorticoid use.

This article summarises the experience of the senior author (TP) over 25 years between 1980 and 2004 at a weekly academic clinical setting in the treatment of RA patients with prednisone, usually with concomitant methotrexate after 1990. A database was maintained of all visits of all patients over this period, which included medications and scores for functional status, pain and routine assessment of patient index data (RAPID3) (33) on a multidimensional health assessment questionnaire (MDHAQ) (34). MDHAQ data allowed recognition of clinical improvement, as well as self-report of possible adverse effects queried specifically at each visit, although some patients may omit mention of adverse effects.

Table I. The use of disease-modifying anti rheumatic drugs (DMARDs) in the QUEST-RA countries (9).
[The highest percentage for each drug is in **bold**, *and the lowest in* ***bold italic****].*

Country	Median delay to initiation of DMARDs (months)	Mean DMARD exposure (years)	Selected DMARDs evertaken: Percentage of patients in the QUEST-RA study per country					
			Prednisone	MTX	HCQ	SSZ	LEF	Any Biologic Agent
Denmark	10	7.9	43%	85%	39%	64%	11%	23%
Finland	7	14.4	74%	85%	**74%**	**84%**	21%	17%
France	8	9.9	83%	86%	55%	49%	**42%**	**53%**
Germany	15	8.4	54%	78%	30%	36%	25%	29%
Ireland	11	6.3	71%	**92%**	***15%***	33%	24%	41%
Italy	9	7.1	69%	79%	42%	14%	31%	26%
Netherlands	5	8.1	***26%***	91%	28%	35%	6%	19%
Poland	4	7.2	69%	87%	34%	60%	18%	8%
Spain	14	7.3	67%	82%	43%	29%	34%	27%
Sweden	12	8.8	66%	83%	34%	62%	9%	31%
UK	12	7.9	51%	***67%***	39%	46%	***4%***	16%
Turkey	12	8.9	69%	88%	27%	61%	22%	7%
Serbia	11	6.6	**88%**	69%	55%	17%	7%	***2%***
USA	9	7.9	77%	85%	49%	12%	19%	33%
Argentina	13	3.7	83%	68%	49%	***6%***	16%	3%
TOTAL	9	8.1	66%	83%	41%	43%	21%	23%

MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; LEF: leflunomide.

Analyses of these long-term, observational data are affected by limitations not seen in randomised data. Nonetheless, the data appear informative concerning:

a) decline of mean initial prednisone dose from 10.3 mg/day in 1980–1984 to 3.6 mg/day in 2000–2004, with initiation of prednisone in doses <5 mg/day in 86% of patients seen in 2000-2004;

b) higher mean initial doses in patients with higher scores for MDHAQ physical function, pain, and RAPID3;

c) similar improvement over 12 months in MDHAQ scores in patients whose initial dose was less than, equal to, or greater than 5 mg/day;

d) maintenance of improved long-term outcomes in patients treated with low-dose (<5 mg/day) prednisone over long periods;

e) substantially better average clinical status in all RA patients seen in 2000 *versus* all patients seen in1985;

f) few adverse events in patients treated with low-dose (<5 mg/day) prednisone over 5-15 years (25% for longer than 8 years).

The evidence for these conclusions is documented briefly in this article.

a) Decline of mean initial prednisone dose from 10.3 mg/day in 1980–1985 to 3.6 mg/day in 2000–2004

The initial prednisone dose in 308 patients with RA treated between 1980 and 2004 was analysed in 5-year periods: 1980–84, 1985–99, 1990–94, 1995–99, and 2000–04 (Table II). The mean initial prednisone dose was 10.3 mg/day in 1980-84 and fell in each 5-year period to 3.6 mg/day in 2000-04 (Table II). The proportion of patients whose initial dose was <5 mg/day was zero in 1980-84, 4% in1985–89, 23% in 1990–94, 67% in 1995–99, and 86% in 2000–04 (Table II). The proportion treated initially with 5 mg/day was 51%, 80%, 70%, 26% and 10%, in the 5-year periods, respectively. The pro-

Table II. Initial prednisone dose in 308 patients with rheumatoid arthritis (RA) seen from 1980 through 2004.

