CONCISE REPORT

Response to intramuscular methyl prednisolone in inflammatory hand pain: evidence for a targeted clinical, ultrasonographic and therapeutic approach

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Background: Hand pain with stiffness is a common clinical presentation to early arthritis clinics, with outcome varying from resolution to the development of rheumatoid arthritis.

Objective: To assess the response and predictors of response to intramuscular methylprednisolone (MP) and hydroxychloroquine (HCQ) using a standardised treatment protocol.

Methods: Patients with inflammatory hand pain (IHP), defined as predominantly hand pain and morning stiffness of at least 30 min duration, received a standardised assessment prior to receiving intramuscular MP. Response (primary outcome) at 4 weeks was a 50% improvement in symptoms as perceived by the patient; responders who relapsed received repeat intramuscular MP and HCQ.

Results: 102 patients were recruited, of which 21% were rheumatoid factor (RF) positive, 23% had clinical synovitis, 25% had raised C-reactive protein level and 55% had ultrasound-detected synovitis. 73% responded, with associated significant reductions in morning stiffness, Health Assessment Questionnaire, painful and tender joint counts, and visual analogue scores ($p \leq 0.006$ for all). Ultrasound-detected synovitis ($p < 0.001$) and RF ($p = 0.04$), but not clinical synovitis ($p = 0.74$), were significantly associated with response to intramuscular MP. 86% who remained on HCQ long term reported a benefit.

Conclusions: Patients with IHP have significant improvement in symptoms and function following intramuscular MP. Further placebo-controlled trials are required to assess the role of intramuscular MP and ultrasonography in managing this patient group.

The presence of hand pain and concomitant stiffness is common, accounting for 5–50%^{1–3} of presentations to rheumatologists. Outcome varies from spontaneous resolution of symptoms to the development of a persistent, joint-damaging disease such as rheumatoid arthritis (RA). Studies that have assessed similar groups of patients have usually defined their cohort by a failure to satisfy other accepted diagnostic criteria, but with features suggesting the potential to evolve into a persistent inflammatory arthritis.^{1–4}

Ultrasonography (US) is able to detect synovitis in joints without clinically detectable synovitis^{5–6} sub-clinical synovitis. It could be envisaged that imaging-detected synovitis might be used to enhance existing classification criteria, facilitating earlier diagnosis and therapeutic intervention, with consequent improved outcome.

Corticosteroids are used to treat flares of inflammatory symptoms and to maintain disease control in oligoarthritis,⁷ RA⁸ and osteoarthritis.⁹ Intramuscular methylprednisolone (MP) is used as an alternative to oral prednisolone in an attempt to reduce long-term side effects. Hydroxychloroquine (HCQ), a disease-modifying antirheumatic drug with a

low-toxicity index, has been used with benefit in RA,¹⁰ connective tissue disease¹¹ and inflammatory osteoarthritis.¹²

In this proof of concept study based on the logic that inflammation is suppressed by steroids and disease-modifying antirheumatic drugs, we tested the hypothesis that symptoms in patients presenting with hand pain and stiffness have an inflammatory aetiology and should respond to corticosteroids, with those who have objective evidence of synovitis most likely to respond. The primary aim of the study was to assess response to intramuscular MP.

METHODS

Patients

Patients presenting to the Leeds Early Arthritis Clinic, Leeds, UK, with >3 months of symptoms of inflammatory hand pain (IHP), defined as predominantly hand pain with diurnal variation of symptoms and early morning stiffness (EMS) of the hands lasting for ≥ 30 min, and failing to respond to non-steroidal anti-inflammatory drugs, were recruited. Patients with predominant hand pain were assessed due to the increased probability of persistence and disease evolution,¹³ and to minimise overlap of patients with classic oligoarthritis (mainly affecting the lower limbs).

Patients with clinical synovitis in ≥ 5 joints or satisfying the American College of Rheumatology classification criteria for RA or the European Spondyloarthropathy Study Group criteria for spondyloarthropathy were excluded. Patients with other inflammatory arthritis including gout or connective tissue illness were also excluded, as were those with a history of sensitivity to corticosteroids or HCQ. Written informed consent was obtained from patients before entry into the study and approval obtained from the local research ethics committee.

Clinical assessments

Baseline assessment included full history, metrology and physical examination. Clinical synovitis was documented by the assessing physician, as defined by any two of the following (1) joint swelling, (2) joint tenderness and (3) reduced range of movement.^{1–7} Other data collected included EMS, and scores on a 10 cm visual analogue scale (VAS) for hand pain and stiffness assessed by the patient, and for disease activity assessed by the patient and physician. Functional disability was assessed using the Health Assessment Questionnaire (HAQ). Laboratory tests included tests for standard C-reactive protein (CRP), rheumatoid factor (RF) and antinuclear antibodies.

