Low-dose Prednisolone in Rheumatoid Arthritis: Adverse Effects of Various Disease Modifying Antirheumatic Drugs

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ABSTRACT. ***Objective.*** To assess the incidence and severity of disease modifying antirheumatic drug (DMARD)-induced adverse effects (AE) in patients with rheumatoid arthritis (RA) taking/not taking glucocorticoids (GC). More specifically, we tested whether GC can prolong the survival time of DMARD in patients receiving combination therapy.

Methods. In a retrospective study of 154 patients with RA, data were examined for DMARD therapy and duration of low-dose GC (≤ 7.5 mg prednisone equivalent/day). Patients were followed for 2–62 months, and AE were graded following WHO criteria.

Results. GC therapy significantly increased the duration of therapy with sulfasalazine (SSZ) from 10.4 ± 2.3 to 22.5 ± 1.9 months and for methotrexate (MTX) from 21.8 ± 2.9 to 43.3 ± 2.7 months. Stratifying the withdrawal of DMARD for occurrence of AE and loss of efficacy revealed that GC comedication significantly increased the time until AE for users of MTX (3.0 ± 0.6 vs 18.8 ± 1.3 mo; $p < 0.05$), hydroxychloroquine (HCQ; 34.5 ± 4.6 vs 54.4 ± 5.1 mo; $p < 0.05$), and gold (6.6 ± 0.9 vs 10.5 ± 0.9 mo; $p < 0.05$). In patients taking SSZ the time until cessation due to loss of efficacy increased significantly under GC comedication (16.8 ± 1.2 vs 31.3 ± 2.9 mo; $p < 0.05$). However, in patients taking azathioprine (AZA) the duration of therapy decreased from 44.4 ± 2.6 to 22.3 ± 1.6 months under GC due to both time until AE and loss of efficacy. Patients under comedication of MTX + GC, HCQ + GC, and AZA + GC experienced significantly more AE compared to the respective DMARD monotherapy. A highly significant reduction was observed in the frequency of erosive RA in patients with GC comedication (n = 30; 49.1%) compared to patients without low-dose GC (n = 81, 80.4%; OR 4.05, 95% CI 1.91–8.66, $p < 0.0001$).

Conclusion. Low-dose GC retard radiological progression of RA and exhibit a differential effect on survival of DMARD and degree of AE due to DMARD. Further studies are warranted to address safety and interactions of chronic low-dose GC in RA patients treated with DMARD. (First Release April 15 2008; J Rheumatol 2008;35:979–85)

Key Indexing Terms:
ADVERSE EFFECTS
LOW-DOSE GLUCOCORTICOIDS
RHEUMATOID ARTHRITIS
DISEASE MODIFYING ANTIRHEUMATIC DRUG

Rheumatoid arthritis (RA) is a chronic, debilitating disease that affects an estimated 1% of the population and that induces considerable healthcare costs. A limited number of antirheumatic drugs are available to modify disease activity and progression of joint destruction with subsequent disability. There are 4 general classes of drugs commonly used in the treatment of RA: nonsteroidal antiinflammatory agents, corticosteroids, disease modifying antirheumatic drugs (DMARD), and biologicals. DMARD include methotrexate (MTX), leflunomide, antimalarials, gold salts, sulfasalazine (SSZ), D-penicillamine, cyclosporin A, cyclophosphamide, and azathioprine (AZA). In most cases the pharmacological therapy of RA is based on DMARD with or without coadministration of glucocorticoids (GC). The main problem of drug treatment in RA is cumulative toxicity and frequent adverse effects (AE)[1,2]. In addition, drug toxicity is a common cause for discontinuation of any type of therapy in RA[3]. Low-dose GC are often given orally to achieve better symptomatic control or as bridge therapy before the onset of action of DMARD. Recent evidence suggests that low-dose GC also slow the radiographic progression of articular disease in early RA, although joint damage increased following the withdrawal of GC therapy[4-7]. Still, GC are used commonly in the treatment of RA, and the percentage of patients taking GC is rising[8,9]. In a retrospec-

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Accepted for publication January 24, 2008.

tive study we tested whether GC are able to prolong the survival time of DMARD in patients receiving combination therapy.

