Treatment of frozen shoulder with subcutaneous TNF-alpha blockade compared with local glucocorticoid injection: a randomised pilot study

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BRIEF REPORT

Treatment of frozen shoulder with subcutaneous TNF-alpha blockade compared with local glucocorticoid injection: a randomised pilot study

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Abstract We compared the effect of subcutaneous adalimumab injections with intraarticular glucocorticoid injections on frozen shoulder of 18 patients with unilateral joint involvement. Ten patients were randomised to subcutaneous injections with adalimumab and eight to intraarticular glucocorticoid injections administered every other week for a total of three administrations. The evaluation included validated scores. No effect of subcutaneous injections of adalimumab on frozen shoulder symptoms was demonstrated.

Keywords Adalimumab · Adhesive capsulitis · Frozen shoulder · Periarthritis humeroscapularis · TNF-alpha blockade

Introduction

The frozen shoulder (FS) is a condition characterised by inflammation, fibrosis and contracture of the capsule leading to pain, restricted motion, and longstanding impairment of function. The condition is self-limited and usually carries a good prognosis, but it can last for many years. The treatment used at the present time may reduce the duration and severity of symptoms, but they are generally unable to restore natural function rapidly [1–3]. Some studies have suggested that tumour necrosis factor (TNF)-α may be involved in the development of the frozen shoulder capsulitis [4]. Adalimumab and other TNF-α inhibitors are already used successfully in the treatment of rheumatoid arthritis and other inflammatory joint diseases [5–9]. The purpose of this study was to evaluate the effect of TNF-α blockade with subcutaneousadalimumab compared with intraarticular steroid injections on pain and range of motion of patients with frozen shoulder. An additional purpose was to assess the safety of adalimumab in the treatment of frozen shoulder.

Patients and methods

Study design

The study was designed to include a total of 30 patients, with 15 patients in each treatment arm; the purpose was to detect a difference of 50 % improvement in "constant score–objective assessment" between adalimumab and steroid injections, assuming a steroid response rate of 10 and 80 % power, at a statistical significance at $p<0.05$.

Between 10 April 2007 and 25 September 2008, 18 patients referred to the clinic were consecutively included in the study after informed consent, if they fulfilled the inclusion criteria and presented none of the exclusion criteria.

Inclusion criteria

- Age above 18 years
- Frozen shoulder in the first stage of the disease as defined by Codman [10]:

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  - Pain and stiffness of one shoulder for at least 3 weeks
  - Reduced passive motion of at least 30 degrees in at least two planes as compared with the other shoulder
  - Reduced passive external rotation of at least 50 % as compared with the other shoulder
- Pain as defined in the constant score of at least 20 in "subjective assessment of pain" (maximum score of 35)
- Negative pregnancy test (serum HCG) for potentially pregnant women. Ability and will for all women with potential pregnancy to use a reliable anticonception
- Skill and will to give informed consent and to fulfil the requirements of the project protocol

Exclusion criteria

Medical history of, or ongoing inflammatory joint disease other than frozen shoulder, severe radiologic glenohumeral osteoarthritis, or recent (under 3 months) traumatic rotator cuff lesion as seen on ultrasound or magnetic resonance imaging scan; other painful condition of any kind that might interfere with the evaluation of pain; and any condition that represents a contraindication for anti-TNF-α treatment, or whatever condition, which, according to the investigators opinion, might constitute a risk factor for the participant.

The patients included in the study were randomised, using sealed envelopes, to either adalimumab (treatment group A) or intraarticular steroid injection (group B). Group A was given 1 ml adalimumab by subcutaneous injection. Group B was treated with 4 ml of lidocain 1 % and 40 mg methylprednisolone acetate in the affected glenohumeral joint under ultrasonographic guidance. In each group, the treatment was repeated once every second week for a maximum of three treatments. The treatment was stopped if the patient reached full recovery of shoulder function.

The patients were evaluated at admission, on the days of treatment, and after 1, 3, and 6 months. Evaluation at the start included clinical examination with standard tests and scores, ultrasonography and radiography of the affected shoulder and blood tests. Follow-up evaluation included only clinical examinations with standard tests and scores. Evaluations were performed by the same physician who administered the treatment. Due to the nature of the treatments, blinding was not possible.