US-detected synovitis was defined as the presence of abnormally hypoechoic intra-articular tissue that was non-displaceable

Abbreviations: CRP, C-reactive protein; EMS, early morning stiffness; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; IHP, inflammatory hand pain; MP, methylprednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor; US, ultrasonography; VAS, visual analogue score

Table 1 Baseline characteristics for all patients, responders and non-responders, with odds ratios for response to intramuscular methylprednisolone adjusted for age and sex

Variable	All patients (n=91) n (%)	Responders (n=66, 73%) n (%)	Non-responders (n=25, Age/sex-adjusted OR 27%) n (%)	(95% CI)	p
Age (years)					
<41	24 (26)	15 (23)	9 (36)	(Reference category)	—
41–49	21 (23)	16 (24)	5 (20)	2.12 (0.59 to 7.64)	0.25
50–61	23 (25)	18 (27)	5 (20)	2.45 (0.64 to 9.36)	0.19
≥62	23 (25)	17 (26)	6 (24)	1.88 (0.52 to 6.86)	0.34
Female	74 (81)	53 (80)	21 (84)	0.75 (0.21 to 2.60)	0.75
Elevated CRP	23 (25)	18 (27)	5 (20)	1.51 (0.48 to 4.78)	0.48
RF positive	19* (21)	18† (28)	1‡ (4)	9.30 (1.15 to 75.39)	0.04
Clinical synovitis	21 (23)	16 (24)	5 (20)	1.23 (0.37 to 4.11)	0.74
Arthralgia	70 (77)	50 (76)	20 (80)	0.81 (0.24 to 2.72)	0.74
US synovitis	50 (55)	45 (68)	5 (20)	9.28 (2.84 to 30.35)	<0.001
EMS (min)					
30–59	32 (35)	23 (35)	9 (36)	(Reference category)	—
60–119	35 (38)	24 (36)	11 (44)	0.72 (0.24 to 2.19)	0.56
≥120	24 (26)	19 (29)	5 (20)	1.48 (0.41 to 5.39)	0.55

CRP, C-reactive protein; EMS, early morning stiffness; RF, rheumatoid factor; US, ultrasonography.

RF data not available for two patients; —, not applicable.

*Total n=89.

†Total n=65.

‡Total n=24.

and poorly compressible. The second to fifth metacarpophalangeal and proximal interphalangeal joints of the hand with the most symptoms (dominant hand if similar) were examined using an ATL (Advanced Technology Laboratories, Bothel, Washington, USA) HDI 3000 US machine with a linear array 10–5 MHz hockey stick transducer.

Treatment and outcome assessment

Patients received an intramuscular injection of 120 mg MP at baseline assessment. They were reviewed after 4 weeks to assess the response and have all baseline assessments except US and blood tests repeated, and thereafter reviewed every 12 weeks for up to 48 weeks. Responders to intramuscular MP who subsequently relapsed (recurrence of original symptoms) were treated with further intramuscular MP and started on HCQ 200 mg daily and observed to assess response after 24 weeks of HCQ treatment. The primary outcome was response to intramuscular MP at 4 weeks, defined as a 50% improvement in patient symptoms (hand pain and stiffness) in response to a direct question from the assessor.

Statistical analysis

Changes in EMS, HAQ, joint counts and VAS scores after intramuscular injection of MP were compared between responders and non-responders using non-parametric Mann–Whitney U tests.

Separate models were run for each predictor in order to obtain age- and sex-corrected odds ratios (ORs), with age converted to quartiles and EMS assigned three categories. Maximum likelihood logistic regression analysis was then performed to identify any variables that might affect the odds of responding to treatment.

RESULTS

In all, 102 patients were recruited and received intramuscular MP; 11 did not attend the 4-week assessment and were excluded from the study. Most of the remaining 91 (81%) patients were women, mean age 51 years (18–86), with duration of symptoms between 3–18 months (mean 7 months). Four patients weighed ≤55 kg and received 80 mg intramuscular MP.

The RF titre was positive in 21%, CRP raised in 25% and antinuclear antibodies positive in 5% of patients. In all, 23% had clinical synovitis (synovitis group) and the remaining 77% was labelled the arthralgia group (table 1). Synovitis was

detected by US in 55%, including 34 patients without synovitis on clinical examination. In all, 15 of 19 (79%) patients who were RF positive had US synovitis, compared with 33 of 70 (47%) patients who were RF negative (χ^2 $p=0.027$).

The median duration of EMS for the group was 60 min, with a HAQ of 1, painful joint count of 10, tender joint count of 14 and swollen joint count of 2. The patients' VAS scores for hand pain and stiffness, and for disease activity were both 55 mm, whereas the physician VAS for disease activity was 18 mm (table 2).

Response to intramuscular MP

A positive response to intramuscular MP was noted in 66 of 91 (73%) of patients. Compared with non-responders, responders had significant reduction in EMS, HAQ, painful joint count, tender joint count and both patient VAS scores (table 2). Age-adjusted and sex-adjusted logistic regression analyses on individual baseline characteristics confirmed a significant association between response to intramuscular MP and US synovitis (OR 9.28, $p<0.001$) and RF (OR 9.30, $p=0.04$), but not for clinical synovitis (OR 1.23, $p=0.74$) or raised CRP (OR 1.51, $p=0.48$; table 1).