MATERIALS AND METHODS

Patients. Our study was designed as a retrospective, open-label, observational trial. Since 1973 all patients meeting the American College of Rheumatology classification criteria for RA were included to compare effectiveness of various therapeutic strategies. Baseline clinical variables (rheumatoid factor, initial presence of erosion, disease duration) and sociodemographic variables (age, sex) did not differ significantly between groups. Clinical and laboratory findings as well as AE of therapy were recorded for each patient during visits in the outpatient clinics. The final assessment of case histories included duration of various types of therapy, frequency and severity of AE, and clinical outcome of RA. Due to the known AE of lengthy GC therapy the following exclusion criteria were applied: previous history of active gastrointestinal problems; serious complicating disease such as arterial hypertension, psychiatric or mental problems, and diabetes mellitus; and patients with steroid pulse therapy. Thus, 154 patients with RA were enrolled for study, 84% of them female. At the start of the study the mean age was 47.2 ± 5.4 years, at the final examination the mean age was 60.4 ± 12.2 (range 22–85 yrs), with a mean disease duration of 17.8 ± 3.9 years. The mean observation time of patients was 12.7 ± 3.9 (0.6–39 yrs). 84% of the patients had a positive rheumatoid factor test. There was no statistically significant difference between patients taking GC and not taking GC for age at disease onset, disease duration before treatment, sex, or rheumatoid factor and radiological status at first presentation. Radiological progression was determined according to the Steinbrocker radiographic stage[10].

Treatment. Patients entering the study were assigned to various types of therapy due to disease activity and the respective dosing recommendations, as follows: hydroxychloroquine (HCQ; 200–400 mg/day); intramuscular gold (aurothioglucose, final dose 50–100 mg/4 weeks); oral MTX (7.5–20 mg/week); AZA (1–2 mg/kg/day); SSZ (1–2 g/day); cyclosporin A (CSA; 2.5–5 mg/kg/day); and D-penicillamine (D-Pen; 150–450 mg/day) as monotherapy or in combination with low–dose GC (≤ 7.5 mg daily). The range of duration of various therapies was 2–62 months.

At baseline 91 patients (59%) received treatment with HCQ, 23 (14.8%) were given MTX, 19 (12.2%) received gold, 10 (6.4%) took SSZ, and 6 patients (3.8%) took low–dose prednisolone alone. Due to lack of effectiveness or AE, medication had to be changed to other DMARD. In total, 125 patients (81%) received MTX, 91 (59%) received HCQ, 63 (41%) received gold, 48 (31%) received AZA, 47 (30%) received SSZ, 19 (12.3%) received CSA, and 15 patients (9.7%) received D-Pen.

One hundred one patients (65.1%) received a combination therapy including 61 patients (39.3%) with low-dose GC therapy. 54 patients (34.9%) were taking a monotherapy of DMARD without GC. The assigned medication was continued unless adverse reactions or ineffectiveness necessitated discontinuation. All AE were described in the study protocols. The use of pure analgesics and nonsteroidal antirheumatic drugs was allowed in all groups.

Toxicity. Assessments were performed at the start, every 3 months during the first year, and subsequently every 6 months or in any case of clinical problems. Clinical variables, including disease activity variables, medication, and occurrence of AE, were assessed by the physician for each patient on each visit. Safety investigations included clinical examination and laboratory measures. All adverse experiences were reported, regardless of their relationship to the antirheumatic therapy, and are referred to in this report as adverse effects. Due to standardized reporting of AE, they were defined as follows: grade 0, no AE or within normal limits; grade 1, mild AE not requiring treatment; grade 2, moderate AE resolved with treatment; and grade 3, severe AE resulting in inability to carry on normal activities and requiring professional medical attention[11]. Grade 4 and 5 AE were very rare and were therefore excluded from our analysis.

Statistics. Incidence of AE of drug exposure was assessed for each treatment strategy including combination with GC. Differences in the unadjusted rates for combination treatment and monotherapy were estimated using the chi-square test. Odds ratios were calculated using Epi-Info version 3.3.2 2005[12]. The effects of low-dose GC on AE were modelled using multiple logistic regression analysis controlling for covariants including AE, duration of DMARD therapy, duration of low-dose GC therapy, and previous type of DMARD therapy. P values, adjusted odds ratios, and 95% confidential intervals were calculated for outcomes in patients with combination therapy of DMARD with low-dose GC and compared to patients with DMARD alone. All analyses were performed using logistic procedures with SigmaStat 3.1.

