# The CIMESTRA study: intra-articular glucocorticosteroids and synthetic DMARDs in a treat-to-target strategy in early rheumatoid arthritis

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Received and accepted on September 14, 2012.

*Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S44-S49.

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**Key words**: early rheumatoid arthritis, CIMESTRA study, synthetic DMARDs

Competing interests: none declared.

# ABSTRACT

**Objective.** Treatment of early rheumatoid arthritis (RA) include aiming at disease control with early use of methotrexate (MTX) in monotherapy or in combination with glucocorticoids or other disease-modifying drugs (DMARDs). The CIMESTRA study applied an aggressive treatment with DMARD and intra-articular injections of glucocorticoids (i.a. GC) to control disease activity. This paper reviews the results of the five years' study.

Methods. 160 patients with early RA (<6 months duration) were randomised to receive MTX 7.5-20 mg/ week+cyclosporine (CYA) 2.5-4 mg/kg (combination) or MTX+placebo-CYA (monotherapy). At each visit (week 0, 2, 4, 6, 8, thereafter monthly up to 24 months) patients had steroid injections in all swollen joints. During year 2, CYA/ placebo was withdrawn, and hydroxychlorochine added. Clinical responses were assessed by ACR20, 50 and 70, ACR and DAS remission. Radiographic progression by x-rays of hands and feet. **Results.** At year 1 (year 5) treatment responses in mono/combination groups were: ACR20: 68% (85%) / 85% (94%), ACR50: 53% (74%) / 68% (88%), ACR70: 44% (63%) / 59% (72%). After year 1, no significant differences between groups were found. Remission rates were: ACR-remission: 28% (52%) / 35% (60%), DAS28-remission: 34% (76%) / 43% (80%). Radiographic progression in both groups was <1TSS unit/year. After 1 and 2 years, 62% and 56% of the injected joints had not relapsed (both groups). Cumulated i.a.GC dose <1mg prednisolone/day. 19% received biologics by 5 years, 16% no treatment (sustained ACR-remission). Baseline magnetic resonance imaging (MRI) bone oedema best predicted radiographic progression after 2 years. Treatments were well tolerated.

**Conclusion.** *MTX* and *i.a.GC* in a treat-to-target strategy over 5 years halted radiographic progression and induced remission in the majority of patients. I.a. GC had in long-lasting effect and cumulated dosages were low.

# Introduction

A most important challenge remains to improve and optimise the medical treatment of rheumatoid arthritis (RA). Modern treatment strategies aim at reducing inflammation and halting erosive damage. The cornerstones include early treatment with use of methotrexate (MTX) in adequate dosages either in monotherapy or in combination with glucocorticoids, other synthetic diseasemodifying drugs (DMARD) or biological agents, and treatment regimes that aim at disease control.

The CIMESTRA study was an investigator-initiated randomised controlled trial (1), designed to investigate whether an aggressive and intensive treatment with DMARDs and intra-articular injections of glucocorticoids to suppress clinical synovitis could lead to disease control and suppression of disease activity by clinical and radiographical measures. The patients were followed in a GCP monitored treatment protocol for 2 years (2) and the initial double-blinding was maintained for five years (3). In addition, a number of baseline variables (demographic, serological markers, imaging) were investigated for their potential as predictors of radiographic progression and response to joint injections (4, 5).

The aim of this paper is to review the design and the results of the CI-MESTRA study, which have previously been published (1-5), and to present long-term treatment adherence after 5 years of follow-up.

# Material and methods

The CIMESTRA study was a randomised, double-blind, parallel-group, placebo-controlled, investigator-initiated trial, which included 160 patients with early, DMARD naïve RA (1). The initial double-blinding was maintained through the study period of 5 years.

In brief, patients were recruited who fulfilled the ACR 1987 criteria for RA, had less than 6 months of disease duration, were DMARD naive, had at least 2 swollen joints and were aged 18–75 years.

After enrolment, they were seen by two investigators at baseline and every fortnight for 8 weeks, thereafter every 4 weeks during the first 2 years of the study. One investigator performed the joint score and did the joint injections and was blinded to all other aspects of treatment; the other investigator was responsible for treatment adjustments and handling of side effects. From year 3, the patients were seen by one investigator according to the local guidelines (3–4 times per year or more) with annual study visits (year 3, 4, and 5). All excluded patients were followed on intention-to-treat basis and encouraged to show up for the annual visits.