Assessments

Constant score

The constant score is a validated score system consisting of a subjective and an objective part [11].

Shoulder rating questionnaire

Shoulder rating questionnaire (SRQ) is a validated score system based upon the patient's own assessment of pain and function [12].

Shoulder pain and disability index

Shoulder pain and disability index (SPADI) is a validated score system based upon the patient's own assessment of pain and function [13, 14].

Targets
- Change in the shoulders active and passive range of motion from baseline until week 8
- Change in constant score, SRQ and SPADI from baseline until weeks 2, 4, 8, 12 and 24.

Safety At each visit, patients were asked for side effects which were registered.

Statistics

The data were analysed by non-parametric statistics. Results are shown as median (range). The Friedman test was used to examine differences in treatments across multiple test attempts in each treatment group. Comparisons of paired measurements within each treatment group were made using the Wilcoxon signed-rank test. Comparisons of the two treatment groups were performed by the Mann–Whitney U test. A two-tailed p value less than 0.05 was considered statistically significant. The statistical analyses were conducted using the statistical package SPSS for Windows 7.5.3.

Results

Ten patients (eight women and two men) were randomised to adalimumab injections and eight (five women and three men) to glucocorticoid injections. The study was designed to include 30 consecutive patients with frozen shoulder, but the investigator decided to interrupt the study after the inclusion of the first 18 patients because four out of ten patients from the adalimumab group withdrew or were excluded from the study, either because of lack of effect, or because of side effects. One patient was excluded because of raising liver enzymes and one because of paresthesias in the ring and small fingers. Liver enzymes normalised rapidly, and the paresthesias disappeared 3 months after discontinuation of adalimumab. Two patients withdrew

because of lack of effect on their shoulder pain. No patients withdrew from the glucocorticoid group.

The median age of the 18 included patients was 51 (37–64) years in the glucocorticoid group and 51 (41–67) years in the adalimumab group (NS). The results of the shoulder scores are shown in Table 1.

An overall statistically significant difference between the time points was found for all tests in the glucocorticoid group ($p<0.05$–0.0001). When comparing the different tests pairwise in this group, most of the scores were significantly improved compared to that in baseline ($p<0.05$). However, no consistent trend toward a persistent improvement of the scores during follow-up was found.

In the adalimumab group, no overall difference between test results at different time points was demonstrated, and no consistent pattern was observed when comparing the tests pairwise. Baseline values for active and passive flexion were significantly lower in the adalimumab group than in the glucocorticoid group. No significant differences between the adalimumab- and glucocorticoid-treated groups were found for any other time points.

Ethics and consents

The study was approved by the local ethical committee and by the National Medical Agency ref. no. H-KA-20060167.

Discussion

Treatment of frozen shoulder with local glucocorticoid injections has been investigated in several RCT's,[1–3, 15]. Most studies tend to show that glucocorticoid injections reduce pain and slightly improve motion, and though distension with glucocorticoid may further accelerate restoration of movement, full recovery takes up to several years [1].

This study is the first to examine the effect of subcutaneous adalimumab injections in patients with frozen shoulder. The number of patients was low, and the results should therefore be interpreted with caution. At least, however, the study indicates that no pronounced effect of adalimumab should be expected. In addition, two out of the ten patients in the adalimumab group developed side effects that lead to their exclusion. The study demonstrated as well that some effect of

Table 1 Results of shoulder scoring [median (range)]