Year first seen	n.	Mean (median) initial dose: mg/d	Percentage of patients taking initial dose		
			<5 mg/d	=5 mg/d	>5 mg/d
1980–1984	37	10.3 (5)	0	51%	49%
1985–1989	74	6.5 (5)	4%	80%	16%
1990–1994	77	5.1 (5)	23%	70%	7%
1995–1999	61	4.1 (3)	67%	26%	7%
2000–2004	59	3.6 (3)	86%	10%	3%

portion treated initially with >5 mg/day was 49%, 16%, 7%, 7%, and 3%, in the 5-year periods, respectively (Table II).

These data indicate a decline of more than 60% in the initial dose over the 25-year period.

The decline in prednisone dose was associated with a reciprocal rise in the use of methotrexate, which increased from 22% of patients in 1980-84 to 48% in 1985-89, 80% in 1990–94, 66% in 1995–99, and 80% in 2000-04 (35), as well as a greater likelihood for patients to be seen earlier in disease course, and be treated on the first or second visit. However, these phenomena reflect only associations, which cannot explain definitively the decline in dosage, although they indicate that many if not most patients with RA who are treated with DMARDs at this time may have initial and long-term doses of <5 mg/day prednisone, and may not ever "require" higher doses.

b) Higher mean initial prednisone doses in patients with higher MDHAQ scores

A version of an MDHAQ (36, 37) was completed by every patient at every visit. The MDHAQ includes the 3 self-report measures in the RA core data set – physical function, pain, and patient estimate of global status. RAPID3, an index of these 3 patient-reported Core Data Set measures without a formal joint count (33) was also calculated.

Patient global estimate was not available prior to 1996. Therefore, RAPID3 was estimated as "RAPID3-EST," a composite of 2 measures of physical function score plus pain score multiplied by 2, without a patient global estimate score. RAPID3-EST is correlated with RAPID3 scores at rho = 0.85 in patients in this database for whom RAPID3 scores were available.

Mean baseline MDHAQ physical function scores (recoded from 0–3 to 0–10) were 2.4 (on a scale of 0-10) in patients treated initially with <5 mg/day, and 3.5 in patients treated with ≥5 mg/day (maximum 20 mg/day) (Table III). Mean pain scores were 5.2 (on a scale of 0–10) in patients treated initially with <5 mg/day, and 6.3 in patients treated with ≥5 mg/day. In patients treated initially with <5 mg/day, mean RAPID3-EST was 12.4 (on a scale of 0–30), compared to 15.9 in those treated with ≥5 mg/day; in patients for whom the full RAPID3 was available, mean RAPID3 was 13.2 in patients treated initially with <5 mg/day compared to 17.3 in those treated with ≥5 mg/day (data not shown). These data indicate that patients with more severe clinical status were more likely to be treated with higher doses of prednisone >5 mg/day, but rarely more than 10 mg/day – after 1990, fewer than 7% were prescribed >5 mg day (Table II), and fewer than 2% 10 mg/day – no-one received a higher dose than 10 mg/day.

c) Similar improvement in clinical status over 12 months in patients treated with <5 mg/day *versus* ≥5 mg/day of prednisone

Mean changes over the first 12 months of prednisone therapy were computed for MDHAQ scores for physical function, pain and RAPID3-EST in all 308 patients treated from 1980-2004 for whom data one year later were available (Table IV). Changes were compared in patients treated with <5 *vs.* ≥5 mg/day, as few patients received >5 mg/day.

In patients with initial prednisone dose ≥5 mg/day, scores for function, pain, and RAPID3-EST fell by 40%, 37% and 38%, respectively, over the subsequent 12 months (Table IV). In patients with initial dose <5 mg/day, scores for function, pain, and RAPID3-EST fell by 34%, 37% and 37% over the subsequent 12 months. Substantially better results were seen after 1990, likely associated with early concomitant methotrexate in most patients as well as earlier treatment. Little difference in improvement

Table III. 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.

Year first seen	Mean (median) initial dose: mg/d	Initial dose <5 mg/day					Initial dose ≥5 mg/day				
			MDHAQ-FN		MDHAQ-Pain			MDHAQ-FN		MDHAQ-Pain	
		n.	Baseline	12 months	Baseline	12 months	n.	Baseline	12 months	Baseline	12 months
1980–1984	10.3 (5)	0	–	–	–	–	37	4.1	2.7	6.4	4.8
1985–1989	6.5 (5)	3	1.4	1.5	5.3	5.7	71	3.3	1.8	6.3	3.7
1990–1994	5.1 (5)	18	1.7	1.3	4.7	2.7	59	3.2	1.8	5.9	3.3
1995–1999	4.1 (3)	41	2.7	1.8	4.6	3.2	20	3.9	2.9	6.3	5.1
2000–2004	3.6 (3)	51	2.6	1.6	5.9	3.5	8	4.3	3.2	7.0	5.3
TOTAL	5.6 (5)	113	2.4	1.6	5.2	3.3	195	3.5	2.1	6.3	4.0

Table IV. 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.

