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Lemmey, Andrew; Wilkinson, Thomas; Perkins, Celine M.; Nixon, Luke A.; Sheikh, Fazal; Jones, Jeremy; Ahmad, Yasmeen; OBrien, Thomas

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Chapter 1

Muscle Loss Following a Single High-Dose Intramuscular Injection of Corticosteroids to Treat Disease Flare in Rheumatoid Arthritis Patients

Andrew B Lemmey[1]*, Thomas J Wilkinson[1,2], Celine M Perkins[1], Luke A Nixon[1], Fazal Sheikh[3], Jeremy G Jones[1,3], Yasmeen A Ahmad[3] and Thomas D O'Brien[4]

[1]School of Sport, Health & Exercise Sciences (SSHES), Bangor University, UK
[2]Leicester Kidney Exercise Team, Department of Infection, Immunity and Inflammation, University of Leicester, UK
[3]Peter Maddison Rheumatology Centre, Llandudno Hospital, Betsi Cadwaladr University Health Board, UK
[4]Research Institute for Sport & Exercise Sciences, Liverpool John Moores University, UK

*__Corresponding Author:__ Prof. Andrew B Lemmey, School of Sport, Health & Exercise Sciences (SSHES), Bangor University, Bangor, Gwynedd, LL57 2PZ, UK, Email: a. b. lemmey@ bangor. ac. uk

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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 (~2kg) in an RA patient following a single intramuscular (IM) corticosteroid (CS) injection to treat a disease flare. The current study aimed 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 8 established RA patients who received a 120mg 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 by 1-way ANOVA's.

Results: There was significant loss of ALM (-0.93kg, *P*=0.001, 95% CI [-0.49, -1.36]) and a trend towards reduced LM (-1.10kg, *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 RA patients following IM CS injection to treat a disease flare. Thus, this recommended treatment appears to exacerbate RC, thereby potentially increasing disability and comorbidity 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.

Key Messages

- Significant loss of muscle mass was observed in 8 established rheumatoid arthritis (RA) patients administered an intramuscular (IM) injection of high-dose corticosteroids (CS) to treat a disease flare.
- This muscle loss was apparent 4 weeks after injection and persisted for at least 6-9 months despite good control of inflammation and disease activity.
- Given the routine use of this recommended treatment for suppressing high disease activity in RA,

IM CS injection is likely to be an important contributor to the muscle loss and, as a consequence, the disability that characterise RA.

- These findings raise important concerns about the routine use of IM CS injection for RA patients with active disease, and justify investigating the efficacy of alternative treatments, such as short-term biologics, for resolving uncontrolled RA.

Introduction

Patients with rheumatoid arthritis (RA) typically experience substantial loss of lean mass (LM), primarily muscle mass (MM), and increased fat mass (FM), especially trunk FM, in a process known as 'rheumatoid cachexia' (RC) [1]. Thought to be driven by inflammation, specifically pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α [1], RC is a major contributor to the decreased strength and impaired physical function, and the exacerbated co-morbidity risk, that characterize RA [1-3]. Unfortunately, despite usually achieving good control of inflammation and disease activity, current treatment of RA does not reverse these adverse changes in body composition [3].

When RA is 'active' (i.e. before starting drug treatment, or during a disease flare in established RA), one-off high-dose corticosteroids (CS), often administered by

intramuscular (IM) injection, is recommended in clinical guidelines [e.g. American College of Rheumatology (ACR), 4; European League against Rheumatism (EULAR), 5; British Society for Rheumatology (BSR), 6,7; NICE Clinical Guidelines 79, 2009, 8]. This treatment has been shown to rapidly reduce inflammation and pain in RA [e.g., 6,7]. While long term high-dose CS treatment is known to have detrimental effects on body composition including loss of lean mass (LM) and an increase in FM [e.g., 9], the effects on body composition of single high-dose CS treatment, including IM CS injection, are unclear.

Our interest in the body composition effects of acute CS treatment was stimulated by the observation of a substantial loss of dual-energy x-ray absorptiometry (DXA)-assessed muscle mass (-2.0 kg in appendicular LM, ALM; i.e. ~7% of total ALM) in an RA patient 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 which we recently reported persists even in aggressively, and successfully, pharmacologically-treated contemporary RA patients [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.

Subjects and Methods

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

Established RA patients presenting with a disease flare and treated with an IM injection of CS were recruited from rheumatology outpatient clinics of the Peter Maddison Rheumatology Centre, Llandudno Hospital. For inclusion, participants had to: (a) fulfil the American College of Rheumatology/EULAR 2010 revised classification criteria for the diagnosis of RA; (b) have uncontrolled RA disease activity for which IM CS injection was deemed 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, previous hypersensitivity to CS injections).

