Efficacy of the switch to modified-release prednisone in rheumatoid arthritis patients treated with standard glucocorticoids

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Abstract

Objective

In rheumatoid arthritis (RA), low-dose glucocorticoids (GCs) demonstrate disease-modifying potential when added to DMARDs. Modified-release (MR) prednisone taken at bedtime (released 2am) is more effective than immediate-release (IR) GC taken in the morning.

Methods

In an open-label observational study, 950 RA outpatients (mean age 57 ± 13 years; 75% females) treated with GCs and DMARDs (83.7% methotrexate, 10.5% leflunomide; 15.8% biologics) were switched from IR-prednisone or 6-methyl (6M)-prednisolone to low-dose MR-prednisone and followed for 4 months. Morning stiffness duration (MS), pain intensity (numerical rating scale [NRS], 0–10), patient and physician global assessment (GA, 0–10 scale) and disease activity score (DAS28) were assessed at baseline, 2 and 4 months.

Results

513 patients were switched to MR-prednisone from IR-prednisone (9.4±5.4 mg) and 437 from 6M-prednisolone (6.7±3.7 mg). Among 920 patients (96.8%) completing 4-months' MR-prednisone treatment, MS decreased from 58±37 min at T1 to 32±24 min at endpoint ($p<0.001$); NRS pain intensity reduced from 5.4±1.8 to 3.5±1.4 ($p<0.001$), and patient and physician GA scores improved from 5.4±1.7 to 3.5±1.4 and 5.1±1.7 to 3.3±1.4, respectively ($p<0.001$). DAS28 score decreased from 4.2±1.4 to 3.3±1.2 ($p<0.001$). Mean daily MR-prednisone dosage decreased from 8.2mg to 6.7mg between baseline and endpoint and significantly higher improvements in MS, NRS pain and GA scores were seen in patients switched from 6M-prednisolone versus IR-prednisone. MR-prednisone was well tolerated.

Conclusions

Switching GC-treated RA patients to low-dose MR-prednisone significantly improved outcomes over 4 months.

Key words

rheumatoid arthritis, glucocorticoids, circadian rhythms, morning stiffness, modified release.

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Introduction

Rheumatoid arthritis (RA) is a multifactorial, chronic, immune-mediated and inflammatory syndrome, with a prevalence ranging from 0.5–1.5% in the population in industrialised countries and with an incidence of around 1.5 men and 3.6 women per 10,000 people per year (1). RA causes mainly joint destruction, but in selected patients it can present with different tissue and organ involvement (2).

In the last decade, the use of disease-modifying anti-rheumatic drugs (DMARDs), in particular methotrexate (MTX) (3), and the availability of new biologic agents such as TNF inhibitors (4), have significantly improved RA management.

Glucocorticoids (GCs), used for decades in the treatment of RA, are effective in relieving signs and symptoms and interfering with radiographic progression, either as monotherapy or in combination with synthetic DMARDs (5, 6). Although GCs anti-inflammatory and immunosuppressive effects are well characterised, their precise mode of action is highly complex and remains unclear; they appear to elicit different types of responses and different adverse event profiles depending on the target cell, type of GC, dosages and administration routes used (7-9). The addition of low-dose (equivalent to a maximum of 7.5 mg prednisone daily) GCs to DMARD therapy has been investigated in a number of RCTs providing robust evidence supporting a beneficial effect of GCs on clinical disease efficacy and on radiographic progression in both early and advanced RA (10, 11). These findings have renewed the debate on the risk/benefit ratios of this treatment and have motivated new efforts to improve drugs and their delivery, aiming at reducing toxicity and increasing effectiveness (5).

The symptoms of RA, including fatigue, joint pain and swelling and morning stiffness of the joints (MS), display pronounced circadian rhythms, with the highest severity in the early morning. In RA patients, a clear temporal relationship exists between increased nocturnal levels of the proinflammatory cytokines such as interleukin (IL)-6 and the insufficient production of the anti-inflammatory cortisol (12, 13). Accordingly, it has been shown that administration of low doses of GC seems to improve acute RA symptoms if given shortly before the circadian nocturnal peak in inflammatory activity (14-16). A new formulation of modified-release prednisone (MR-prednisone) has been recently developed and was approved for use in RA in several countries.