Year first seen	Mean (median) initial dose: mg/d	Percent clinical change over 12 months*							
		Initial dose <5 mg/day				Initial dose ≥5 mg/day			
		n.	FN	PN	RAPID 3-EST	n.	FN	PN	RAPID 3-EST
1980-1984	10.3 (5)	0	–	–	–	37	+33%	+25%	+28%
1985-1989	6.5 (5)	3	-5%	-8%	-24%	71	+45%	+42%	+43%
1990-1994	5.1 (5)	18	+26%	+43%	+38%	59	+44%	+44%	+42%
1995-1999	4.1 (3)	41	+33%	+30%	+37%	20	+27%	+19%	+25%
2000-2004	3.6 (3)	51	+37%	+41%	+39%	8	+25%	+25%	+30%
TOTAL	5.6 (5)	113	+34%	+37%	+37%	195	+40%	+37%	+38%

*"+" indicates improvement and "–" worsening in function (FN), pain (PN), and RAPID3-EST scores.

was seen within 5 year periods according to prednisone dosage (Table IV).

d) Maintenance of improved long-term outcomes in patients treated with low-dose (<5 mg/day) prednisone over long periods

Mean prednisone doses appeared to be largely unchanged in patients monitored over ≤1, 1.1–4, 4.1–8, and >8 years, representing quartiles of all patients (Table V). Clinical improvement was maintained for up to 8 years in most patients (Table V), 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 in physical function began after 2-3 years in most patients (12, 38).

e) Substantially better clinical status in all RA patients seen in 2000 *versus* 1985

A cross-sectional comparison of all RA patients seen by this rheumatologist in this clinical setting in 1985 (125 patients) *versus* 2000 (150 patients), many of whom are included in the above analyses, indicated substantially better status in 2000 according to MDHAQ function, swollen joint count, radiographic damage, ESR, and other measures in 2000 *versus* 1985 (39) (Table VI). Mean radiographic Larsen scores in this cross-sectional analysis were only 3% of maximum in 2000 (disease duration 9 years), compared with 20% in 1985 (disease duration 7 years). Most patients who were sero-negative for rheumatoid factor had no radiographic progression at all in 2000 (39).

In 1985, 51% of patients were taking prednisone with a mean daily dose of 7.8 mg per day, 10% were taking methotrexate, and 37% no DMARDs or prednisone. In 2000, 86% were taking prednisone at a mean dose of 4.6 mg per day, 77% were taking methotrexate and only 3% were taking no DMARDs or prednisone (Table VI). Age and duration of disease were 2-3 years higher in 2000 (39) (Table VI), reflecting a more mature practice, so the differences in clinical status are not explained by differences in demographic measures.

These findings suggest better control

Table V. Baseline and last available prednisone dose, 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.

