Muscle loss following a single high-dose intramuscular injection of corticosteroids to treat disease flare in patients with rheumatoid arthritis


Abstract

Objective: Adverse changes in body composition, specifically decreased muscle mass (MM) and increased fat mass, characterize rheumatoid arthritis (RA). These changes, termed rheumatoid cachexia (RC), are important contributors to the disability and elevated co-morbidity risk of RA. Recently, we observed substantial muscle loss (~2 kg) in a patient with RA following a single intramuscular (IM) corticosteroid (CS) injection to treat a disease flare. The aim of the current study is to determine whether this apparent iatrogenic effect of IM CS is typical, i.e., does this routine, recommended treatment contribute to RC?

Methods: Body composition was assessed by dual-energy X-ray absorptiometry (DXA) in eight patients with established RA who received a 120 mg IM methylprednisolone injection to treat a disease flare. DXA scans estimated appendicular lean mass (ALM; a surrogate measure of MM), total lean mass (LM), and total and regional adiposity at baseline (injection day) and 4 weeks and 6-9 months post-injection. Statistical analysis was performed using one-way ANOVA.

Results: There was significant loss of ALM (-0.93 kg, p=0.001, 95% CI [-0.49, -1.36]) and a trend toward reduced LM (-1.10 kg, p=0.165, 95% CI [0.58, -2.79]) at 4 weeks relative to baseline. At 6-9 months despite control of inflammation and disease activity, these losses remained.

Conclusion: Substantial muscle loss occurred in patients with RA following IM CS injection to treat a disease flare. Thus, this recommended treatment appears to exacerbate RC, thereby potentially increasing disability and co-morbidity risk. If this effect is confirmed by larger studies, the role of one-off high-dose CS in the treatment of RA should be reviewed.

Keywords: Rheumatoid arthritis, body composition, rheumatoid cachexia, corticosteroids, disease flare
mass, ALM; i.e., ~7% of total ALM) in a patient with RA following a single CS injection given to treat a disease flare (10). A search of the literature revealed only one other case report of local muscle loss following CS injection (11). However, in this report, assessment of muscle loss was only made by visual observation. Nonetheless, these two reported cases raise concerns that high-dose CS injection treatment may be contributing to the reduced MM that we recently reported persists even in patients with aggressively and successfully, pharmacologically treated contemporary RA (3).

To our knowledge, this pilot study is the first to investigate the effects on body composition of a single high-dose IM CS injection. We hypothesized that this routine, recommended treatment for high RA disease activity exacerbates muscle loss and thus could contribute to the impaired physical function seen in patients with RA.

**Methods**

**Participants**

Patients with established RA presenting with a disease flare and treated with an IM injection of CS were recruited from the rheumatology outpatient clinics of the Peter Maddison Rheumatology Centre, Gwynedd Hospital. For inclusion, participants had to: (a) fulfill the ACR/EULAR 2010 revised classification criteria for the diagnosis of RA, (b) have uncontrolled RA disease activity for which IM CS injection was deemed to be the appropriate treatment, (c) be aged ≥18 years, (d) not be cognitively impaired, (e) be free of other cachectic diseases or conditions, (f) not be pregnant, and (g) not have any contraindication to high-dose IM CS injection (e.g., uncontrolled diabetes mellitus, active infection, and previous hypersensitivity to CS injections).

This pragmatic, uncontrolled, pre-post-intervention pilot study was approved by the North Wales Research Ethics Committee - West (15/WW/0013).

**Clinical assessments and treatment**

Active disease (i.e., flare) was determined by the attending consultant rheumatologist following clinical assessment. If considered appropriate by the same rheumatologist, and patient consent was obtained, a standard CS injection, 120 mg of Depomedrone (methylprednisolone acetate aqueous solution), was administered into the gluteal muscle.

Patient’s disease activity (Disease Activity Score in 28 joints, DAS28-CRP) and systemic inflammation (C-reactive protein, CRP) were determined at baseline (immediately prior to injection) and during routine rheumatology follow-up clinics at approximately 4 weeks (27-32 days) and 6-9 months post-injection.

**Body composition measures**

DXA scans were performed within 1 hour of the patient receiving the injection (baseline) and repeated at ~4 weeks and 6-9 months post-injection. Total and regional lean and fat masses, along with bone mineral content (BMC) and density (BMD), were estimated using a whole body fan beam DXA scanner (Hologic, QDR Discovery 45615, software V12.4). ALM (the summed LM of the arms and legs) served as a surrogate measure of total body MM (3). The in-house coefficient of variation of 1.4% of our scanner complies with the manufacturer’s guidelines (3).

**Statistical analysis**

The primary outcome measure was DXA-assessed ALM, with secondary outcome measures of: disease activity (DAS28-CRP) and systemic inflammation (CRP) and other body composition variables: total LM, % ALM relative to body mass (BM) (ALM/BM %), total FM, trunk FM, % FM relative to BM (% body fat), % trunk FM relative to total FM (trunk FM %), BMC, and BMD.