Response to HCQ

Following intramuscular MP, 24 of 66 (36%) responders remained well to the end of the study period (48 weeks). A total of 42 of 66 (64%) responders relapsed (all within 24 weeks) and were treated with repeat intramuscular MP and HCQ. In all, 28 responders remained on HCQ long term and 24 of 28 (86%) reported a benefit. Of 42 patients, 14 (33%) stopped taking HCQ within the first 3 months (11 were unable to tolerate HCQ, 3 compliance/patient choice), and most (11/14) relapsed.

Other outcomes

In all, 8 (9%) patients developed RA during the course of the study (6 had responded to intramuscular MP; 3% of these 6 also responded to HCQ given later). Two developed psoriatic arthritis, with one each labelled as having reactive arthritis and gout. No patient developed diabetes or osteoporotic fracture.

DISCUSSION

This study suggests that most patients with IHP respond well to intramuscular MP. Our definition of response was patient-perceived, but using this definition responders had significant reductions in most baseline assessments. In addition, the reduction in HAQ of 0.38 following intramuscular MP (table 2)

Table 2 Baseline characteristics and change after 4 weeks following intramuscular methylprednisolone injection for all patients, non-responders and responders to steroid

Variable	Baseline			Change over 4 weeks			Mann Whitney U test, p value
	All patients	Non-responders	Responders	Overall	Non-responders	Responders	
EMS (min)	60 (30 to 320)	60 (30 to 320)	60 (30 to 320)	-30 (-320 to 120)	0 (-120 to 120)	-35 (-320 to 30)	<0.001
HAQ	1 (0 to 2.75)	1 (0 to 2.13)	1.06 (0 to 2.75)	-0.13 (-1.50 to 0.75)	0 (-0.38 to 0.38)	-0.38 (-1.50 to 0.75)	<0.001
PJC*	10 (0 to 72)	9 (0 to 44)	10 (1 to 72)	-3 (-48 to 22)	0 (-36 to 22)	-6 (-48 to 16)	<0.001
TJC	14 (0 to 72)	18 (0 to 72)	10 (0 to 58)	-2 (-43 to 30)	0 (-24 to 30)	-3 (-43 to 18)	0.006
SJC	2 (0 to 24)	2 (0 to 16)	2 (0 to 24)	-1 (-17 to 6)	0 (-11 to 3)	-1 (-17 to 6)	0.500
VAS (mm)							
Pain/stiffness	55 (3 to 98)	53 (3 to 96)	59.5 (9 to 98)	-16 (-71 to 44)	-1 (-63 to 44)	-26.5 (-71 to 42)	<0.001
Disease activity	55 (2 to 100)	50 (2 to 100)	56 (2 to 98)	-16 (-82 to 49)	0 (-47 to 49)	-20.5 (-82 to 43)	<0.001
†Physician	18 (0 to 91)	18 (4 to 64)	21 (0 to 91)	-3.5 (-57 to 23)	2 (-52 to 12)	-6.5 (-57 to 23)	0.007

EMS, early morning stiffness; HAQ, Health Assessment Questionnaire; PJC, painful joint count; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue score.

Values presented are medians (range). p Values are for improvement in baseline assessments between responders and non-responders using non-parametric Mann-Whitney U tests (following Bonferroni correction for multiple comparisons, critical p for testing at the 5% significance level was set at 0.006).

*Total n = 90.

†Total n = 80.

is greater than the minimum clinically significant difference in HAQ for RA (0.22)¹⁴ and a combination of arthritides (0.20),¹⁵ suggesting that our definition of response is likely to be clinically significant.

US synovitis, and less so RF, was significantly associated with response which may provide an insight into the pathological basis of these patients' symptoms. Contrary to our expectations, clinical synovitis was not associated with response; however, US detected synovitis in almost half of those without clinically detectable synovitis. This and the lack of significant changes seen in swollen joint count and physician-assessed disease activity VAS may also indicate that traditional methods of assessment are not sensitive enough to detect low levels of synovitis amenable to treatment.

This study highlights the varying outcomes of cohorts of patients with IHP, with one-third of patients remaining well, either due to the effect of corticosteroids or due to spontaneous resolution. Despite excluding patients with polyarthritis and with less-documented clinical synovitis than in previous studies,^{1 4 7 13} similar numbers of patients developed an inflammatory arthritis.

We included patients with a diagnosis of osteoarthritis because this is a common condition that on its own does not exclude the presence or the development of inflammatory arthritis. The response to HCQ could be a result of the repeat intramuscular MP, but most patients who stopped HCQ relapsed, and response was assessed after 24 weeks; other factors not recorded might also have affected response to both intramuscular MP and HCQ.

In summary, this study gives possible insights into the pathology and provides preliminary evidence for an approach to the management of patients with predominant hand pain and features suggestive of inflammation. Further work should include repeating objective measures of inflammation including US to determine whether response is reflected by any change in inflammation. Patients need to be randomised to receive placebo or intramuscular MP to remove any bias and to observe the natural progression of this group.

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