Disease activity was assessed by a 40 joint count (PIP, MCP, wrists, elbows, shoulder, knees, ankles, MTP), the Danish version of the health assessment questionnaire (HAQ), visual analog scales (VAS) for patient pain, patient global estimate and doctor global estimate, serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Treatment responses were assessed by ACR20, ACR50 and ACR70 responses. Remission was defined according to the ACR remission and DAS28 remission criteria. ACR remission must have been present both at the annual visit and the preceding visit to be acknowledged, and no betamethasone injections were allowed to have been given at any of the two visits. Radiographic progression was assessed by x-rays of hands, wrist and forefeet at baseline and annually thereafter and scored according to the Sharp-van der Heijde method (TSS, total Sharp score).

The treatment strategy was to achieve early and sustained synovitis suppresTable I. Baseline characteristics of the CIMESTRA population (1).

Gender (% women)	67
Age (years)	53 (42–62)
Seropositive disease (%)	66
Disease duration (years)	0.27 (0.21–0.38)
Disease activity (DAS28 score)	5.3 (4.4–5.9)
HAQ	1 (0.385–1.500)
Erosive disease (%)	61

Unless otherwise indicated, median (IQR) is shown. Some discrepancies compared to (3) arise from lower N, where data were drawn on paired analyses. Modified from (23).



: Visit – i.a. betametasone and step-up if any swollen joint



**Fig. 1.** The CIMESTRA treatment strategy during the first 2 years, in which the treatment was protocollated. Each visit is indicated by an arrow. Intra-articular injections were given, and DMARD dose escalated, if any swollen joint was present. For details, read text. Modified from (1, 2).

sion by aggressive use of i.a. glucocorticoidsteroids and disease-modifying drugs (DMARDs). At enrolment, the patients were randomised into one of two treatment arms (see Fig. 1A). In one arm, patients were treated with methotrexate (MTX) 7.5 mg weekly plus cyclosporine 2.5 mg/kg/day (combination therapy group). In the other arm, the patients were treated with MTX 7.5 mg weekly plus placebo-cyclosporine (monotherapy group). At all visits (marked with arrows on figure 1), the patients were given intra-articular betamethasone (7mg/ml) injections in all swollen joints (max 4 joints or 28

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Α.

mg per visits). If the patients at any visit after the  $2^{nd}$  month presented with swollen joints MTX dosages were escalated stepwise with 2.5 mg/week up to 20 mg/week, followed by a stepwise increase in cyclosporine/placebo-cy-closporine with 0.5 mg/kg/day up to 4.5 mg/kg/day.

During year 2, cyclosporine/placebo was tapered to zero, while hydroxychlorochine was added in all patients (Fig. 1B). Oral glucocorticoids were not allowed during the first 2 years. The treatment strategy of strict suppression of clinical synovitis by intraarticular glucocorticoids and escalation of MTX was sustained over 5 years. If an ACR20 response was not achieved after the first year despite 20 mg MTX and cyclosporine/placebo-cyclosporine 4.5 mg/kg/day, the patient was switched to receive parenteral MTX, followed by triple therapy (MTX, hydroxychlorochine and sulphasalazine), and after this switched to TNF-blocker treatment. Patients in ACR remission for more than one year at 3, 4 or 5 years were offered withdrawal from treatment. All patients received folic acid, calcium and vitamin D. If Z-score was <0 at baseline, alendronate 10 mg daily was started.

# Results

The fraction of patients who achieved ACR20/50/70 in each of the two treatment arms is shown in Fig. 2A. In the monotherapy group (treated with MTX and intra-articular glucocorticods), 68% of patients had achieved an ACR20 response after one year, increasing to 85% after 5 years (1-3). For ACR50, it was 53%, increasing to 74%, and for ACR70 it was achieved in 44% of patients, increasing to 63% after 5 years (1-3). In the combination therapy group (in which cyclosporine was given in addition to MTX and intra-articular glucocorticoids), the corresponding response rates were significantly higher after one year (ACR20/50/70: 85%/68%/59%), but after withdrawal of cyclosporine during year 2, no statistically significant differences remained between the two treatment arms (2).

The numbers of patients, who went into ACR remission during the five years,



#### Remission Β. 100 100 90 90 80 76 80 80 70 70 60 60 60 52 50 50 40 40 27 28 30 30 20 20 10 10 0 0 0 DAS Rem Sust ACR DAS Rem Sust ACR ACR Rem ACR Rem Rem Rem

# Monotherapy

#### Combination therapy

**Fig. 2.** Treatment responses at 1, 2, 3, 4 and 5 years in the monotherapy group (to the left) and the combination therapy group (to the right). Numbers indicate percentages of patients fulfilling the criterion. Modified from (1-3). A: ACR20/50/70. B: ACR remission, DAS remission and sustained remission (*i.e.* ACR remission at 3, 4 and 5 years).

