

Treatment of polymyalgia rheumatica and giant cell arteritis. II. Relation between steroid dose and steroid associated side effects

V KYLE AND B L HAZLEMAN

From the Rheumatology Research Unit, Addenbrooke's Hospital, Cambridge

SUMMARY In a prospective study of 74 patients and a retrospective study of 35 patients with polymyalgia rheumatica/giant cell arteritis steroid related side effects occurred in at least one third of patients, and in two thirds if weight gain was included. Side effects were significantly related to an initial prednisolone dose of more than 30 mg and to the cumulative prednisolone dose. Patients taking a mean daily dose of 5 mg prednisolone or less were significantly less likely to develop side effects.

There are no prospective studies examining the incidence of corticosteroid associated side effects in relation to different prednisolone doses; most studies quote an overall incidence of side effects for a wide range of prednisolone doses or do not specify the dose used. Side effects in 'more than half' the patients were recorded in a study using an initial dose of 30-80 mg prednisolone/day,¹ and increased mortality was reported in patients taking a maintenance dose of more than 10 mg/day.² Forty five per cent of patients with giant cell arteritis experienced side effects when treated with unspecified high doses of prednisolone.³ In one study 48% developed steroid related complications, though 71% patients stopped taking steroids within one year.⁴ The initial prednisolone dose was not stated but the median period while taking 20 mg prednisolone/day was two months. Ayoub *et al* found that neither the initial prednisolone dose (<20 mg in 67% but range unspecified) nor the maintenance dose related to a 22.7% incidence of side effects, but the duration of treatment did.⁵ A study in which the mean initial prednisolone dose was 33 mg found only 16% patients experienced side effects and felt many were coincidental.⁶ In a different study a low incidence (19%) of side effects was also recorded despite an initial dose of more than 20 mg prednisolone in 58% of the patients.⁷ Behn *et al* recorded side effects in 16% patients, mostly treated with 10-20 mg prednisolone/day initially.⁸ Two studies reported that

low dose steroids, usually 10 mg or less, rarely caused side effects—an incidence of 2-8%.^{3,9}

Thus although side effects appear uncommon with low dose steroids, the reported incidence of complications when more than 10 mg is used is unclear (ranging from 16% to over 50%), and the relation between side effects and initial and maintenance prednisolone dose is controversial.

Patients and methods

PROSPECTIVE STUDY

Seventy four patients with active polymyalgia rheumatica/giant cell arteritis (PMR/GCA) were randomly allocated to high or low dose treatment regimens. Thirty nine patients with PMR were treated initially with 10-20 mg prednisolone/day. Thirty five patients with GCA were treated with 40 mg/day for five days, followed by either 40 or 20 mg/day. Full details are given in Table 1 of the accompanying paper.¹¹ After two months no formal regimen was used, but the prednisolone dose was altered according to the patient's condition and the erythrocyte sedimentation rate (ESR). Length of treatment, maximum daily prednisolone dose, mean daily dose, and cumulative prednisolone dose were calculated. Possible side effects and weight changes were recorded. Patients were reviewed fortnightly for two months then every two to three months.

RETROSPECTIVE STUDY

Thirty five patients with PMR/GCA diagnosed and treated for at least 18 months were identified from a computerised diagnostic index. All fulfilled the

diagnostic criteria of Jones and Hazleman.¹⁰ Age, sex, diagnosis, length of follow up, maximum daily prednisolone dose, and cumulative prednisolone dose were recorded. A questionnaire presented at interview was used to record steroid related side effects. Patients were then classified into three groups depending on the severity of side effects: (a) no side effects; (b) mild side effects—either weight gain or steroid related skin changes; (c) major side effects—for example, fracture, diabetes mellitus, or the presence of both weight gain and skin changes.

STATISTICAL ANALYSIS

Analysis of variance (age, length of treatment, and follow up) and Kruskal-Wallis tests (prednisolone dose) were used.

Results

PROSPECTIVE STUDY

Patients were followed up for 12–177 weeks (mean 68.5, SE 5.4). Thirty six complications (excluding weight gain) attributable to steroid treatment occurred in 27 patients (Table 1). The most common fracture was of a vertebral body (five cases). Two patients had peptic ulcer perforation, and one both gastric and duodenal ulcers. The four patients with diabetes mellitus required the addition of oral hypoglycaemic drugs or insulin to control previously mild disease. One woman developed five complications: a moderately large pulmonary embolus, pyelonephritis, glaucoma, cataract, and deep venous thrombosis. In addition, four patients, (all following the GCA high dose regimen)¹¹ complained of feeling generally unwell while taking 40 mg prednisolone/day. Their symptoms (agitation, insomnia, malaise, and palpitations) had not been present before treatment and settled when the

prednisolone dose was reduced to 30 mg/day. Many patients also complained of hair thinning.

