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Intramuscular methylprednisolone in hand osteoarthritis: a retrospective cohort study

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Abstract

Objectives: To explore patient characteristics associated with response to intramuscular methylprednisolone (MP) therapy in hand OA.

Methods: We performed an exploratory monocentric retrospective study. Patients with a clinical diagnosis of hand OA who visited our outpatient clinic between July 2016 and June 2021 and received at least once an intramuscular MP injection were included. Clinical data, including laboratory and radiologic results, were retrieved from electronic patient records (EPRs). Patients' reported response to MP and its duration in the first 6 months after injection was based on free text from the EPRs. Response was categorized into three groups: no response or worsening of symptoms, modest response and good response. Duration of response was categorized as short-term (<2 weeks) or long-term (≥2 weeks). Multivariable logistic regression models were performed to determine factors associated with good response to therapy with MP.

Results: Data from 262 hand OA patients (76% female) were analysed. A good response was experienced by 150 patients (57.2%). Among those with modest–good response, the perceived response of 162 patients (80.6%) lasted ≥2 weeks. Univariate regression analysis indicated that the level of CRP was associated with good response [odds ratio 1.08 (95% CI 1.00, 1.17)]. However, multivariate regression analysis showed no statistically significant associations.

Conclusion: In this retrospective study, more than half of hand OA patients displayed good response to intramuscular MP administration. The possible relation between the presence of low-grade inflammation and the response to this therapy warrants further investigation.

Lay Summary

What does this mean for patients?

Osteoarthritis (OA) is a common disease among adults and older people, being characterized by a decline in articular cartilage, high levels of pain and limited joint function. The development of OA is complex, but most evidence suggests that inflammation contributes to pain and increased structural damage. Current therapeutic options are insufficient in many patients. To reduce inflammation, several drugs have been investigated, for example, corticosteroids and non-steroidal anti-inflammatory drugs, although most fail to show clear benefits or only work in the short-term. Methylprednisolone (MP) injected in the muscle seems to reduce symptoms in patients with hand and hip OA. With this study we wanted to search for patient characteristics associated with response to MP therapy in hand OA. A total of 262 patients with a clinical diagnosis of hand OA who visited the Sint Maartenskliniek between July 2016 and June 2021 and received at least one MP injection in the buttock were included. Among them, 201 patients reported less pain after this injection. Analysis indicated that the level of inflammation in the blood and the use of other painkillers were associated with a good response to MP therapy. In contrast, diabetes seemed to lower the response to this therapy.

Keywords: hand osteoarthritis, corticosteroids, methylprednisolone, therapy, inflammation.

Key messages

- Intramuscular methylprednisolone may improve symptoms in hand osteoarthritis.
- In hand osteoarthritis, a higher degree of systemic inflammation seems to be associated with a better effect of methylprednisolone.
- Prospectively designed controlled studies should determine the role of intramuscular corticosteroids in osteoarthritis management.

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Introduction

OA is a chronic disease leading to the deterioration of articular cartilage, pain and decreased joint function. The pathogenesis of OA is complex and a large amount of evidence supports (at least in a subset of patients) the contribution of inflammation to the generation of pain and progression of structural damage [1–4]. Inflammatory effectors are mainly generated inside the affected joint, but systemic inflammatory mediators could also contribute to the progression of OA, such as in the case of obesity-associated low-grade inflammation originating in the adipose tissue (e.g. adipokines and other pro-inflammatory cytokines) [5].

Currently, pharmacotherapy in OA is inadequate for many patients, as available pharmacotherapy is only effective in pain alleviation without the ability to prevent or cure the disease. Several anti-inflammatory strategies have been explored so far, with some drugs (hydroxychloroquine, methotrexate) failing to show a clear benefit and others (NSAIDs, corticosteroids) demonstrating modest and often short-lived benefits on pain [6–9]. Intramuscular administration of glucocorticoid-based medication, including methylprednisolone (MP) and triamcinolone acetate, significantly reduced symptoms in patients with hand OA and hip OA, respectively [10, 11]. Of note, intramuscular administration of MP might also be associated with a lower risk of local cartilage destruction as compared with intra-articular administration [12], as well as with a lower incidence of systemic side effects as compared with oral corticosteroids [9]. In the present daily practice, intramuscular MP is sometimes administered to OA patients based on shared-decision principles. Nevertheless, shortcomings still need to be addressed in terms of identification of those OA patients who will benefit the most from this therapy. Given the evidence suggesting that OA is a heterogeneous disease with multiple molecular and clinical phenotypes, administration of intramuscular MP to phenotypes with the highest likelihood of response is desirable in order to maximize patient benefits while minimizing serious side effects [13]. Therefore, the present study aims to identify patient-related characteristics associated with a higher probability of response to intramuscular MP in hand OA in the daily clinical practice.