If taken at 10 pm, this new formulation releases prednisone at about 2am, therefore timing drug release to best suit the circadian rhythms of plasma concentration of IL-6 and endogenous cortisol (decreased), including disease symptoms when compared to standard immediate-release (IR) steroid (17, 18).

The present prospective, non-interventional, observational study was designed to evaluate the efficacy and safety of MR-prednisone under conditions of daily practice, in a large group of RA patients already receiving active treatment with other GC formulations, focusing particularly on changes in associated RA symptoms and disease activity.

Methods

Study design and patients

This study was a 4-month, multicentre longitudinal, open-label observational study assessing the efficacy of switching from oral IR-prednisone or 6-methyl (6M)-prednisolone to MR-prednisone in RA patients. Consecutive patients referred to 100 rheumatologists from February 1st to April 30th 2011 were screened at baseline evaluation (T1). The inclusion criteria were the following: male or female patient aged >18 years, diagnosed with RA for at least 6 months, already receiving eraly morning treatment with oral IR prednisone or 6M-prednisolone at dosages >2.5 mg/day prednisone or equivalent.

At their physicians' discretion, patients fulfilling these criteria either continued on their existing GC therapy, or were switched to MR-prednisone at a corresponding dosage and enrolled in this prospective evaluation. All selected patients gave their informed consent for the study. After enrolment, patients entered a 16-week observation period

(4 months) during which they received MR-prednisone at a dose determined by the treating physician, and similar to that of their previous GC, administered once a day, at bedtime in non-fasting conditions.

Dose adjustments of MR-prednisone as well as of analgesic co-medication, rescue-medication and other treatments (*e.g.* DMARDs) could be performed at any time-point during the observation period by the physician according to medical demand.

Follow-up visits were scheduled after the first 2 months (T2) and at the end of the observation period (4 months, T3). Additional controls according to specific clinical need could be arranged for those patients who, according to the physician, had to be closely monitored due inadequate disease control or occurrence of adverse events (AEs).

Clinical evaluations

At the first visit, a detailed history was taken, including time of resolution of MS, maximal intensity of pain during the day, patient and physician global assessment of disease activity on a 0–100 mm visual analogue scale (VAS, 0 = not active and 100 = extremely active), concomitant analgesic treatment, and degree of functional and social disability assessed using an 11-point Numerical Rating Scale (NRS), in which the maximal intensity of pain during the day was reported from 0 = no pain to 10 = worst imaginable pain. Disease activity score was also determined using the 28-joint Disease Activity (DAS28) (19). Outcome measures for testing the efficacy of MR-prednisone also included the European League Against Rheumatism (EULAR) response criteria measures (20-22). Data were gathered using interview-administered questionnaires. At each visit, investigators recorded all AEs, but no checklists with predefined AEs were used.

Statistical analysis

For analysis purposes, patients were divided into two groups (6M-prednisolone or IR-prednisone), based on the steroid they were taking at enrolment.

Continuous variables were expressed as mean±standard deviation [SD] (the normality of distribution was assessed using the Shapiro-Wilks test), and discrete variables were presented as percentages. Statistical significance of baseline differences between the two groups was assessed using the unpaired *t*-test for continuous variables and Fisher's exact test for discrete variables.

Repeated-measures analysis of variance with a *post-hoc* Bonferroni test was used to analyse the change over time of continuous variables. Analyses were performed using STATISTICA 8 software (StatSoft Inc., Tulsa, USA).

Results

Patient demographics and baseline characteristics

Of 2081 consecutive outpatients with documented RA screened at baseline, 103 (5%) were not receiving GCs on a daily basis, 138 other patients (6.6%) were already receiving MR-prednisone and 50 additional patients (2.4%) were taking GCs other than oral IR-prednisone or 6M-prednisolone (*i.e.* dexamethasone, betamethasone, etc.). The remaining 1790 patients (mean disease duration 76.7±76 months; median 49 months) were registered and evaluated: of these, 950 patients (53.1%) were switched to low-dose MR-prednisone and entered the 16-week follow-up period.

Baseline clinical and demographic characteristics of the IR-prednisone or 6M-prednisolone patients excluded or enrolled in the present study are reported in Table I.