Treatment	Baseline	Week					
		2	4	8	12	24	*p* value[a]
Glucocorticoid							
n	8	8	8	7	8	8	7
Active flexion	90 (60–110)b	105 (75–130)a	115 (90–160)a	100 (90–180)a.	113 (75–180)a	115 (65–180)	0.02
Active abduction	53 (30–70)b	70 (45–90)a	83 (65–120)a	100 (50–180)ab	90 (55–180)ab	80 (55–180)a	0.0001
Active outrotation	10 (0–35)	15 (0–30)	25 (10–45)a	40 (5–45)	28 (0–45)a	28 (0–45)	0.02
Passive flexion	90 (60–110)b	105 (75–130)a	115 (90–160)a	100 (90–180)a	113 (75–180)a	115 (65–180)	0.02
Passive abduction	52 (30–70)b	80 (55–180)a	70 (45–90)ab	83 (65–120)ab	100 (50–180)a	90 (55–180)a	0.0001
Passive outrotation	10 (0–35)	28 (0–55)	15 (0–30)a	25 (10–45)a	40 (5–45)	28 (0–45)	0.02
Constant score	10 (0–35)b	15 (0–30)a	25 (10–45)ab	40 (5–45)ab	28 (0–45)	28 (0–55)a	0.004
SRQ	47 (35–73)	38 (25–62)	61 (36–89)ab	66 (44–85)ab	69 (37–95)ab	68 (39–84)ab	0.02
SPADI	63 (50–91)b	57 (36–85)a	25 (7–74)ab	23 (9–80)ab	20 (5–73)a	27 (3–67)ab	0.0001
Adalimumab							
n	10	9	6	5	4	4	4
Active flexion	73 (30–90)	70 (30–80)	55 (30–90)	65 (40–90)	100 (60–120)	95 (80–120)	0.2
Active abduction	40 (20–60)	45 (20–60)	43 (30–80)	45 (25–90)	45 (40–70)	65 (50–80)	0.1
Active outrotation	3 (0–30)	15 (0–35)	10 (0–40)	15 (10–30)	13 (10–40)	15 (0–40)	0.1
Passive flexion	72 (30–90)	70 (30–80)	55 (30–90)	65 (40–120)	105 (60–120)	95 (80–120)	0.3
Passive abduction	40 (20–60)	65 (50–80)	45 (20–60)	42 (30–80)	45 (30–80)	53 (40–70)	0.2
Passive outrotation	3 (0–30)	15 (0–35)	10 (0–40)	15 (10–30)	13 (10–40)	15 (0–40)	0.1
Constant score	14 (4–30)b	18 (9–42)a	15 (4–56)	23 (13–50)ab	34 (14–61)	46 (27–49	0.1
SRQ	28 (17–54)	28 (20–47)	30 (18–71)	43 (36–63)ab	55 (29–81)	57 (35–91)	0.1
SPADI	79 (45–95)	75 (44–91)	79 (27–93)	75 (33–89)	62 (12–83)	26 (11–48)	0.1

Values with a are different from baseline ($p<0.05$). Values with b are different from week 2 ($p<0.05$)

[a] Friedman test for multiple comparisons

glucocorticoid injections may be present, which is in accordance with findings of previous studies. Rodeo and et al. [16] have demonstrated excessive levels of pro-inflammatory cytokines including TNF-α by immunohistochemical localization in samples from patients with adhesive capsulitis as compared to normal controls. In another study performed on patients with frozen shoulders, shoulder capsule biopsies showed a slight increase of TNF-α compared to controls [4]. These findings were the triggers of this study, as we assumed that TNF-α blockade might be of importance in the treatment of frozen shoulder. The results of our study seem to indicate otherwise, and it may now be speculated why.

We can think of three reasons. First, it may well be that TNF-α is no major player in the inflammatory process leading to adhesive capsulitis. When trying to understand the inflammatory process leading to adhesive capsulitis, it is crucial to examine the capsule at a time where the inflammation is still active. In Bunker's study on expression of cytokines in frozen shoulders, the biopsies were all performed on patients with a mean duration of 21.8 months of the disease, meaning that they were in the third stage of the condition. In this stage, the acute inflammation is over, and the fibrotic process dominates. Had the biopsies been performed during the first stage of the disease where the inflammation is at its peak, the results might have been different. Also, several of the patients from whom the biopsies were taken had received steroid injections which may also have affected the composition of the cytokines found in the biopsies. There are, in addition, arguments for comparing the frozen shoulder with the Dupuytren contracture, where biopsies of Dupuytren tissue showed TNF-α in 40 % of cases [17]. Based on this knowledge, it was, in our opinion, not possible to discard TNF-α as a major player in the inflammatory process taking place in frozen shoulders, but the results of our study seem to prove otherwise.