RESULTS

Frequency measures and relative risk of AE for all therapies are presented in Table 1.

Use of GC significantly increased the time until withdrawal of DMARD therapy due to AE (18.6 ± 2.3 vs 12.5 ± 1.4 mo; $p < 0.05$). However, timing of withdrawal of DMARD due to loss of efficacy was not different between RA patients taking GC and GC-naïve patients, probably due to higher level of disease activity in RA patients with GC comedication. Stratifying for DMARD revealed that comedication with GC significantly increased the duration of therapy with SSZ from 10.4 ± 2.3 to 22.5 ± 1.9 months (SSZ + GC; $p < 0.05$) and for MTX from 21.8 ± 2.9 to 43.3 ± 2.7 months (MTX + GC; $p < 0.01$). However, in patients taking AZA the duration of therapy decreased from 44.4 ± 2.6 to 22.3 ± 1.6 months (AZA + GC; $p < 0.05$) (Figure 1).

Investigation for the reason for DMARD withdrawal due to AE or loss of efficacy revealed that GC comedication significantly increased the time until occurrence of AE for MTX (3.0 ± 0.6 vs 18.8 ± 1.3 mo; $p < 0.05$), HCQ (34.5 ± 4.6 vs 54.4 ± 5.1 mo; $p < 0.05$), and gold (6.6 ± 0.9 vs 10.5 ± 0.9 mo; $p < 0.05$). However, the decrease of AZA survival was due to earlier withdrawal under GC comedication because of AE (AZA 15.5 ± 1.4 mo vs AZA + GC 4.9 ± 0.8 mo; $p < 0.05$) as well as loss of efficacy (AZA 47 ± 3.1 mo vs AZA + GC 26 ± 1.1 mo; $p < 0.05$).

Of interest, in patients taking SSZ, the time to cessation due to loss of efficacy increased significantly under GC comedication, from 16.8 ± 1.2 to 31.3 ± 2.9 months ($p < 0.05$).

In total, 64 patients (41.2%) experienced AE, with differences in frequency between various DMARD. The highest incidence of AE was observed for D-Pen (40%), followed by HCQ (34%), AZA (27%), gold (23%), MTX (20.8%), SSZ (19.1%), and CSA (15.7%).

Also, the main AE varied between DMARD; i.e., for D-Pen, hematological AE (50%) such as leukopenia and thrombocytopenia prevailed. For HCQ, the majority of AE affected the eye (84%) and led to gastrointestinal complaints. AZA caused mainly gastrointestinal (23%) and hematological (15%) AE, followed by intolerance to AZA (15%). For patients treated with gold, renal (12%), mucocutaneous (8%), and gastrointestinal (8%) AE as well as aller-

Table 1. Frequency of adverse effects in RA patients with and without low-dose glucocorticoids (GC).

	Treatment by DMARD													
	MTX, n = 125		HCQ, n = 91		Gold, n = 63		SSZ, n = 47		AZA, n = 48		DPA, n = 15		CYC, n = 19	
	Mono, n = 74	+GC, n = 51	Mono, n = 69	+GC n = 22	Mono, n = 49	+GC n = 14	Mono, n = 28	+GC n = 19	Mono, n = 30	+GC n = 18	Mono, n = 10	+GC n = 5	Mono, n = 13	+GC n = 6
No. of patients with adverse effects (%)	9 (12.1)	17 (33.3)	19 (27.4)	12 (54)	17 (34.6)	8 (57.4)	4 (14.2)	5 (26.3)	5 (16)	8 (50)	4 (40)	0 (0)	2 (15.3)	1 (16.7)
Odds ratio	3.6*		4.3*		0.4		0.47		4.0*		0.3		0.91	
95% Confidence	1.3–9.9		1.6–11.7		0.10–1.55		0.08–2.49		1.1–9.1		0.07–3.14		0.04–32.5	
p	0.008		0.003		0.12		0.3		0.04		0.3		0.54	

Mono: Disease modifying antirheumatic drug (DMARD) monotherapy; +GC: DMARD in combination with low-dose glucocorticoids; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; AZA: azathioprine; DPA: D-penicillamine; CYC: cyclosporine. * Significant.