Patients who were not switched to low-dose MR-prednisone and were therefore excluded from further evaluation were substantially different from those enrolled: they were younger, with a higher mean NRS pain score, and higher disease activity by patient and physician global assessment. However, a smaller proportion had moderate/high disease activity by DAS28 score and the mean DAS28 score was lower. They were substantially less likely to use methotrexate and more likely to use other DMARDs, particularly biologic agents ($p<0.001$ for most variables). Excluded patients also had a higher rate of bone erosions and a higher prevalence of rheumatoid factor (RF) compared with enrolled (switched) patients.

The proportion of RA patients receiving other therapies (NSAIDs, analgesics, opioids) and with absent/reduced leisure and physical activity were similar in switched and not switched groups.

In the enrolled population, the mean patient age was 57±13 years (females 75%, bone erosions present in 55%); 83.7% were taking methotrexate, 10.5%, leflunomide, 12.2% other DMARDs, and 15.8% were receiving biologics. In addition, 29.5% RA patients were taking daily doses of non-steroidal anti-inflammatory drugs (NSAIDs) or other pain medications, while 49.5% were taking these medications only occasionally (Table I).

Patient disposition and overall efficacy

During the 16-week subsequent evaluation, 30 patients withdrew from the study: 24 (2.5%) switched back to their previous oral GC (15 to 6M-prednisolone and 9 to IR-prednisone); 6 patients (0.6%) discontinued the GC treatment due to their unwillingness to proceed with GC medication.

Among the remaining 920 (96.8%) patients who completed the observation after switching to MR-prednisone, all evaluated parameters displayed a significant improvement between the initial T1 and final T3 visits. In particular, morning stiffness decreased from 58±37 min at T1 to 32±24 min at T3 visit ($p<0.001$); pain intensity reduced from 5.4±1.8 to 3.5±1.4 ($p<0.001$), patient- and physician-GA improved from 5.4±1.7 to 3.5±1.4 and from 5.1±1.7 to 3.3±1.4, respectively (both $p<0.001$) and DAS28 score decreased from 4.2±1.4 to 3.3±1.2 ($p<0.001$).

During the 16-week follow-up, 33/800 (4.1%) biologic-naïve patients started taking biologics at their physicians' discretion.

Analysis according to the sourcing steroid

– Baseline

At enrolment, 513 (54%) patients were receiving IR-prednisone (average daily dose 9.4±5.4 mg) and 437 [46%] were receiving 6M-prednisolone (average dose 6.7±3.7 mg). At baseline, the two groups presented some differences in

Table I. Demographics and baseline characteristics of patients with rheumatoid arthritis (1790) on immediate-release prednisone or 6-methyl-prednisolone and either switched to low-dose modified-release prednisone (Enrolled) or not switched (Not included).

	Not included	Enrolled	*p*-value[a]
Number of patients, %	840 (46.9)	950 (53.1)	
Male/Female, %	28/72	25/75	NS
Age, years ± SD	55 ± 15	57 ± 13	<0.01
Duration of morning stiffness, min ± SD	56 ± 57	58 ± 37	NS
Pain, NRS score ± SD	5.8 ± 2.1	5.4 ± 1.8	<0.001
Disease activity (patient assessment), score ± SD	5.9 ± 2.1	5.4 ± 1.7	<0.001
Disease activity (physician assessment), score ± SD	5.5 ± 2.0	5.1 ± 1.7	<0.001
DAS28 score ± SD	3.9 ± 1.5	4.2 ± 1.4	<0.01
Moderate or high disease activity (DAS28), %	69.8	79.0	<0.001
Bone erosions, n (%)	571 (68)	526 (55)	<0.001
Positive rheumatoid factor, n (%)	637 (76)	564 (59)	<0.001
Absent or reduced leisure activity, %	71.1	74.3	NS
Absent or reduced physical activity, %	71.3	73.5	NS
On Methotrexate, n (%)	617 (73.4)	795 (83.7)	<0.001
On other DMARDs, n (%)	339 (41.0)	285 (29.9)	<0.001
On biologic agents, n (%)	216 (25.7)	150 (15.8)	<0.001
On other therapies (NSAIDs, analgesics, opioids), %	79.8	78.5	NS

[a]Baseline differences between patients not included and those enrolled in the prospective study; NS: non-significant.
Values are Mean ± SD unless otherwise indicated.

Table II. Demographics and baseline characteristics of enrolled patients receiving 6-Methyl (6M)-prednisolone or Immediate-release (IR) prednisone.