Side effects occurred from within one week of starting treatment to up to three years later. In 16 patients whose side effects arose within the first three months all but two had GCA. Dyspepsia, peptic ulceration, oedema, and loss of control of diabetes were the most common early complications. Two women developed vertebral collapse in the first three months, but most fractures occurred after at least one year of treatment.

Only five of the 27 patients with side effects had PMR alone and all were following the PMR high dose regimen. Of the remaining 22, 20 presented with GCA and two with PMR developed GCA. Only six continued with the GCA low dose regimen over the first two months. Two patients who required more than 40 mg prednisolone/day for GCA developed complications. The maximum daily dose of prednisolone was therefore higher in patients who developed steroid related side effects

Table 2 Cumulative prednisolone dose and mean daily prednisolone dose in relation to steroid associated side effects which occurred after three months

	Patients with side effects	Patients without side effects
Cumulative prednisolone dose (g)	6.86	4.05
Mean daily prednisolone dose (mg)	11.42	9.91

Table 1 Prospective study: steroid related side effects

Side effects	Numbers of cases
Fracture	10
Peptic ulcer	4
Diabetes mellitus	4
Dyspepsia	5
Cataract	2
Deep vein thrombosis	2
Grafts to lacerations	2
Severe ankle oedema	2
Pulmonary embolus	1
Severe bruising	1
Infection	1
Herpes zoster	1
Glaucoma	1

MAXIMUM WEIGHT GAIN

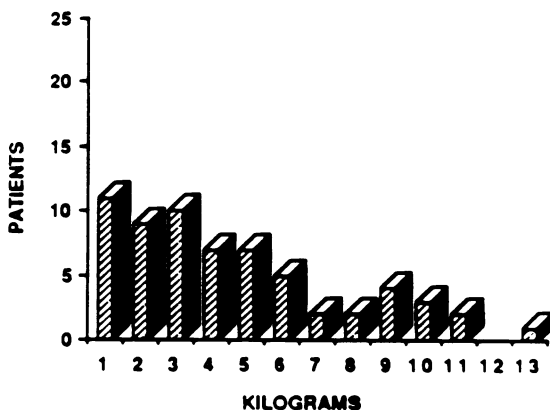


Fig. 1 Maximum weight gain in all patients followed up for at least one year. Blocks=numbers of patients.

because almost all were following high dose regimens. The cumulative and mean daily prednisolone doses were higher in those who developed side effects after three months than in those who did not (Table 2).

In addition, 40 patients (33 female) gained at least 2 kg and had maintained this increase at the end of

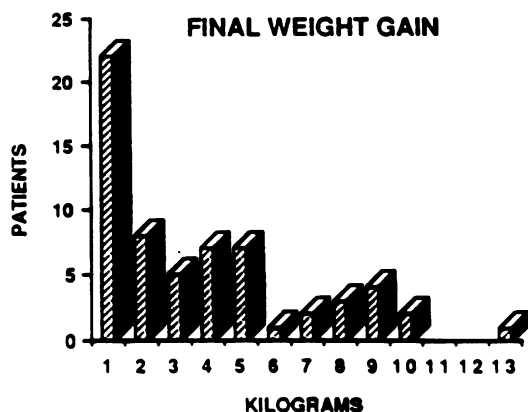


Fig. 2 Final weight gain in all patients followed up for at least one year at the end of the study. Blocks=numbers of patients.

the study; half the group had PMR only. Sixteen patients with PMR and 18 with GCA either required an increase in steroid dose in the first two months or had been following a high dose regimen from the start. Figures 1 and 2 show the maximum and final weight gains. These patients were followed up for a mean period of 62.7 weeks compared with a mean follow up period of 73.5 weeks in all the other patients. The mean cumulative prednisolone dose was higher in those who gained weight (4.68 g) than in those who did not (4.40 g) despite the shorter follow up period. Eleven patients gained more than 2 kg (mean maximum gain 3.64 kg) but had returned to within 1 kg of their baseline weight by the end of the study. These patients had a longer mean follow up (115.5 weeks) and a lower mean daily dose (6.36 mg) than those who persistently gained weight (11.55 mg). The remaining patients either had no change or a small decrease.