Data analyses were performed by one-way ANOVAs (three time-points), with effect size (small=0.20-0.49, medium=0.50-0.79, and large=0.80) calculated for each variable. Data analyses were performed using the Statistical Package for the Social Sciences 22 (IBM Corp.; Armonk, NY, USA). Data are generally presented as mean (±SD), with between-time differences presented as mean (±95% confidence intervals, 95% CI), and, where appropriate, range is also given. Significance was set at p<0.05.

**Results**

Nine patients with RA who received an IM CS injection to treat a flare of disease were deemed eligible for the study and consented to participate. Assessments at baseline, 4 weeks, and 6-9 months post-injection were performed on eight patients, as one participant withdrew from the study after baseline measurements owing to suspected meningitis. The mean interval between CS injection and baseline DXA scan was 0.7 h (~42 min; range: 18-60 min).

Table 1 shows the baseline demographic data for the eight patients who completed the study. All patients had established disease (mean duration ~11 years, range: 2.0-46.8 years) and were on standard disease-modifying anti-rheumatic drug therapy. None of these patients, either at the time of the CS injection or over the ensuing 6-9 months, were treated with either biologics or oral steroids. Patients reported no substantial changes to lifestyle (e.g., diet or exercise) or adverse health events, over the trial period.

Significant reductions in DAS28-CRP (p=0.049, 95% CI [-0.82, -2.30]) and CRP (p=0.023, 95% CI [-0.78, -28.95]) from baseline to 4 weeks indicated that the patients were responsive to the anti-inflammatory effects of IM CS (Table 2). This response is also reflected in 5 out of 8 patients experiencing clinically meaningful improvements in DAS28 (reduction >1.2) and CRP (reduction >10 mg/L) in the 4 weeks following CS injection (Table 2). Measures at 6-9 months indicated continued maintenance of control of disease activity and inflammation (data not shown), which was consistent with no reports of flares during this period.

Mean body composition changes over the study duration are shown in Table 3. Four weeks following IM CS injection, an average of 0.93 kg ALM (i.e., MM) was lost, whereas mean total LM was reduced by 1.10 kg. All eight patients lost ALM in the month following IM CS injection, with seven losing >0.50 kg (Table 2). Mean proportional ALM (ALM/BM %, i.e., relative MM) was significantly reduced at 4 weeks post-injection. Although all mean measures of adiposity increased over this period, i.e., total FM (+0.70 kg), trunk FM (+0.53 kg), % body fat (+0.89%), and trunk FM % (+1.01%), none of these changes were statistically significant. Although there were no significant changes in any of the body composition measures between the follow-up assessments at 4 weeks and 6-9 months (p values=0.32-0.54), during which time control of inflammation and disease activity was maintained, LM measures

| Table 1. Baseline demographics of patients with rheumatoid arthritis receiving intramuscular corticosteroid injection to treat a disease flare (n=8) |
|------------------------|---------------------|---------------------|
| Age (years)            | 61.4 (±7.2)         |
| Sex (n female) (%)     | 6 (75)              |
| Disease duration (months) | 130.5 (±158.8)     |
| DAS28-CRP              | 4.51 (±0.97)        |
| CRP (mg/L)             | 23.4 (±20.9)        |

Data presented as mean (±SD)

DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein
tended to decline further, whereas FM measures regressed back to baseline levels (Table 3). Thus, 6-9 months after IM CS injection, the depletion in ALM observed at 4 weeks had not spontaneously reversed, and patients remained significantly muscle reduced relative to their baseline levels.

No changes in BMD or BMC were detected at 4 weeks or 6-9 months (data not shown; p values=0.620 or 0.664, respectively).

**Discussion**

To our knowledge, the present study is the first to objectively investigate the consequences of a single, high-dose administration of CS on body composition. Although only preliminary, results from eight patients, taken with a similar observation from our case study, suggest that a single, high-dose IM CS injection used to treat active RA disease results in significant loss of ALM - a surrogate measure of skeletal MM (10). As this reduction in MM is likely to have adverse effects on physical function, these findings raise important concerns about the routine use of this treatment for patients with RA with active disease.

Patients presenting with uncontrolled RA are often treated by IM CS injection. Indeed, such injections are recommended by national guidelines for the management of active RA (e.g., ACR, EULAR, BSR, and NICE) because of their efficacy in rapidly attenuating inflammation and pain (4-8). Consistent with these recommendations and its regularly observed clinical benefit, the CS injections administered in the present study ameliorated disease activity and inflammation, with mean DAS28 and CRP at 4 weeks being reduced, relative to baseline, by 35% and 64%, respectively.