	Total	6M-prednisolone	IR-prednisone	*p*-value[a]
Number of patients	950	437	513	
Male/Female	25/75	30/70	21/79	<0.01
Age, years ± SD	57 ±13	59±12	57 ±13	<0.05
Duration of morning stiffness, min ± SD	58 ±37	67±42	50 ±31	<0.001
Pain, NRS score ± SD	5.4 ±1.8	5.7±1.7	5.2 ±1.8	<0.001
Disease activity (patient assessment), score ± SD	5.4 ±1.7	5.7±1.7	5.2 ±1.7	<0.001
Disease activity (physician assessment), score ± SD	5.1 ±1.7	5.4±1.7	4.8 ±1.7	<0.001
DAS28, score ± SD	4.2 ±1.4	4.1±1.4	4.2 ±1.3	NS
Moderate or high disease activity (DAS28), %		80.1	78.0	<0.05
Absent or reduced leisure activity, %		80.5	69.0	<0.001
Absent or reduced physical activity,%		80.3	68.4	<0.001
Bone erosions, n (%)	526 (55)	61	50	<0.01
Positive Rheumatoid Factor, n (%)	564 (59)	65	69	NS

6M-prednisolone, switched from 6-methyl-prednisolone; IR-prednisone (immediate-release prednisone), switched from immediate-release prednisone; NS: non-significant.
[a]Baseline differences between 6M-prednisolone and IR-prednisone.
Values are Mean ± SD unless otherwise indicated.

terms of demographics, disease activity and disability parameters, as illustrated in Table II. Their pharmacologic treatment at enrolment was also somewhat dissimilar (Table III). However, no significant differences between the two groups were observed for baseline DAS28 score (Table II). Analysis of patients by DAS28 disease activity (Fig. 1) showed that at baseline, a slightly higher proportion of patients on IR-prednisone at enrolment were in remission or had low disease activity (22%), and a lower proportion had moderate or higher disease activity (78%) compared with those switched from 6M-prednisolone (19.9% and 80.1%, respectively), although these differences were not statistically significant.

– *Week 16*

Differences in clinical outcome between patients who switched from 6M-prednisolone or IR-prednisone are reported in Table IV. All evaluated efficacy parameters displayed a significant mean improvement between baseline (T1) and week 16 (T3). According to the post-hoc Bonferroni analysis between T1 and T3, patients previously on 6M-prednisolone before switching to MR-prednisone slightly outperformed those switched from IR-prednisone for all the evaluated parameters except for DAS28 (Table IV). MR-prednisone was associated with a significant increase in the proportion of patients achieving low disease activity (defined as having a DAS28 ≤3.2) after 4 months of treatment (from 21.0 % at baseline to 47.3%, p=0.01) (Fig. 1). After 4 months of MR prednisone treatment, 25.9% patients switched from 6M prednisolone and 27.3% of those switched from IR prednisone (NS) had achieved a DAS28 score <2.6 (disease remission or minimal disease activity, according to Felson *et al*.). (Fig. 1).

According to DAS28-based EULAR response criteria, a little higher proportion of patients switched from 6M-prednisolone had a positive (moderate to good) response by week 16 compared with those switched from IR-prednisone and correspondingly the proportions with no response were reversed, but none of these differences were statistically significant between groups (Fig. 2).

While large improvements in ability to perform leisure and physical activities were reported in both groups, no significant between-group differences were observed (Fig. 3).

Discussion

In the present study the efficacy of MR-prednisone was assessed under real-life conditions, and over a medium-term observation period of 4 months. Our findings showed a significant improvement from baseline of MS, patient- and physician-GA scores, significant reduction in pain intensity, as well as in DAS28 scores, when RA patients switched from their conventional GCs (IR-prednisone or 6M-prednisolone) to modified-release prednisone.

During the study, the daily dosages of GC were kept as low as possible, in accordance with EULAR Guidelines. The study permitted dosages to be adjusted at each visit, and the mean daily

Table III. Drugs taken at baseline in enrolled patients receiving 6-methyl (6M)-prednisolone or Immediate-release (IR) prednisone.