Methods

Study design and population

In this exploratory retrospective cohort study we analysed medical records data of patients in the outpatient clinic of the Sint Maartenskliniek (SMK) treated with an intramuscular MP injection for their hand OA complaints. The SMK is a specialized hospital for orthopaedic surgery, rheumatology and rehabilitation medicine.

Patients were eligible if they attended the SMK between 2016 and 2021 with a clinical diagnosis of hand OA by the rheumatologist and received at least one intramuscular MP injection for their OA complaints. Patients who developed OA secondary to other inflammatory joint disease, such as RA, as well as patients with concomitant fibromyalgia were excluded. Considering the exploratory nature of the study, no formal sample size was calculated and a maximal convenient sample size was strived for by including all eligible patients in the above-mentioned 5-year period. The study was approved by the local review board of the Sint Maartenskliniek, in agreement with the present Dutch and international laws and regulations (case number RR-242). The need of informed consent was waived.

Outcome and other parameters

For each eligible patient, we included data from two different time points: baseline, defined as the moment patients received the first intramuscular injection, and one follow-up moment, defined as the first documented visit after baseline, within the first 6 months. The primary outcome of the study was the patient's reported response to treatment at the first visit after baseline. The patient's reported duration of response to the intramuscular MP injection was also assessed. The patients' reported responses to MP and their duration were determined based on free text recorded during consultations in the electronic patient records (EPRs). Based on this free text, two researchers (M.H. and C.P.) agreed on categories for the response and the duration of the response. Patients' reported responses were categorized into three groups: no response or an increase in symptoms, modest response and (very) good response. No response or an increase in symptoms was indicated by text phrases such as: 'the therapy did not have an effect', 'I don't notice any difference' or 'I have more complaints than before the injection'. Modest response was mostly indicated in text by 'the therapy helped a bit, or a little'. A (very) good response was mostly indicated by 'the therapy did an awesome job', 'it had a good effect' or 'my complaints are completely gone'. The duration of response was categorized as short-term ($<$2 weeks) or long-term ($\geq$2 weeks). The use of 2 weeks as a cut-off point has to do with logistical reasons. In our clinic, it is standard practice to make an appointment 2 weeks after the first visit to the outpatient clinic, when the intramuscular injection is often administered. This practice extends also to other visits; the rheumatologists are inclined to schedule the next contact with a patient 2 weeks after the MP is administered, due to the fact that corticosteroids start to work shortly after their administration. The duration of response was mostly indicated by the exact number of weeks, or it was stated that the therapy still worked at the time of consultation. If it was not possible to determine the length of effect, it was stated as missing. Free-text answers of patients were interpreted by two researchers (M.H. and C.P.) and disagreement was resolved by discussion. Clinical parameters on presentation, medication (e.g. use of analgesics), comorbidities, laboratory and radiology results and dosage of intramuscular glucocorticoid injection were collected from the EPRs.

Statistical analysis

All statistical analyses were performed using Stata 17 (StataCorp, College Station, TX, USA). Descriptive statistics were used to present group characteristics. Continuous variables were reported as mean and S.D. or median and interquartile range (IQR), where appropriate. For nominal variables, numbers and percentages were presented. Univariate regression analysis was performed initially to establish which demographic, clinical and radiographic baseline characteristics were related to response to therapy with MP. To determine associated factors of the response to MP therapy with the use of multivariable logistic regression models, patients' reported responses were dichotomized into the (very) good response group and the combined group of no response and modest response. Based on the results obtained (the size of the

estimated effect, statistical significance level) and depending on the clinical relevance (e.g. factors or comorbidities commonly seen in OA populations), relevant factors were selected and used in multivariable logistic regression models. The final relevant factors used in the multivariable analysis to assess the association with response to therapy were sex, age, CRP level, having multiple joints with an OA diagnosis, having radiological abnormalities, having diabetes, having a BMI ≥30 and the amount of different painkillers used. The multivariable regression models were performed after multiple imputations of the missing baseline characteristics; 100 imputation sets were performed. For stepwise backward selection, a *P*-value of 0.157 was used to compute the final model, following the Akaike information criterion method [14]. In all analyses, a two-tailed significance level of $P < 0.05$ was regarded as statistically significant.

Results

We identified 293 consecutive patients fulfilling the inclusion and exclusion criteria who were treated with intramuscular MP for their hand OA complaints. Of the 293 patients, 31 missed data on the primary outcome, with 262 patients being analysed. The mean age was 65.4 years (S.D. 10.0) and 199 (76.0%) were women. The majority of the patients (62.6%) also had complaints of OA in other joints. Baseline characteristics are described in Table 1.