However, despite rapidly restoring control of inflammation and disease activity, there were mean losses of 0.93 kg and 1.46 kg in ALM (i.e., skeletal muscle), respectively, in the 4 weeks and 6-9 months following IM CS injection. This apparent iatrogenic loss of ALM accounts for approximately 37% of the discrepancy in proportional MM (i.e., ALM/BM %) between patients with RA and healthy age- and sex-matched individuals we have previously reported (3). Additionally, reduced MM, including the magnitude of MM loss observed in the present study (~7% of total MM), is acknowledged as a major contributor to the decreased strength and impaired physical function char-
the established effect on skeletal muscle of... Additionally, our findings of reduced MM... S6 kinase 1, PI3K/Akt, and insulin-like growth inhibition of anabolic pathways (e.g., mTOR/... atrogenes (genes, such as FOXO, Atrogin-1, MuRF-1, involved in muscle atrophy) brought about by increased expression of... ed muscle protein breakdown via stimulation of the catabolic ubiquitin-proteasome system brought about by increased expression of atrogenes (genes, such as FOXO, Atrogin-1, and MuRF-1, involved in muscle atrophy) and attenuated muscle protein synthesis via inhibition of anabolic pathways (e.g., mTOR/S6 kinase 1, PI3K/Akt, and insulin-like growth factor-I) have been observed... Given that IM CS injection is often administered to patients following diagnosis of RA and in treatment of MM and physical functioning in patients with RA (12). With regard to the muscle loss we observed, an obvious question is whether this was a consequence of the inflammation associated with the disease flare. In response to this, we consider that systemic inflammation was unlikely to be a major contributor to the ALM loss seen in the present study because of i) the rapidity of the anti-inflammatory effects of high-dose CS, ii) the meaningful muscle loss (>0.5 kg ALM) observed 4 weeks following IM CS injection experienced by subjects (#2; Table 2) who did not have systemic inflammation according to blood CRP level at baseline, and iii) the lack of association (determined by linear regression) between ALM loss and either DAS28 or CRP at baseline (R²=0.009, p=0.822 or R²=0.063, p=0.549, respectively). Additionally, our findings of reduced MM following IM CS injection are consistent with the established effect on skeletal muscle of chronic high-dose CS treatment. While the exact mechanism underlying glucocorticoid-induced reduction in MM is unclear, augmented muscle protein breakdown via stimulation of the catabolic ubiquitin-proteasome system brought about by increased expression of atrogenes (genes, such as FOXO, Atrogin-1, and MuRF-1, involved in muscle atrophy) and attenuated muscle protein synthesis via inhibition of anabolic pathways (e.g., mTOR/S6 kinase 1, PI3K/Akt, and insulin-like growth factor-I) have been observed... (three occasions (range: 2-4) on average for the patients in the current study). Thus, this recommended treatment could be a significant contributor to RC and, in particular, the deficiency in MM observed in patients with RA.

Chronic CS use has also been implicated in the redistribution of fat to the truncal area (14). Although we saw no mean change in patients’ total FM, we did observe a non-significant 3.5% increase in trunk FM % at 4 weeks following acute administration of high-dose CS. As such, this is another aspect of body composition that warrants attention in a future large study evaluating the effects of one-off high-dose CS treatment. A shift in adiposity, if confirmed, would be worrying as trunk obesity, a feature of RA body composition, exacerbates cardiovascular disease risk (2, 3, 15). However, it should be noted that, in contrast to the changes in LM measures observed at 4 weeks, the apparent changes observed in FM measures at 4 weeks had all been resolved by 6-9 months. Although chronic and acute IM CS uses are known to increase osteoporosis risk, we saw no changes in bone measures (BMD or BMC) at either time-point (14, 16).

We acknowledge several limitations of our pilot study. First, the low n of our sample, and the inclusion of only patients with established RA who were experiencing a disease flare. These make it difficult to generalize the effect of IM CS injection we observed in all patients with RA, notably patients recently diagnosed with RA. Accordingly, to confirm the generality of these body composition effects of IM CS treatment for active RA, we have recently commenced a large, clinic-based study (n≈100) which will mostly include treatment-naive patients recently diagnosed with RA. However, in defense of the results from our pilot study, we feel that the very consistent pattern of muscle loss (Table 2, plus our case study) justifies concerns that IM CS injection may cause clinically meaningful muscle loss in patients with RA (10). The lack of random and controlled treatment assignment may also be considered a weakness of our study design. However, this was unavoidable in a pragmatic, observational study of routine clinical practice. Additionally, denying treatment to patients with highly active RA would be unethical.

The results from this pilot study indicate that a single IM injection of high-dose CS, a recommended and standard treatment for uncontrolled disease activity in RA, causes substantial and clinically relevant loss of MM. Since short-term, high-dose treatment with CS, including administration by IM injection, is undoubtedly the most cost-effective treatment currently available to combat high levels of inflammation in RA, we are not suggesting that this treatment is discontinued, as unresolved inflammation will also result in muscle loss (1). However, we are advocating that ways of attenuating this apparent iatrogenic effect of IM CS injection should be investigated, as should potential alternative treatments for rapidly resolving the inflammation and pain of uncontrolled RA.

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