Drugs	Total	6M-prednisolone	IR-prednisone	*p*-value[a]
N	950	437	513	
Methotrexate, n (%)	795 (83.7)	354 (81)	441 (86)	<0.05
Sulfasalazine, n (%)	38 (4)	21 (4.8)	17 (3.3)	NS
Azathioprine, n (%)	3 (0.3)	2 (0.5)	1 (0.2)	NS
Leflunomide, n (%)	100 (10.5)	57 (13)	43 (8.4)	<0.05
Cyclosporine, n (%)	28 (2.9)	16 (3.7)	12 (2.3)	NS
Other DMARDs, n (%)	116 (12.2)	52 (11.9)	64 (12.5)	NS
Biologics, n (%)	150 (15.8)	72 (16.5)	78 (15.2)	NS
Other therapies (NSAIDs, analgesics, opioids), n (%)	750 (78.9)	346 (79.1)	404 (78.8)	NS

6M-prednisolone, switched from 6-methyl-prednisolone; IR-prednisone (immediate-release prednisone): switched from immediate-release prednisone; NS: non-significant.
[a] Baseline differences between 6M-prednisolone and IR-prednisone.

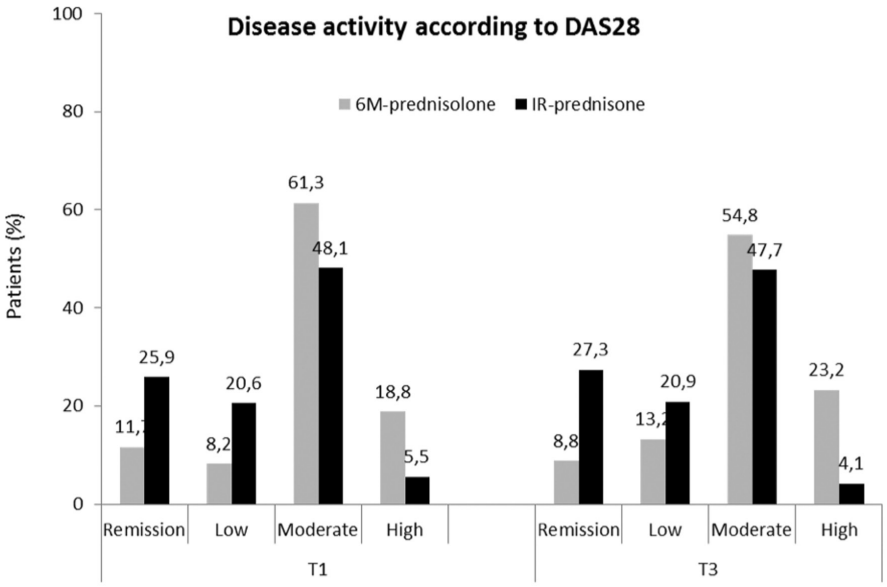

Fig. 1. Proportion of patients switched from 6-methyl (6M)-prednisolone (6M) or immediate-release (IR) prednisone who were in remission or with low, moderate or high disease activity according to DAS28 score at baseline (T1) and after 4 months (T3) of modified-release prednisone treatment (differences not significantly different between subgroups; *p*=NS).

MR-prednisone dose decreased during the study; of note, only 4.1% biologic-naïve patients required biologic therapy during the study.

Different from other countries, in Italy, 6M-prednisolone is commonly used, with a current GC market share of 38% in RA (Mundipharma Pharmaceuticals, Italy data on file). The efficacy reported with MR-prednisone could have been expected to be very different depending on whether the patient was switched from IR-prednisone or 6M-prednisolone. 6M-prednisolone has greater GC and less mineral corticoid activity than IR-prednisone (23). Substantial pharmacokinetic and pharmacodynamic differences have been reported between the two GCs, in particular, greater anti-inflammatory activity and longer biologic half-life (18–36 *vs*. 8–12 hours) for 6M-prednisolone compared with IR-prednisone (6, 24); although the two agents show similar total plasma clearance, are both predominantly plasma protein bound, the corrected volume of distribution of prednisolone is half that of 6M-prednisolone (23). Moreover, the latter has markedly different effects on GC receptor-DNA binding dynamics from native cortisol and other GCs (25), a characteristic very likely to contribute to the greater biological effects of this drug. Thus, switching from 6M-prednisolone to MR-prednisone could cause substantial response variability beyond the traditional dose equivalence simply based on relative GC potency.

One might expect that patients switched from IR would have a greater improvement than those switched from 6MP due to the greater duration of action of 6MP. However, the opposite was seen, probably due to differences in compliance between 6MP and IR formulations.