Another possibility could be that our patients received treatment at a time where the inflammatory process was no longer active. Our patients had poor constant and SRQ scores at baseline though, reflecting severe pain and poor function, and we therefore believe that they still were in stage I.

Finally, baseline values for active and passive flexion were significantly lower in the adalimumab group than in the glucocorticoid group, which makes a comparison on the effects of glucocorticoid and adalimumab difficult. But even though there was a slight difference in the groups at baseline as regards to active and passive flexion, the groups were comparable for all other points. In addition, there was no detectable effect of adalimumab at any time, and we therefore believe that it can be concluded that the lack of effect was not a result of biases.

Although the study suffers from several limitations, the results may be hypothesis-generating for future studies aiming at assessing the effects of biological agents in frozen shoulder. A useful approach might be to perform biopsies of the capsule in patients with frozen shoulder in stage I and to compare them with biopsies from the capsule of patients with other painful conditions of the shoulder. Further investigation in this field might give us better insight as to the inflammatory process involved in the development of frozen shoulder, and thereby lead us to more efficient treatment strategies.

Conclusion

The effect of adalimumab on frozen shoulder has not previously been examined. In this randomised study, no effect was demonstrated for subcutaneous adalimumab compared to intraarticular steroid injections in patients with FS. Intraarticular glucocorticoids seemed to have some effect over time but not to a significant degree compared to adalimumab.

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References

1. Gam A, Schydlowsky P, Rossel I, Remvig L, Jensen EM (1998) Treatment of "frozen shoulder" with distension and glucorticoid compared with glucocorticoid alone. Scand J Rheumatol 27:425–430
2. Rizk TE, Pinals RS, Talaiver AS (1991) Corticosteroid injections in adhesive capsulitis. Arch Phys Med Rehabil 72:20–22
3. Bulgen DY, Binder AI, Hazleman BL, Dutton J, Roberts S (1984) Frozen shoulder: prospective clinical study with an evaluation of three regimens. Ann Rheum Dis 43:353–360
4. Bunker TD, Reilly J, Baird KS, Hambien DC (2000) Expression of growth factors, cytokines, matrix metalloproteinases in frozen shoulder. J Bone Joint Surg 82B:768–773
5. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D et al (2003) Adalimumab, a fully human anti-tumor necrosis factor-a monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (safety trial of adalimumab in rheumatoid arthritis). J Rheumatol 30:2563–2571
6. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS et al (2004) Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. Arthritis Rheum 50:1400–1411
7. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA et al (2003) Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment

of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 48:35–45
8. van de Putte LBA, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL et al (2004) Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 63:508–516
9. Abbott Laboratories (2002) Adalimumab (Humira): product summary. North Chicago 1–14
10. Codman EA (1934) The shoulder: rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa. Thomas Todd Co., Boston
11. Constant CR, Murlay AHG (1987) A clinical method of functional assessment of the shoulder. Clin Orthop Relat Res 214:160–164
12. L'Insalata JC, Warren RF, Cohen SB, Altchek DW, Peterson MG (1997) A self-administered questionnaire for assessment of symptoms and function of the shoulder. J Bone Joint Surg 79A:738–748
13. Williams JW, Holleman DR Jr, Simel DL (1995) Measuring shoulder function with the shoulder pain and disability index. J Rheumatol 22:727–732
14. Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y (1991) Development of a shoulder pain and disability index. Arthritis Care Res 4:143–149
15. Buchbinder R, Hoving JL, Green S, Hall S, Forbes A, Nash P (2004) Short course prednisolone for adhesive capsulitis (frozen shoulder or stiff painful shoulder): a randomised, double blind, placebo-controlled trial. Ann Rheum Dis 63:1460–1469
16. Rodeo SA, Hannafin JA, Tom J, Warren RF, Wickiewicz TL (1997) Immunolocalization of cytokines and their receptors in adhesive capsulitis of the shoulder. J Orthop Res 15:427–436
17. Bunker TD, Anthony PP (1995) The pathology of frozen shoulder—a Dupuytren-like disease. J Bone Joint Surg Br 77:677–678