RETROSPECTIVE STUDY

Thirty five patients were assessed, 24 of whom were female. Twelve had experienced no side effects and 11 had minor side effects. Twelve complained of more numerous or major side effects (Table 3). The age at diagnosis ranged from 53 to 85 years (mean 74.3) with a follow up of 1.5 to 11 years (mean 4.6)

Table 3 Retrospective study: major steroid related side effects

Patient No	Weight gain	Skin changes	Fracture	Dyspepsia	Infection	Haematoma	Myopathy	Hypertension	Cataract	Mood
1		+			+					
2	+				+				+	
3	+	+								
4	+	+							+	+
5	+	+	+	+			+			
6	+	+		+	+					
7	+	+	+	+			+			
8						+				
9	+	+	+	+				+		
10	+	+								
11	+	+								
12			+							
Total	9	9	4	4	3	1	2	1	2	1

Table 4 Retrospective study of steroid related side effects. Figures shown are mean values

Side effects	Number of patients	Age	Duration of treatment (years)	Follow up (years)	Max. daily dose (mg)	Cumulative dose (mg)
None	12	71	3.2	4.1	11.8	5.8
Minor	11	75.4	3.9	4.3	34.3	10.3
Major	12	76.5	4.5	5.5	39.1	10.7
All patients	35	74.3	3.8	4.6	27.9	8.9

since starting steroid treatment. Steroids had been taken for from 1.5 to 10 years (mean 3.8). The maximum daily dose taken ranged from 5 to 80 mg prednisolone (mean 27.9) and the total amount consumed ranged from 2.31 to 30.6 g (mean 8.9) (Table 4). The maximum daily dose taken in each group was significantly different ($p < 0.001$). This was mainly owing to the much lower doses in those with no side effects (11.8 mg) than in those with minor side effects (34.3 mg) and major side effects (39.1 mg). It can be seen that those with the most serious side effects had taken the largest daily doses. The cumulative doses in each subgroup were also significantly different ($p < 0.01$), and again this was mainly because of the much lower dose consumed by those with no side effects (5.8 g) compared with the amount taken by those with minor side effects (10.3 g) and major side effects (10.7 g).

The mean age, duration of steroid treatment, and period of follow up were not significantly different when the subgroups were analysed. Although the mean duration of steroid treatment tended to be shorter in those with no side effects (3.2 years) than in those with major side effects (4.5 years), this did not reach statistical significance.

Discussion

The incidence of steroid associated side effects in the prospective group was higher (27/74, 36%) than that reported in many retrospective series with much longer follow up periods. If sustained weight gain was included the incidence rose to 76% (56/74). Possibly some side effects, such as osteoporotic fracture, were coincidental in patients of this age group, and the true incidence was lower. The follow up period for this study was relatively short, however, and further steroid related complications could have developed. The lower incidence of side effects in some retrospective studies may arise because data were obtained from case notes in which only major problems were noted. The retrospective study reported here used direct questioning of the patients as well as references to hospital notes. One third of patients reported major complications, rising to two thirds of patients when skin changes or weight gain were included—very similar to the incidence of side effects in the prospective study. It is of interest that the side effects of which the patients complained were not always recorded in the case notes. It has also been shown that individual sensitivity to steroids is genetically related^{12 13} and may be HLA linked.¹⁴ This may account for some of the reported variation in the incidence of steroid side effects.

Results of the prospective study suggest that side effects are more likely to occur in patients treated

with higher doses of prednisolone initially. All took at least 20 mg prednisolone initially, and 80% 30 mg or more. The cumulative dose was 70% higher in those who developed side effects. The mean daily dose was higher in patients with side effects, but the difference was less marked, probably because of the relatively short follow up. Weight gain was less strongly related to the initial prednisolone dose, and it may be that there is a subgroup of patients who are at risk of gaining weight. Most of the weight gain occurred over the first year, and some patients may with time lose the weight gained.

The retrospective study provided information on a group of patients in whom a wide range of prednisolone had been used over many years, and the follow up period was sufficiently long to ensure that most steroid related complications would be detected. Side effects were significantly related both to the maximum daily dose of prednisolone used and to the cumulative dose taken. The maximum daily dose was at least three times greater and the cumulative dose double in those with side effects.

Side effects were similar to those seen in other diseases treated with steroids. Whether steroids cause or exacerbate peptic ulceration remains controversial, but proved and possible upper gastrointestinal ulceration have been shown to be increased, though not to statistically significant levels, in patients taking steroids, and the incidence of peptic ulceration has been shown to be related to both dose and duration of treatment.¹⁵ Another study showed a statistically significant increase of peptic ulcers and gastrointestinal bleeding in patients treated with steroids compared with controls.¹⁶ Thromboembolism has been reported in relation to steroid treatment,^{17 18} and high dose steroids have been shown to induce a state of hypercoagulability.^{19 20} Patients in this study who developed pulmonary embolus or venous thrombosis were taking high doses of prednisolone without other risk factors for thrombosis, and probably these were steroid related complications.

These findings suggest that corticosteroid related side effects in PMR/GCA occur more frequently than previous retrospective studies have suggested. Side effects are significantly more common in patients treated with an initial high dose of prednisolone of more than 30 mg/day and in patients in whom prednisolone is continued for many years at a mean dose of more than 5 mg/day. A high cumulative prednisolone dose was also associated with the development of side effects. It is clear that attention should be given to monitoring the steroid dose so that the lowest dose of steroid is used to control symptoms, and thus frequent careful follow up is required.

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