In this regard, caution is required when interpreting the positive results of Bonferroni analysis (Table IV): although the robustness of sample size allowed for the detection of even quite modest significant differences between the two therapeutic subgroups, the clinical relevance of a documented greater benefit for 6M-prednisolone patients switched to MR-prednisone deserves further confirmation from ad hoc randomised trials.

The efficacy of low-dose GC when given concomitantly with DMARDs has been previously reported (10, 11, 26). The benefits of adding low-dose GC to DMARD therapy is acknowledged in the latest EULAR guidelines, which state that '*GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible*' (3).

For best effect, low-dose GC should be given before the circadian surge in inflammatory activity (and thus RA symptoms) caused by elevated nocturnal levels of proinflammatory cytokines, especially IL-6 (15, 27).

Of note, EULAR guidelines also emphasise that timing of GC administration might influence its efficacy (28).

The importance of timing of prednisolone administration in suppressing the diurnal inflammatory process in RA was shown in an early study comparing two different daily times for administration of low dose prednisolone (5 or 7.5 mg) at 2.00 am or 7.30am; the 2am administration was more effective than the later administration in improving symptoms and reducing morning

Table IV. Efficacy parameters evaluated during the study in enrolled patients switched from either 6-methyl (6M)-prednisolone or Immediate-release (IR) prednisone to modified-release prednisone at T1 (baseline), T2 (2 months) and T3 (4 months).

Parameter	Subgroup	T1	T2	T3	Baseline *p*-value[a]	Interaction *p*-value[b]
Morning stiffness, min ± SD	6M-prednisolone	67 ± 42	49 ± 35	37 ± 27	<0.001	<0.001
	IR-prednisone	50 ± 31	35- ± 24	27 ± 21		
Pain, NRS score ± SD	6M-prednisolone	5.7 ± 1.7	4.6 ± 1.5	3.6 ± 1.4	<0.001	<0.001
	IR-prednisone	5.2 ± 1.8	4.2 ± 1.5	3.5 ± 1.4		
Global Assessment (patient), score ± SD	6M-prednisolone	5.7 ± 1.7	4.6 ± 1.5	3.6 ± 1.4	<0.001	<0.001
	IR-prednisone	5.2 ± 1.7	4.2 ± 1.5	3.4 ± 1.4		
Global Assessment (physician), score ± SD	6M-prednisolone	5.4 ± 1.7	4.3 ± 1.5	3.4 ± 1.4	<0.001	<0.001
	IR-prednisone	4.8 ± 1.7	3.9 ± 1.5	3.3 ± 1.5		
DAS28, score ± SD	6M-prednisolone	4.1 ± 1.4	3.7 ± 1.3	3.2 ± 1.3	NS	NS
	IR-prednisone	4.2 ± 1.3	3.7 ± 1.3	3.3 ± 1.2		

6M-prednisolone, switched from 6-methyl-prednisolone; IR-prednisone (immediate-release prednisone), switched from immediate-release prednisone; NRS (11-point Numerical Rating Scale), maximal intensity of pain during the day on scale from 0 = no pain to 10 = worst imaginable pain.
[a] Baseline difference between the two groups (ANOVA *p*-value); [b] Difference from T1 to T3 between groups.
Values are Mean ± SD unless otherwise indicated.

IL-6 concentrations (14). Modern trials have confirmed that the efficacy of GC therapy can be significantly improved by administration as chronotherapy (16).

In the randomised, double-blind Circadian Administration of Prednisone in Rheumatoid Arthritis (CAPRA 1) study, RA patients receiving a stable dose of predniso(lo)ne 2.5–10 mg/day were switched to either immediate-release prednisone administered at 6–8 am or MR-prednisone given at 10 pm (17). After 3 months, a greater reduction in MS (the primary endpoint of the study) was documented in the patients switched to MR-prednisone (33.1% reduction in MS *vs*. no change with IR-prednisone), and this was associated with greater reductions in IL-6 levels; the safety profile showed no differences between the two treatments. Patients were then followed for a further 9 months in an open-label extension in which all patients received MR-prednisone (18). The advantages in terms of reduced MS and IL-6 levels seen at 3 months with MR-prednisone were maintained at 12 months.