	Duration of prednisone use					
	No follow-up (n=44)	0.1–1.0 years (n=72)	1.1–4.0 years (n=70	4.1–8.0 years (n=75)	>8 years (n=73)	TOTAL (n=334)
Prednisone dosage (mg/day)						
Baseline mean (SD)	4.8 (2.3)	6.7 (7.9)	4.6 (2.3)	5.0 (4.8)	6.2 (5.1)	5.5 (5.1)
Baseline median (IQR)	5.0 (2.0)	5.0 (2.0)	5.0 (2.0)	5.0 (2.0)	5.0 (0)	5.0 (2.0)
Last visit mean (SD)	–	6.1 (6.6)	4.8 (3.6)	5.9 (6.9)	5.7 (5.2)	5.6 (5.7)
Last visit median (IQR)	–	5.0 (2.0)	4.0 (2.0)	4.0 (4.0)	5.0 (3.0)	5.0 (2.0)
Clinical MDHAQ variables, mean (SD)						
Baseline MDHAQ-FN [0–10 scale]	3.4 (2.0)	3.2 (2.0)	2.8 (1.6)	3.0 (2.1)	3.3 (1.9)	3.1 (2.0)
Last visit MDHAQ-FN [0–10 scale]	–	2.7 (2.3)	2.3 (1.8)	2.7 (2.3)	3.3 (2.4)	2.8 (2.2)
Baseline MDHAQ-pain [0–10 scale]	5.8 (2.8)	5.9 (2.5)	5.8 (2.6)	6.1 (2.4)	5.9 (2.6)	5.9 (2.6)
Last visit MDHAQ-pain [0–10 scale]	–	4.0 (3.0)	4.0 (2.7)	4.1 (3.0)	4.5 (3.2)	4.2 (3.0)
Baseline RAPID3-EST [0–30 scale]	14.8 (6.7)	15.1 (6.4)	14.4 (5.9)	15.0 (6.6)	14.9 (6.6)	14.8 (6.3)
Last visit RAPID3-EST [0–30 scale]	–	10.6 (7.8)	10.3 (6.7)	10.9 (7.6)	12.3 (7.9)	11.0 (7.5)
Possible adverse events						
Baseline weight (lbs), mean (SD)	177.0 (51.8)	163.3 (39.1)	167.3 (40.0)	161.5 (36.7)	163.5 (38.8)	165.7 (40.7)
Last visit weight (lbs), mean (SD)	–	169.8 (36.4)	165.6 (38.6)	160.0 (42.4)	161.4 (41.2)	164.2 (39.7)
Hypertension, n (%)	–	1 (1.4%)	4 (5.7%)	5 (6.7%)	9 (12.3%)	19 (6.6%)
Cataracts, n (%)	–	0	1 (1.4%)	0	8 (11.0%)	9 (3.1%)
Diabetes, n (%)	–	0	0	3 (4.0%)	5 (6.9%)	8 (2.8%)

SD: standard deviation; IQR: interquartile range.

Table VI. Demographic, disease, and therapy variables in two cohorts of all patients with rheumatoid arthritis seen by TP in 1984–86 ("1985") *versus* 1999–2001 ("2000").

	Cohort	
Variable	1985	2000
Number of patients	125	150
Demographic variables		
Age (mean n. years)	55 years	58 years
% Female	65%	71%
Duration of disease (median n. years)	7 years	9 years
Year of education (mean n. years)	11 years	13 years
Years of followup (median n. years)	0	3
Clinical status variables – median values		
Swollen joint count (0–28)	12 (6, 16)	5 (2, 10)
Larsen radiographic score (0–100)	20 (2, 36)	3 (0, 13)
Erythrocyte sedimentation rate (mm/hr)	33 (16, 50)	20 (9, 33)
Functional disability score on MHAQ (0–3)	1.0 (0.6, 1.4)	0.4 (0.1, 1.0)
Disease activity score (DAS) 28 (0–10)	5.7 (4.9, 6.5)	4.4 (3.2, 5.3)
Therapy variables		
Prednisone + any other drug	51%	86%
Mean daily dose	7.8 mg	4.6 mg
Median daily dose	5 mg	4 mg
Minimum daily dose	4 mg	1 mg
Maximum daily dose	30 mg	15 mg
Methotrexate + any other drug	10.4%	76.7%
No DMARDs, no prednisone	36.8%	3.3%

** Values depict unadjusted median values and interquartile range; *p*-values derived from a median regression model adjusted for age, education, duration of disease and rheumatoid factor status all <0.01.

in most patients in 2000 compared to 1985, associated with long-term low-dose prednisone. However, almost all patients had methotrexate and/or other DMARDs according to a policy of tight control (40, 41), and the data are not from a clinical trial. Therefore, the findings cannot be regarded as definitively documenting either clinical efficacy or inhibition of structural damage through prednisone, but are consistent with these possibilities. Improved outcomes were associated with long-term low-dose prednisone, generally maintained indefinitely.

f) Few adverse events in patients treated with low-dose (<5 mg/day) prednisone over long periods

Adverse events were ascertained on the MDHAQ 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 hypertension was 25%, diabetes 8% and cataracts 9% (Table VII). There were 6 new cases of hypertension over 557 patient-years, 5 new cases of diabetes over 632 patient-years, and 4 new cases of cataracts over 617 patient-years (Table VII). Mean (median) weight gain was 1.45 kg (1.13 kg) over 48 weeks after initiation of prednisone. Weight gain was lowest in patients who began prednisone ≤3 mg/day (mean 0.44 kg), and greatest in patients who began prednisone >5 mg/day (mean 2.63 kg) (Table VII).