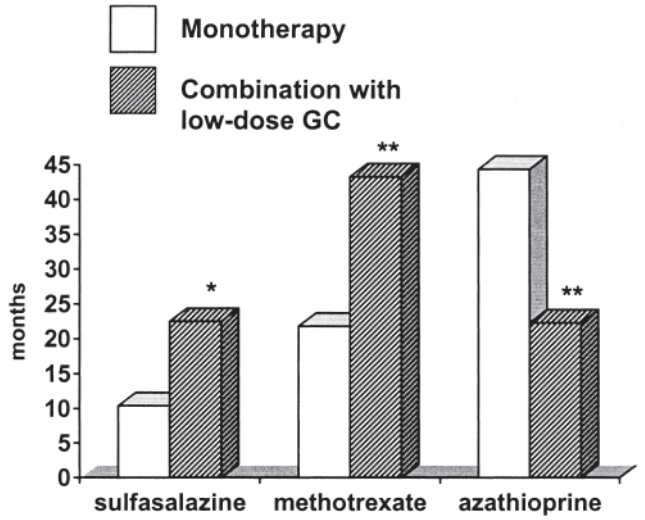

Figure 1. Duration of DMARD therapy and frequency of adverse effects in RA patients with and without low-dose glucocorticoid (GC) therapy. For hydroxychloroquine, intramuscular gold, D-penicillamine, and cyclosporine, no significant difference was detected for therapy adherence between DMARD monotherapy and GC comedication. *p < 0.05, **p < 0.001.

gy (12%) prevailed. For MTX, mucocutaneous (30.7%, including alopecia, 15.3%) and gastrointestinal (23%) AE were the most frequently noted, together with intolerance to MTX (15.5%). AE for SSZ comprised gastrointestinal problems (33%) and allergic reactions (22%). Thus, each medication exhibited a specific array of AE.

GC comedication was associated with a significant increase of AE for various DMARD. Besides the typical AE for GC (reported below), comedication with DMARD exhibited different AE compared to monotherapy. Patients taking HCQ + GC had significantly more AE (54%; OR 4.3, 95% CI 1.6–11.7, p = 0.003) compared to HCQ alone (27.5%), with thyroid disease (goiter; 9% vs 1.4%; p < 0.05) as the main AE not directly associated with GC therapy. Patients under comedication of MTX + GC experienced significantly more AE (33.3%) compared to those with MTX monotherapy (12.1%; OR 3.6, 95% CI 1.3–9.9, p = 0.008) due to chronic obstructive pulmonary disease in the comedication group (3.9% vs 0%; nonsignificant). Similarly, combination therapy of AZA + GC (n = 18) resulted in more AE (50%) compared to AZA alone (16%; OR 4.0, 95% CI 1.1–9.1, p = 0.04) due to increased hematological complications (leukocytopenia, thrombocytopenia, anemia, 11% vs 3.3%; nonsignificant). Patients taking gold + GC had significantly more functional disorders of the nervous system such as sleep disorder and headache compared to those with gold monotherapy (14.2% vs 2%; p < 0.05). Finally, comedication of SSZ + GC led to peripheral edema due to functional venous insufficiency in 5.2% of patients versus 0% in patients with SSZ monotherapy.

However, a reduction of AE was observed in patients receiving a combination therapy of D-Pen and GC (0% vs 40% in D-Pen monotherapy). Examination of the severity of AE (Table 2) revealed differences between the DMARD studied. In most cases AE were self-limited and mild (grade ≤ 2). In patients taking HCQ or MTX severity grade 2 prevailed, while in patients taking gold mostly grade 2 and 3 AE and in patients taking SSZ predominantly grade 3 AE were observed. In patients treated with gold + GC a significant increase of grade 3 AE occurred [3.7% in the gold group vs 27.8% in gold + GC (OR 2.9, 95% CI 2.1–9.58, p = 0.005)], while gold monotherapy led to predominantly grade 0 AE [77.4% vs 33.3% in gold + GC (OR 10.2, 95% CI 2.5–43.6, p < 0.001)]. GC reduced the rate of grade 0 AE in patients taking MTX [68% vs 87.8% in MTX monotherapy (OR 3.4, 95% CI 1.2–9.4, p = 0.006)] and grade 1 AE in patients taking AZA [(5.5% vs 10% in AZA monotherapy (OR 4.2, 95% CI 1.4–9.5, p = 0.004)]. Overall, there were 5 patients diagnosed with cancer, 2 with non-Hodgkin lymphomas, 1 myocardial infarction, 1 stroke, and 1 with nephrectomy.