Of the 262 patients, 201 (76.7%) exhibited a response to intramuscular MP. Among these, 51 (19.5%) patients were categorized as having modest response, while 150 (57.2%) patients demonstrated a (very) good response. Of the 201 patients who exhibited a response, 36 (17.9%) experienced a short-duration response (<2 weeks), while 162 (80.6%) demonstrated a prolonged response (≥2 weeks). The duration of response could not be determined for three patients due to insufficient data (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

In the univariate logistic regression, a higher level of circulating CRP at baseline was associated with a greater chance of having a response to the therapy, whereas a limited response to this therapy has been noted in patients with diabetes (Table 2). On multivariate regression analysis using sex, OA in more joints, diabetes mellitus, CRP, the number of painkillers, radiological abnormalities and BMI as variables, no collinearity between candidate variables was found. Multiple imputations were performed for CRP, ESR, BMI and radiological abnormalities. After stepwise backward selection using a *P*-value of 0.157, the final model was computed (Table 2). We ended up with a model suggesting that the level of CRP and the number of used analgesics at baseline could be associated with good response, while diabetes could be linked to the absence of response. However, none of these associations exhibited statistical significance. Performing the same multivariate regression analysis for the same subgroup of patients with complete datasets ($n = 36$), we retrieved similar results apart from analgesic use (not shown). No associations between the duration of effect and patient characteristics were identified.

Table 1. Characteristics of the OA patients included in the study

Variables	Baseline value ($n = 262$)	Follow-up value ($n = 262$)
Age at baseline, years, mean (S.D.)	65.4 (10.0)	
Female, *n* (%)	199 (76.0)	
BMI at baseline, kg/m^2, mean (S.D.) ($n = 49$)	27.7 (4.3)	NR
Comorbidities at baseline, *n* (%)		
Cardiovascular diseases	129 (49.2)	
Respiratory diseases	70 (26.7)	
Diabetes mellitus (type 1 or type 2)	37 (14.1)	
Cancer	44 (16.8)	
Neurological disorders	29 (11.1)	
Thyroid disorders	30 (11.5)	
Carpal tunnel syndrome	29 (11.1)	
Hypercholesterolaemia	28 (10.7)	
Osteoporosis	29 (11.1)	
Clinical presentation at baseline, *n* (%)		
Swollen joints	150 (57.3)	NR
Limited joint function	38 (14.5)	NR
Nodules	102 (38.9)	NR
Intramuscular MP, *n* (%)		
120 mg	251 (95.8)	
80 mg	10 (3.8)	
40 mg	1 (0.4)	
High-sensitivity CRP at baseline, mg/l, mean (S.D.) ($n = 142$)	4.0 (5.4)	NR
ESR at baseline, mm/h, mean (S.D.) ($n = 103$)	15.6 (15.7)	NR
Radiologic abnormalities congruent to OA diagnosis at baseline, *n* (%) ($n = 184$)	172 (93.5)	
Follow-up time, days, median (IQR)		28 (16–51)
Use of analgesics, *n* (%)		
Patients using analgesics	160 (61.1)	146 (55.7)
Paracetamol	94 (35.9)	78 (29.8)
NSAIDs	97 (37.0)	100 (38.2)
Opioids	40 (15.3)	38 (14.5)
Neurogenic painkillers	13 (5.0)	11 (4.2)

NR: not recorded.

Table 2. Associations of patients' characteristics with response to therapy with intramuscular MP in univariate logistic regression analyses and multivariate logistic regression analysis with imputations ($n = 262$).

Variables	Odds ratio (95% CI)	*P*-value
Univariate logistic regression analyses		
Age (years)	1.00 (0.98, 1.03)	0.463
Female sex	1.30 (0.73, 2.29)	0.370
BMI (≥30 kg/m^2)	0.95 (0.25, 3.58)	0.945
Comorbidities		
Cardiovascular diseases	1.01 (0.62, 1.65)	0.971
Diabetes mellitus	0.59 (0.29, 1.18)	0.136
Thyroid disorders	0.62 (0.29, 1.33)	0.216
Respiratory diseases	1.49 (0.85, 2.63)	0.166
Neurological disorders	2.12 (0.90, 4.97)	0.085
Osteoporosis	1.25 (0.57, 2.77)	0.579
Carpal tunnel syndrome	1.25 (0.57, 2.77)	0.579
Clinical presentation		
Swollen joints	1.22 (0.74, 2.00)	0.431
Limited joint function	1.03 (0.51, 2.07)	0.931
Nodules	0.70 (0.43, 1.16)	0.168
OA complaints in other joints	1.15 (0.69, 1.91)	0.587
CRP (mg/l) ($n = 142$)	1.08 (1.00, 1.17)	0.047
ESR (mm/h) ($n = 103$)	1.03 (1.00, 1.06)	0.092
Radiologic abnormalities congruent to OA diagnosis ($n = 184$)	0.69 (0.20, 2.39)	0.564
Number of classes of analgesic medication	1.24 (0.94, 1.62)	0.126
Dose of injection (mg)	1.07 (0.99, 1.15)	0.085
Multivariate logistic regression analysis with imputations		
Diabetes mellitus	0.59 (0.29, 1.20)	0.146
Number of classes of analgesic medication	1.25 (0.95, 1.66)	0.117
CRP	1.07 (0.99, 1.15)	0.085