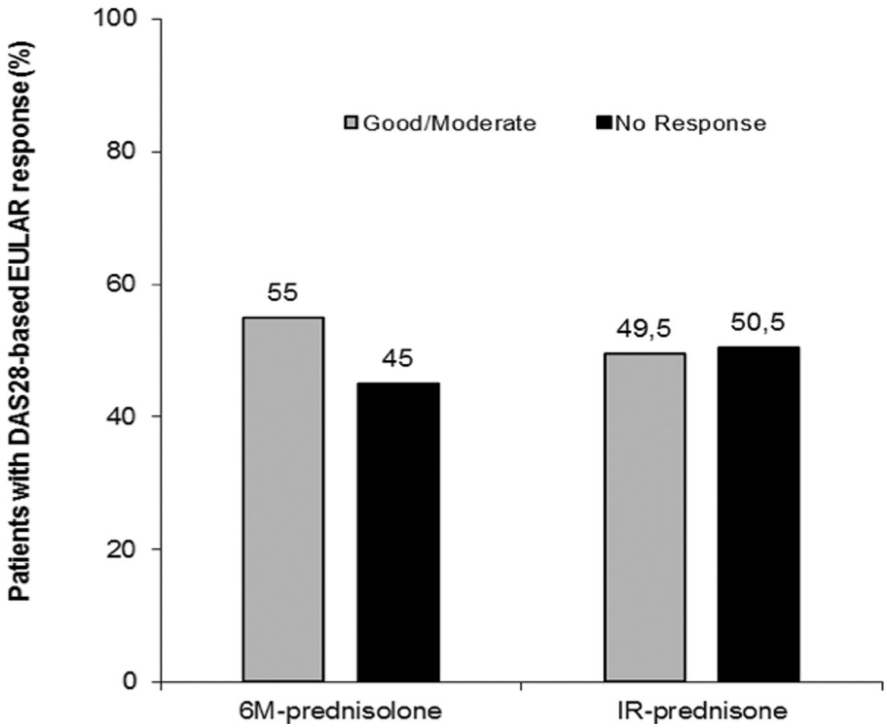

Fig. 2. Proportion of patients switched from 6-methyl (6M)-prednisolone or immediate-release (IR) prednisone with good/moderate or no response after 4 months of modified-release prednisone treatment, according to Disease Activity Score (DAS28) based on EULAR response criteria (differences not significantly different between subgroups; *p*=NS).

In another trial, the CAPRA-2 double-blind, placebo-controlled study, which assessed the efficacy and safety of 5 mg modified-release (MR) prednisone in 350 patients with RA over 12 weeks, the proportion of patients achieving 20% and 50% improvements in signs and symptoms according to the American College of Rheumatology (ACR) criteria at week 12 was significantly higher with MR-prednisone *versus* placebo (ACR20: 48% *vs*. 29%, $p<0.001$; ACR50: 22% *vs*. 10%, $p<0.006$) and significantly greater improvement in symptoms, severity of RA, fatigue, physical function, and similar tolerability were also reported (29).

To our knowledge, the CAPRA-1 study is the only study to date that has compared the efficacy of IR-prednisone (taken in the morning) versus MR-prednisone in RA patients already receiving GC treatment.

Our data are the first to compare the efficacy of MR-prednisone in patients switched from 6M-prednisolone and our findings confirm that even in this subgroup (about half of the cohort), switching to MR-prednisone resulted in significant improvement in symptoms and disease activity.