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 administeredinto the gluteal muscle.

DXA-scans were performed within one hour of the patient receiving the injection, and repeated following routine rheumatology follow-up clinics at approximately four weeks (27-32 days) and 6-9 months post-injection. Patient's disease activity (Disease Activity Score in 28 joints, DAS28-CRP) and systemic inflammation (C-reactive protein, CRP) were also determined at baseline, 4-weeks and 6-9 months.

Body Composition Measures

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 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 rela-

tive 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 was by 1-way ANOVAs (3 time-points), with effect size (small = 0.20-0.49; medium = 0.50-0.79; large ≥ 0.80) calculated for each variable. Data analyses was performed using the Statistical Package for the Social Sciences 22 (SPSS) (Chicago, USA). Data is 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 RA patients 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 8 patients, as 1 participant withdrew from the study after baseline measurements due to suspected meningitis. The mean interval between CS injection and baseline DXA-scan was 0.7 hours (~42 minutes; range: 18-60 minutes).

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 (DMARD) therapy. None of these patients, either at the time of the CS injection or over the ensuing 6-9 months, were treated with biologics or oral steroids. Patients reported no substantial changes to life-style (e.g., diet or exercise), or adverse health events, over the trial period.

Table 1: Baseline demographics of rheumatoid arthritis patients receiving intra-muscular 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.

Significant reductionsin 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 5/8 patients experiencing clinically meaningful improvements in DAS28 (reduction >1.2) and CRP (reduction >10mg/L) in the 4 weeks following CS injection (Table 2).

Table 2: Individual changes in DAS28-CRP score, component DAS28-CRP scores, and ALM over 4 weeks following a single, high-dose intramuscular corticosteroid injection to treat a rheumatoid arthritis disease flare.

Patient	DAS28-CRP		CRP (mg/L)		Swollen joints		Tender joints		Patient Global Score (VAS 0-100)		ALM loss (kg)
	Baseline	4-weeks	Baseline	4-weeks	Baseline	4-weeks	Baseline	4-weeks	Baseline	4-weeks	
1	4.42	1.66	17	5	4	0	8	0	20	4	1.02
2	3.42	1.54	4	4	0	0	4	0	54	0	0.56
3	4.93	2.90	67	15	1	0	4	1	75	27	1.92
4	5.20	4.42	5	5	11	3	6	8	75	53	0.86
5	3.69	2.28	20	5	7	2	0	0	64	20	1.42
6	3.28	2.86	40	19	4	1	0	0	30	39	0.62
7	5.96	3.40	20	5	3	4	15	3	89	19	0.31
8	5.18	4.52	14	10	9	11	11	6	39	28	0.72
Mean(SD)	4.51 (0.97)	2.95 (1.13)	23.4 (20.9)	8.5 (5.7)	4.8 (3.8)	2.6 (3.7)	6.0 (5.2)	2.3 (3.2)	55.8 (24.3)	23.8 (17.4)	0.93 (0.52)

DAS28 = Disease Activity Score in 28 joints; CRP = C-reactive protein; VAS = visual analogue scale; ALM = appendicular lean mass; SD = standard deviation.

Mean body composition changes are shown in Table 3. Four weeks following IM CS injection, an average of 0. 93 kg ALM (i.e. muscle mass) was lost, whilst mean total LM was reduced by 1.10 kg. All 8 patients lost ALM following IM CS injection, with 7 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. No changes in bone mineral density or bone mineral content were detected at 4-weeks (data not shown; *P*'s=0.620, 0.664, respectively).

Table 3: Body composition changes over 4 weeks following a single, high-dose intramuscular corticosteroid injection to treat a rheumatoid arthritis disease flare.

DXA-measures	Baseline	Post-CS (4-weeks)	Absolute difference [95% CI]	% difference	*P*	Effect size
ALM (kg)	19.86 (±1.71)	18.93 (±1.57)	**-0.93 [-0.49, -1.36]**	**-4.7**	**0.001***	**0.54**
ALM/BM %	25.7 (±2.6)	24.8 (±3.0)	**-0.91 [-0.42, -1.40]**	**-3.1**	**0.003***	**0.33**
Total LM (kg)	48.02 (±5.32)	46.91 (±5.10)	-1.11 [-0.58, -2.79]	-2.3	0.165	0.21
Total FM (kg)	31.81 (±6.27)	32.51 (±6.29)	0.70 [-0.99, 2.39]	2.2	0.362	0.11
Body fat % (total FM/BM %)	35.1 (±9.9)	36.0 (±11.0)	0.89 [-0.66, 2.43]	2.5	0.216	0.09
Trunk FM (kg)	14.76 (±4.59)	15.29 (±5.12)	0.53 [-0.66, 1.71]	3.5	0.327	0.12
Trunk FM% (trunk FM/total FM%)	47.5 (±9.7)	48.5 (±11.0)	1.01 [-0.87, 2.89]	2.1	0.243	0.10