Multiple regression logistic analysis revealed that the duration of a combination therapy with various DMARD was a significant factor for developing AE (Table 3). Results were obtained using previous DMARD therapy, duration of DMARD therapy, and duration of GC therapy as factors.

Table 2. Severity and frequency of adverse events under various DMARD therapies. Grade 0, no adverse event or within normal limits; grade 1, mild adverse event not requiring treatment; grade 2, moderate adverse event resolved with treatment; grade 3, severe adverse event resulted in inability to carry on normal activities and requiring professional medical attention[7].

	HCQ, n = 91		Gold, n = 63		SSZ, n = 47		MTX, n = 125		AZA, n = 48		D-Pen, n = 15		CYC, n = 19	
	Mono, n = 69	+GC, n = 22	Mono, n = 49	+GC n = 14	Mono, n = 28	+GC n = 19	Mono, n = 74	+GC n = 51	Mono, n = 30	+GC n = 18	Mono, n = 10	+GC n = 5	Mono, n = 13	+GC n = 6
Grade 0, n (%)	45 (65.2)	10 (50)	41[a] (77.4)	6 (33.3)	24 (77.4)	12 (75)	65[b] (87.8)	34 (68)	25 (80)	17 (68.6)	7 (70)	5 (100)	11 (84.6)	5 (83.8)
Grade 1, n (%)	1 (1.4)	1 (4.5)	1 (1.9)	4[c] (22.2)	2 (6.4)	1 (6.2)	3 (4)	7 (13.7)	2[d] (10)	8 (5.5)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 2, n (%)	17 (27.6)	9 (41)	5 (9)	3 (16.7)	1 (3.3)	2 (12.5)	4 (5.4)	5 (9.8)	3 (10)	0 (0)	3 (30)	0 (0)	1 (7.7)	1 (16.7)
Grade 3, n (%)	4 (5.8)	1 (4.5)	2 (3.7)	5[e] (27.8)	4 (12.9)	1 (6.2)	2 (2.7)	4 (7.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.7)	0 (0)

[a] OR 10.2, 95% CI 2.5–43.6, p = 0.0006. [b] OR 3.4, 95% CI 1.2–9.4, p = 0.006. [c] OR 3.7, 95% CI 2.64–11.4, p = 0.0001. [d] OR 4.24, 95% CI 1.38–9.5, p = 0.004. [e] OR 2.9, 95% CI 2.1–9.58, p = 0.005.

Table 3. Risk factors associated with adverse effects of DMARD therapy with and without low-dose glucocorticoids (GC).

DMARD	OR	95% CI	p
HCQ + GC			
Duration of HCQ treatment > 6 mo	5.53	2.32–13.22	0.0001
Gold + GC			
Duration of gold treatment > 3 mo	2.1	1.02–3.09	0.05
Gold monotherapy			
Duration of gold treatment > 3 mo	2.5	1.07–6.51	0.035
AZA + GC			
Previous therapy with HCQ	8.83	1.03–25.7	0.04
AZA monotherapy			
Previous therapy with D-pen	1.67	1.1–2.76	0.02
MTX + GC			
Previous treatment with AZA	3.19	1.27–7.99	0.01
MTX monotherapy			
Previous treatment with AZA	2.78	1.43–5.4	0.01

For definitions, see Table 1.

Patients on HCQ + GC for more than 6 months had an increased risk (OR 5.5, 95% CI 2.3–13.2, p = 0.0001), as well as patients on gold + GC or gold monotherapy for more than 3 months (OR 2.1, 95% CI 1.02–3.09, p = 0.05 and OR 2.5, 95% CI 1.07–6.51, p = 0.035, respectively). Interestingly, an increased risk for AE due to previous DMARD therapies was observed, i.e., patients receiving AZA + GC after a phase of HCQ or patients on AZA monotherapy after a phase of D-Pen had an increased risk for AE (OR 8.8, 95% CI 1.0–25.7, p = 0.04 and OR 1.67, 95% CI 1.1–2.76, p = 0.02, respectively). Further, patients receiving MTX after AZA also experienced significantly more AE (MTX monotherapy: OR 2.78, 95% CI 1.43–5.4, p = 0.01; MTX + GC: OR 3.19, 95% CI 1.27–7.99, p = 0.01).