Discussion

In this exploratory retrospective cohort study we observed that the majority of patients with hand OA receiving intramuscular MP reported an improvement in their complaints for ≥2 weeks. An initial higher level of systemic CRP seems to predict a good response in univariate regression analysis.

Different proposed phenotypes in OA, each of them sharing distinct pathobiological mechanisms or endotypes, might benefit from different therapies. One of these proposed phenotypes/endotypes is the inflammatory one, characterized by more local inflammation in the affected OA joints as well as systemic low-grade inflammation. Patients belonging to this phenotype would be more likely to benefit from anti-inflammatory therapies than patients belonging to other subgroups, as recently suggested in the literature [9]. Likewise, in the present study, higher CRP levels in hand OA patients seemed to be associated with a (very) good response to intramuscular MP. This finding suggests that low-grade systemic inflammation in hand OA patients might be of clinical relevance, as has been previously indicated for its contribution to atherosclerosis and the risk for future cardiovascular events [15].

In our study we observed that the presence of diabetes tended to be inversely associated with the response to glucocorticoids, although this association was not significant. Although such an association has not been reported in OA, it has been largely indicated in asthmatic patients receiving corticosteroids [16]. A plausible explanation for this is that the interaction of glucocorticoids with glucocorticoid receptors (GRs) is controlled and downregulated by intracellular mechanisms in obesity [17]. Near-normal levels of cortisol in obesity and/or diabetes indicate that it is not the absence of glucocorticoids that results in less glucocorticoid action, but probably impaired signalling through GRs, which leads to increased inflammation instead of suppression [18].

The current study found a (very) good response in 57.2% of the patients receiving intramuscular MP, which is lower than in two other prospective studies: 66.7% in Keen *et al.* [11] and 64% in a previous study by our research group [19]. Keen *et al.* [11] defined a response as a 20% reduction in the most painful joint on a visual analogue pain scale (10 cm) at week 4, while our previous study defined it as a 2-point decrease in pain between baseline and 8 weeks follow-up on a numerical rating scale (0–10). Both studies used validated and uniform measurement tools. In contrast, our current study's use of free-text responses may have led to misclassification of patients with a good response into the modest response group, potentially explaining the observed differences in response rates.

A notable strength of our study is that we analysed data from a substantial group of patients, providing a representative sample of clinical practices for individuals with hand OA. It is important to be cautious when extrapolating our results to all hand OA patients due to selection bias. Our treating physicians offered the option of intramuscular injection only to a selected subgroup of hand OA patients, based on their clinical judgment and taking into consideration all previous therapeutic approaches that had been undergone by a patient and failed. However, this method of treating patients mirrors clinical practice. Another strength of this study is that it is one of the first exploring patient-related characteristics associated with a higher probability of response to intramuscular MP in hand OA.

Our study has several limitations. First, our study lacked a control group, which impeded our ability to account for placebo effects and regression to the mean. In general, larger

placebo effects are observed with injections compared with oral administration [20]. Second, the method used to categorize patients having a response or not was based on what the physicians noted in the EPR, therefore lacking standardized objectivity. Third, the determination of response might be speculative due to not using a validated scale, yet the likelihood of overestimation is minimized through interpretation by two independent researchers. Fourth, although multiple imputation is a robust method to minimize bias from missing data in the EPRs due to the retrospective character of our study, the imputed data may not accurately represent real-world data, warranting cautious interpretation of the conclusions. Nevertheless, similar results were observed when the analyses were repeated for the subgroup of patients with complete datasets.

In conclusion, our study indicates that more than half of hand OA patients displayed a good response to intramuscular MP administration. However, prospective controlled studies are warranted to confirm a possible relation between the presence of low-grade inflammation and the response to this therapy.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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