It is impossible to identify precise statistics concerning expected levels of comorbidities in the total absence of glucocorticoids in a cohort of patients with RA over 5 years or longer outside of a clinical trial in which patients are randomised to receive or not receive glucocorticoids. Paradoxically, however, as discussed in greater detail below, it also is impossible to maintain clinical trial conditions over 5 years in patients with a symptomatic disease such as RA (in contrast to asymptomatic conditions such as hypertension, hyperlipidemia, osteoporosis, etc.). Therefore, short-term (<2 years) clinical trial data and long-term observational data are needed to obtain the best available data concerning long-term adverse effects of glucocorticoids.

In the cohort described, a formal review by a health professional might have revealed a few more adverse events. Nonetheless, self-report has proven quite informative – sometimes more accurate than reports of health professionals – and 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 (42). Even if the level of adverse events were 25-50% 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.

Discussion

The data presented in this review indicate that long-term low-dose prednisone, at doses <5 mg/day, appears well-tolerated, safe and effective for many patients with RA, including initial dose of 3 mg/day and indefinite continuation in most patients. The data are from a long-term observational database of consecutive patients over 25 years, rather than from clinical trials, and characterised by the recognised risks of bias with non-randomised data. Observational data are affected by many limitations, primarily based on "confounding by indication" – *i.e.* that patients who have more severe disease are more likely to receive certain therapies or higher doses of such therapies. Indeed, confounding by indication was documented in the reported series (Table III), as higher doses of prednisone were more likely to be prescribed for patients who had more severe clinical status according to MDHAQ scores for physical function, pain and RAPID3.

A further limitation of observational data to analyse results of a particular therapy (as presented here for prednisone) is that the therapy variable is not isolated, while all other variables are kept constant, as in a clinical trial. Therefore, the likelihood that other therapies may affect patient outcomes

Table VII. Proportion of 109 RA patients who took long-term low-dose prednisone who developed hypertension, diabetes, and cataracts.

Comorbidity	n. (%) at baseline	n. (%) overall	n. new cases (mean number of years)	Patient years at risk
Hypertension	21 (19%)	27 (25%)	6 (5.2 years)	557
Diabetes	4 (4%)	9 (8%)	5 (5.0 years)	632
Cataracts	6 (6%)	10 (9%)	4 (2.5 years)	617

is substantial. Indeed, the proportion of patients in the consecutive patient database treated by the senior author who were taking methotrexate was increased from 22% in 1980–84 to 80% in 2000–04 (35). These data, as well as treatment earlier in disease course in more recent years, may (or may not) explain in part similar results using low doses of prednisone.

In addition, since the patients are not randomised, other confounding variables such as age, duration of disease, education level, and other demographic and clinical variables could affect the results. However, such differences were not seen in comparing patients who were treated with ≥5 *versus* <5 mg/day of prednisone (data not shown). Furthermore, adverse effects were ascertained by patient self-report rather than systematically by a health professional, as they might be in a randomised controlled trial protocol, although, as noted, self-report may be as accurate as and sometimes more accurate than medical records.

At the same time, it is not feasible to conduct a randomised study over periods of 3 to 5 years or longer. 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. Indeed, bruising and skin-thinning were seen as the primary adverse effects, consistent with other observations in Germany of treatment with low-dose prednisone <5 mg/day (31).

Although the incidence and prevalence of more feared complications of glucocorticoids therapy were not ascertained systematically as in a randomised trial, 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. The findings are consistent with the comment of Da Silva *et al*., based on randomised trial data, that "adverse effects associated with [low-dose prednisone] are modest, and often not statistically different from those of placebo" (42).

Furthermore, randomised 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. (43-51).

These limitations can be seen in a comparison of analyses of the efficacy and safety of methotrexate in clinical trials, meta-analyses and systematic reviews *versus* observational databases. In analyses of methotrexate, data from observational databases appear to provide more accurate information concerning clinical care than formal studies, as discussed briefly below.