The limited length of follow-up did

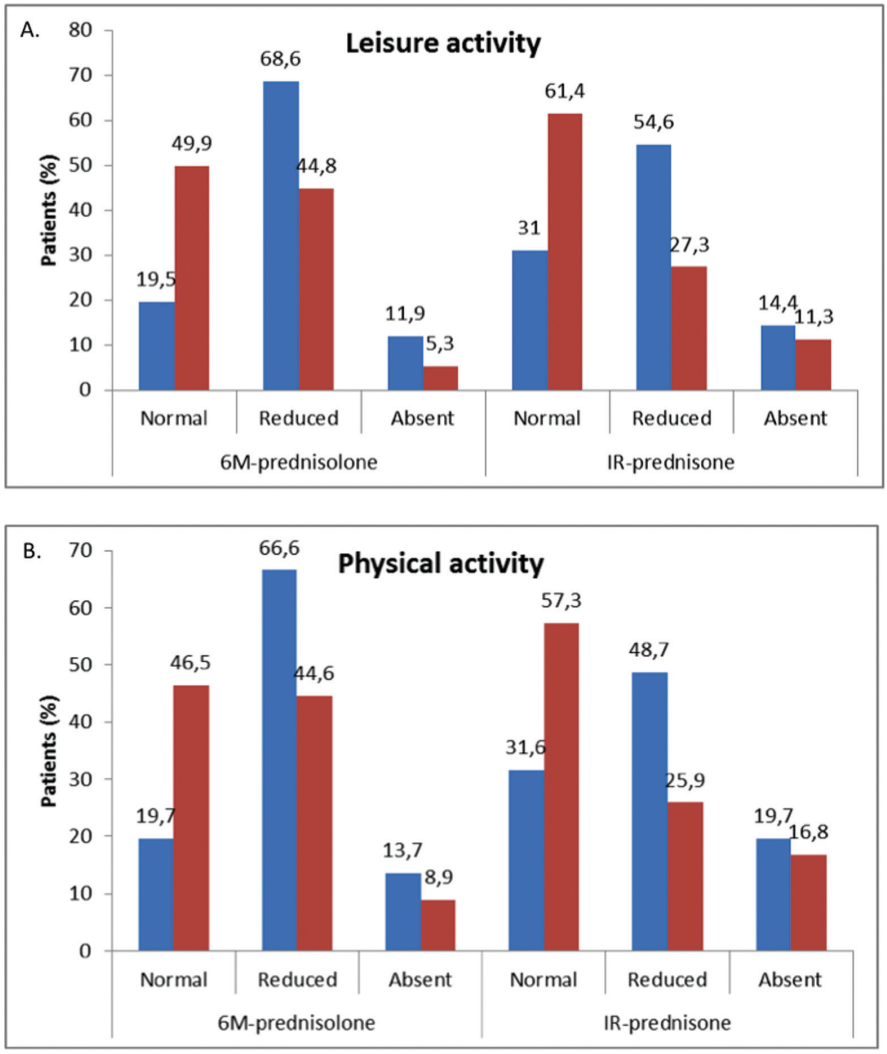

Fig. 3. Proportion of patients with normal, reduced or absent **A**) leisure activity and **B**) physical activity in enrolled patients switched from 6-methyl (6M)-prednisolone or immediate-release (IR) prednisone to modified-release prednisone at baseline (T1 - blue bar) and 4 months (T3 - red-bar).

not allow us to measure the effect of GC on evolution of bone erosion or less frequently occurring side effects. Regarding the safety profile, only six subjects (0.06%) discontinued from the MR-prednisone treatment due to unwillingness to proceed with GC medication – a fairly common reason to stop such medication, as reported in a previous cross-sectional survey (30). The small number of side effects associated with low-dose MR-prednisone seems in accordance with the findings from CAPRA-2, which showed a good safety profile from MR-prednisone in comparison with placebo (29). Furthermore, very few patients had to be downgraded to their previous GC due to either a lack of efficacy of MR-prednisone or side effects.

Study limitations

This study has several limitations including its open-label, observational design, the focus on a limited set of variables, and the lack of a randomised control group, all of which could limit the generalisability of our results. The observational design does not allow for the real benefit of MR-prednisone in comparison with standard treatment to be clearly established. In addition, compared with patients who continued on their existing GC, patients switched to MR-prednisone were significantly older, had a significantly lower baseline NRS pain score and higher DAS28 scores, were less likely to have joint erosion and were less likely to receive different DMARDs other than methotrexate. Finally, of uttermost relevance, biologic agents were used remarkably less frequently in patients switched to MR-prednisone in comparison with patients who were not switched to MR-prednisone. Such important differences did not allow for further comparison between groups. Randomisation to either stay on regular GCs or to switch to targeted MR-prednisone would have been a real option in such a huge population of patients. On the other hand, observational "real-life" studies do play a major role in clinical research, as they allow different questions to be addressed than could be dealt with in randomised controlled trials (31). In our opinion, the population described in this study adequately represents patients with stable disease treated by office-based rheumatologists and, according to the simple inclusion criteria used, our findings may provide useful guidance for the daily management of ambulatory patients with RA.

In conclusion, in unselected RA patients chronically treated with standard oral GC, a switch to MR-prednisone given at bedtime induced a significant improvement in duration of MS, pain and global outcomes over a 4-month follow-up period (32, 33). These observational data require further confirmation in long-term observational studies.

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