The mean duration of low-dose GC treatment was 92.4 ± 12.7 weeks. Hence, it was of interest to look at patients' clinical outcomes. Disease duration was significantly different between those undergoing DMARD monotherapy and DMARD + GC (25.0 ± 5.7 vs 18.4 ± 4.2 yrs, respectively; p < 0.05). Of interest, a highly significant reduction was observed in the frequency of erosive RA in patients with GC comedication (n = 30, 49.1%) compared to patients without low-dose GC (n = 81, 80.4%; OR 4.05, 95% CI 1.91–8.66, p < 0.0001). At the final examination 75 patients (48%) had accompanying health problems in addition to RA. Analysis of these events showed that the highest incidence was for osteoporosis (47.2%), followed by thyroid disease (goiter, 19.4%), diabetes mellitus (11%), malignancy (11%), chronic obstructive pulmonary disease (4.1%), and arterial hypertension (2.7%). Stratifying patients for treatment regimens revealed significant differences: patients treated with GC developed significantly more osteoporosis (OR 4.53, 95% CI 1.95–10.6, p = 0.0001), diabetes mellitus (OR 6.5, 95% CI 1.74-26.5, p = 0.001), and mucocutaneous events (OR 3.3, 95% CI 1.0–8.9, p = 0.03) (Table 4). Further, combination therapy with gold + GC led to an increase of nervous system dysfunctions including stroke (21.4% vs 0% in patients with gold alone), while combination therapy of MTX + GC resulted in an increase of arterial hypertension (5.8% vs 1.3% in MTX monotherapy; p < 0.05). However, only GC treatment of more than 48 weeks was associated with the development of osteoporosis and diabetes mellitus (OR 2.19, 95% CI 1.14–4.22, p = 0.01 and OR 20.2, 95% CI 1.7–42.8, p = 0.001, respectively).

DISCUSSION

The introduction of GC in the 1950s was a revolution in the treatment of a variety of inflammatory diseases. However, in the absence of treatment guidelines, side effects and toxicity of the often administered high doses of GC outweighed the beneficial effects in RA, resulting in a loss of confidence in GC in both physicians and patients. The molecular mechanisms of action of GC have been elucidated over the last 10 years. GC are potent antiinflammatory and immunosuppressive agents mediating their effects through genomic action[13,14]. To date, only 4 randomized trials have looked at combination therapy of GC and various DMARD[15-18]. However, Capell, *et al* described only AE, i.e., in the GC group at Year 1 anti-bone-resorptive treatment was used more often, and a trend toward higher diastolic blood pressure was observed[15]. Thus, to date information is scarce

Table 4. Outcomes in RA patients treated with DMARD alone and with comedication of low-dose glucocorticoids (GC). Only adverse effects of more than 3% are reported. Total number of adverse outcomes was not statistically different between DMARD monotherapy and comedication of DMARD + GC (OR 2.11, 95% CI 0.93–4.84, p = 0.07).

Health outcomes	DMARD Monotherapy, n (%)	DMARD + GC, n (%)	OR	95% CI	p
Osteoporosis	16 (15.2)	22 (44.9)	4.53	1.95–10.6	0.0001
Diabetes mellitus	4 (3.77)	10 (20.4)	6.5	1.74–26.5	0.001
Malignancy	6 (5.6)	3 (6.1)	1.0	0.2–5.2	0.58
Thyroid dysfunction	5 (4.7)	5 (10.2)	2.2	0.5–9.6	0.1
Infections	2 (1.9)	3 (6.1)	3.39	0.44–20.1	0.18
Gastrointestinal complications	11 (10.3)	6 (12.2)	1.21	0.3–3.8	0.6
Mucocutaneous complications	5 (4.7)	7 (14.2)	3.3	1.0–8.9	0.03
Intolerance	6 (5.6)	5 (10.2)	1.8	0.47–7.1	0.24

Table 5. Withdrawal of DMARD due to loss of efficacy with and without glucocorticoids (GC).