Data presented as mean (±SD), unless stated otherwise. DXA = dual x-ray absorptiometry; CS = corticosteroid; CI = confidence interval; ALM = appendicular lean mass; BM = body mass; LM = lean mass; FM = fat mass; * $P < .05$; Effect size: small = 0.20-0.49; medium = 0.50-0.79; large ≥ 0.80.

There was no significant change, or trend toward change, in any of the body composition measures between the follow-up assessments at 4-weeks and 6-9 months (*P*'s=0.32-0.54), during which time control of inflammation and disease activity was maintained. 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.

Discussion

To our knowledge, this study is the first to objectively investigate the consequences of a single, high-dose administration of corticosteroids on body composition. Although only preliminary, results from eight patients, taken with a similar observation from our case study [10], 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. As this reduction in MM is likely to have adverse effects on physical function, these findings raise important concerns about the routine use of thistreatment for RA patients 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, 4; EULAR, 5; BSR, 6,7; NICE, 8] because of their efficacy in rapidly attenuating inflammation and pain. Consistent with these recommendations and its regularly observed clinical benefit, the CS injections administered in this 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 was a mean loss of 0.93 kg ALM (i.e. skeletal muscle) in the 4 weeks following IM CS injection. This apparent iatrogenic loss of ALM accounts for approximately 37% of the discrepancy in pro-

portional MM (i.e. ALM/BM %) between RA patients and healthy age- and sex-matched individuals we have previously reported [3]. Additionally, reduced MM, including the magnitude of MM loss observed in this study (~5% of total MM), is acknowledged as a major contributor to the decreased strength and impaired physical function characteristic of RA [e.g., 1-3]. Further, loss of MM (and therefore loss of 'expendable' protein) impairs the immune system's ability to adequately respond to infection and trauma [2]. It is important to note that despite sustained low disease activity, the muscle lost at 4-weeks was not spontaneously restored by the 6-9 month post-injection follow-up assessment. This finding is not unexpected, as without some form of anabolic stimuli the body does not spontaneously recover lost MM; and in specific regard to RA patients, this remains the case even when disease remission is achieved [3]. This further emphasises the importance for adjunct interventions designed to increase MM in RA. Of the potential anabolic interventions trialled, progressive resistance training [e.g., 12] is clearly the most beneficial intervention for improving both MM and physical functioning in RA patients.

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 this study because of i) the rapidity of the anti-inflamma-

tory effects of high-dose CS, ii) the meaningful muscle loss (> 0.5kg ALM) following IM CS injection experienced by subjects (#2,4; 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 (R^2=0.009, *P*=0.822; R^2=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 bought 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 inhibitionof anabolic pathways (e.g. , mTOR/S6 kinase 1, PI3K/Akt and insulin-like growth factor (IGF)-I), have been observed [for a review see 13].

Given that IM CS injection is often administered to patients following diagnosis of RA, and again when patients with established RA experience disease flares, it is not unusual for RA patients to receive this form of treatment several times during the course of their disease (3 occasions (range: 2-4) on average for the patients in the current study). Thus, this recommended treatment could be a significant contributor to rheumatoid cachexia, and in particular the deficiency in MM observed in RA patients.

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% 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 [2, 3], exacerbates CVD risk [15]. Although chronic [e.g., 14] and acute IM CS [16] use is known to increaseosteoporosis risk, we saw no changes in bone measures (BMD or BMC).

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 generalise the effect of IM CS injection we observed toall RA patients, notably recently-diagnosed RA patients. 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-naïve recently-diagnosed RA patients. However, in defence of the results from our pilot study, we feel that the very consistent pattern of muscle loss (Table 2, plus our case study [10]) justifies concerns that IM CS injection may cause clinically meaningful muscle loss in RA patients. 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.

In summary, 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. In regard to alternative treatments, the efficacy of short-term biologic warrants trialling, with the anti-IL-6 receptor blocker, tocilizumab, and the interleukin-1 receptor antagonist, anakinra, appearing the most likely candidates due to their more rapid treatment response.

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