A meta-analysis of all available randomised trials published in 1990 concerning the efficacy of disease-modifying antirheumatic drugs (DMARDs) (52) indicated similar efficacy for methotrexate, injectable gold salts, penicillamine, and sulfasalazine. These findings were consistent with observational data of 539 patients of 7 rheumatologists reported in 1992 from a clinical database (53), which indicated that courses of the initial DMARD over 12 months were continued similarly for all DMARDs (52). However, analyses of all DMARD courses over 5 years in the identical clinical database indicated that methotrexate was continued by 50% of patients compared to fewer than 20% for injectable gold, penicillamine, azathioprine and hydroxychloroquine (53). These observations indicate that information regarding therapies over the course of one year, whether from clinical trials or clinical care, do not necessarily depict accurately results over 5 years in actual care.

Almost two decades later, a "systematic review" of DMARDs, published in 2008 (54), reported similar efficacy for methotrexate, leflunomide and sulfasalazine. However, again, the conclusions drawn from this systematic review are not consistent with practices in actual care. In the QUEST-RA international database of 4,363 patients in 2005, the proportions of patients taking methotrexate, sulfasalazine and leflunomide, respectively, were 83%, 41% and 43% (9). In the senior author's clinical care in 2000, these proportions were 77%, 1% and 3%, respectively (39). Although the latter data reflect biases beliefs, and experience of one treating physician, the QUEST-RA data reflect the practices at 48 sites, many with several treating rheumatologists. It appears unlikely that twice as many patients would be treated with methotrexate *versus* leflunomide or sulfasalazine if methotrexate were not a superior DMARD for most (but not all) patients over time. Therefore, data from randomised trials – even including meta-analyses and systematic reviews, often regarded as the highest form of evidence (55) – may give information that is considerably less accurate for clinical practice than data from observational studies (56, 57).

Another limitation of randomised clinical trials involves patient selection, as seen in the ATTRACT trial of infliximab+methotrexate *versus* placebo+methotrexate – the first trial to indicate efficacy of a biological agent in RA. Only 5% of patients seen in the senior author's clinical care were eligible for participation in the ATTRACT trial (58), confirmed at other sites (59, 60). This problem is seen with many clinical trials.

Even if all pragmatic limitations of clinical trials could be overcome, intrinsic limitations of the clinical trial methodology are seen (45). The design of a trial may strongly influence results – a control group does not eliminate bias in design. Furthermore, results generally

are reported for groups of patients, and some individual patients usually have better responses in the control group. For example, in most clinical trials of biological agents in RA, about 60% of patients who take the biological agents experience ACR 20 responses, which are seen in about 15% (or more) of patients in the control group. The clinical trials which showed greatest efficacy for patients with RA involve a "treat-to-target" strategy, generally without biological agents, rather than treatment with any biological agent (20, 61-68).

If an adverse effect is seen in 20% of patients, it is not possible at this time to predict which 1 of 5 individual patients seen in practice will experience this problem. Therefore, results of clinical trials do not provide definitive information to a clinician regarding management of an individual patient with RA. Individual physicians and patients vary widely in their interpretations of risk vs benefit of most medications, even when far more definitive information is available from rigorous clinical trials than for adverse effects of low-dose glucocorticoids in RA. The intellectual and ethical responsibility of the treating physician is to present the best available information to the patient, to provide the basis for an informed decision, which likely will vary among different doctors and patients.

A database of consecutive patients may provide data that are not available through randomised controlled clinical trials (69), which may be quite relevant to patient care. The most important consideration involves a need to include all consecutive patients, to avoid patient selection. Indeed, selection of patients in most reported clinical series provides an important rationale for a randomised clinical trial, to isolate the therapy variable compared to another therapy or a placebo while all other variables are hoped to be similar through randomisation. If all patients are included, however, observational data may provide considerable information that is not available from clinical trials, although nonetheless biased by the beliefs and practices of the treating physician(s). The findings may even be in conflict with results of clinical trials but, in some instances, may portray actual clinical care more accurately than clinical trials and even meta-analyses and systematic reviews of these trials, as noted above for methotrexate, which may be quite relevant to patient care.

The data presented here that long-term prednisone, at doses <5 mg/day, appears tolerable, safe and effective for many patients with RA at this time, including initial dose of 3 mg/day and indefinite continuation, appears quite well-established. 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 analyse risks and benefits of low-dose prednisone in shorter clinical trials and to collect rigorous quantitative data in usual clinical care to analyse results of treatment over long periods. Improvements in methodologies of both clinical trials and observational studies appear required to advance knowledge concerning strategies using low-dose prednisone to achieve optimal outcomes for our patients with RA.

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