	No. of Patients									
	HCQ		Gold		SSZ		MTX		AZA	
	Mono, n = 69	GC, n = 22	Mono, n = 49	GC, n = 14	Mono, n = 28	GC, n = 19	Mono, n = 74	GC, n = 51	Mono, n = 30	GC, n = 18
n	5	5	9	6	5	9	9	7	6	5
p	NS		NS		NS		NS		NS	

NS: nonsignificant.

about effects of low-dose GC on development of AE in combination with DMARD. Studies suggest that concomitant[19] or prior[20] GC use is associated with an increased likelihood of discontinuation of DMARD. In a very recent study a weak effect of early GC medication on a higher likelihood of discontinuation was observed, while previous or concomitant GC use had no effect on discontinuation of DMARD[21]. However, our study and one other[22] revealed that there might be a DMARD-specific effect of GC comedication on DMARD survival time. The DMARD-specific effect of GC could arise as the integrative result of multiple possible interactions between the compounds. GC may interact via genomic and nongenomic mechanisms with the pharmacodynamic and pharmacogenetic characteristics of the various DMARD[23,24]. Further, interaction of active as well as inactive metabolites may interfere with the kinetics, efficacy, and toxicity of DMARD[2,25,26]. One study with higher doses of prednisolone demonstrated decreased total body and renal clearance of MTX under GC[27].

The modulated DMARD survival might be due to better disease control, which would be in contrast to a negative analysis of GC in RA[28]. However, recent studies demonstrated a disease-modifying effect of low-dose GC on radiological progression of RA, and the question has arisen whether the effect of DMARD in early RA may result in part because of the use of concomitant GC[1,5,6,29,30]. In particular, our results showing an increased survival time for SSZ with GC comedication point in this direction. As well, one trial revealed fewer withdrawals of SSZ under combination therapy with GC[31]. Still, a recent metaanalysis found only a few trials involving GC in RA therapy, and asked for more primary research on the GC-DMARD combination[2]. In this respect our retrospective study revealed a positive effect of GC comedication on radiological progression of RA, with overall frequency of erosive disease being in the same range as in previous observational studies[20,32], underlining the necessity of further prospective trials. However, our results point to a potential synergistic effect of GC in augmenting the effectiveness of other DMARD.

GC comedication changed the severity of AE, which varied between the DMARD. The rather higher frequency of AE for HCQ was in the range of previous studies[33]. In concordance with other investigators we observed that HCQ exhibited the longest survival time, followed by AZA, MTX, D-Pen, SSZ, and gold[20,32-35]. As others have done, we identified prior DMARD use as a risk factor for discontinuation of subsequent DMARD therapy. This might be due to increased disease activity[21,32] or increased AE of the subsequent DMARD[34], possibly indicating an increased individual risk to react with AE upon DMARD therapy.

It is thought that the side effects caused by GC are related to the dose given daily and cumulatively. A recent review of low-dose GC in RA therapy stated that AE were modest and mostly not statistically different from those with placebo[36]. In our study with low-dose GC we found the well known AE of osteoporosis and diabetes. However, low-dose

GC therapy longer than 48 weeks conferred increased risk for only these AE. Thus, in low-dose GC duration of therapy is a crucial factor for developing AE.

Our findings should be interpreted in light of some potential limitations. We performed a retrospective observational study that relied on clinical information from the patients' medical records. Therefore, information not adequately recorded about disease or therapy characteristics may have been missed. Further, we cannot exclude a prescription bias that patients with higher disease activity received GC comedication, explaining the even distribution of DMARD withdrawal due to loss of efficacy between DMARD monotherapy and GC comedication. Second, our study was conducted mostly before the introduction of biologic therapies so that we cannot draw any conclusion on the comedication of GC and biologics. However, although randomized trials are regarded as the gold standard in assessment of therapeutic effects of drugs, they may not be feasible under certain circumstances. Randomized trials typically run for no longer than a year, and only 20% of RA patients in the community would be eligible for inclusion into clinical trials due to strict inclusion and exclusion criteria. Moreover, for the management of patients with RA it is important to know about the longterm outcomes with different DMARD as well as AE of various therapeutic approaches. This is an area in which observational studies are invaluable for investigating real-life medication in patients with longstanding disease.

Our data show that in daily life, comedication of low-dose GC with DMARD had a profound effect on DMARD survival and AE due to the DMARD utilized. Patients with RA receiving GC comedication had a better outcome regarding radiological progression, but experienced more GC-related AE. However, in our study only long exposure to low-dose GC (> 48 weeks) increased the risk for developing osteoporosis or diabetes. Additional longterm studies, focusing on timing of administration and duration and identification of risk factors for developing AE, are warranted to establish the role of GC in the treatment of RA.

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