are shown in Figure 2B. Here, a similar pattern was seen: High remission rates (monotherapy group: 28% after one year), increasing significantly over time (to 52% after 5 years), and slightly higher rates, although not statistically significant, in the combination therapy group. DAS remission was achieved in 76% and 80% of patients, respectively, after 5 years, and 27% and 28%, respectively, remained in sustained ACR remission at both year 3, 4 and 5 (1-3). At baseline, 61% of patients had erosive disease. In spite of an estimated yearly rate of progression was 19 Sharp score units (2), the radiographic progression was effectively halted in both treatment arms with an observed annual progression rate of less than one Sharp score

unit. Almost 50% of patients had not progressed after 5 years (3). At no time point were there any differences between the two treatment groups (1-3). The anchor treatment in the CI-MESTRA study was MTX with intraarticular betamethasone. After 5 years, this treatment was ongoing in approximately 50% of patients (except that hydroxychlorochine had been added in all patients during the second year irrespective of disease activity), 16% were taking triple therapy, 18% taking biological agents, and 16% had been withdrawn from treatment because of sustained ACR remission (Fig. 3) (3). During the first two years, 1,373 unique joints were injected. Of these, 531 received a second injection, and 262 a

# Treatment responses



# Treatments

Fig. 3. Treatments given at baseline and during 3 to 5 years' follow-up. Modified from (3).

third (5). After one and two years, 62%and 56% of the joints injected at baseline had not relapsed. For all joint areas (PIP, MCP, wrist, elbow, shoulder, knee, ankle, MTP) the long-term effect of a joint injection was good, and it was best for PIP joints in which 79% of the injected joints had not relapsed after 2 years (Fig. 4). The effect of the injection was best for the first-time injections (in which 57% had not relapsed after 2 years) compared to the 2<sup>nd</sup> time injections (43%) and the  $3^{rd}$  time injections (31%) (5). The cumulative doses of betamethasone are shown in Fig. 4. During the first two years, less than one joint injection was given per visit (median: 0.55, IQR: 0.38-0.96), corresponding to less than one mg of oral prednisolone daily. Also in year 3 to 5, the glucocorticoid dosages were low (corresponding to median 0.09 mg prednisolone/day (0-0.38mg), mean (SD): 0.60 (1.42) mg/day(5).

MTX, cyclosporine and joint injections were well tolerated, with few adverse events, as previously described in detail (1-3, 5).

In a subgroup of patients (n=130) additional analyses were performed to identify predictors of radiographic progression and response to the intra-articular injections (4-5). A panel of potential predictors had been identified at baseline (including age, gender, clinical measures of disease activity, acute



Fig. 4. Long-term effect of joint injections (from (5)).

phase reactants, anti-CCP, rheumatoid factor of the IgM and IgA subclasses, HLA-DRB1 shared epitope, TSS and MRI erosion score, MRI synotivis score and MRI bone marrow oedema). These were tested in a multiple linear regression model, which showed that MRI bone marrow oedema was the best predictor of radiographic progression after 2 years (4). At 5 years, also anti-CCP and baseline TSS were independent predictors (3). A high MRI synovitis score and anti-CCP negativity were associated with a poorer effect of intra-articular injections of betamethasone (5). In a number of spin-off projects, the performance of various experimental biomarkers have been investigated in the CIMESTRA study (6-13).

#### Discussion

Two significant lessons from the CI-MESTRA study include: 1) excellent disease control (no synovitis and halt-

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ing of erosive disease) can be achieved with low-cost synthetic DMARDs (MTX alone or in combination with other DMARDs) in early RA if an aggressive and flexible treatment strategy is applied (1-3). Thus, only one in five patients needed biological therapy after 5 years, and one in six had been withdrawn completely from therapy because of sustained remission (3). 2) The use of intra-articular injections with betamethasone in any swollen joint – whether small or large – led to long-lasting remission of the individual joint, and was well tolerated (5).

At five years, more than 75% of patients were in DAS28 remission, more than 50% were in ACR remission and more than 25% had achieved sustained remission, defined as ACR remission at 3, 4 and 5 years (3). The CIMESTRA strategy led to halting of erosive progression. Almost 50% did not progress during 5 years, and the average increase in TSS was less than 1 unit per year. Compared to other trials of early RA treated with synthetic DMARDs e.g. (14, 15), these results are impressive and match those reported in RCTs of biologic therapies in RA early in the disease course (16-18).

The joint injections rapidly brought the inflammatory process under control. Two weeks after inclusion in the project, 50% of patients had achieved a good EULAR response, 39% were in DAS28 remission and 50% had no swollen joints (5). The good response was also reflected in the patient-reported outcomes (VAS for pain, global, HAQ). The joint effect of intra-articular injections and MTX treatment was longlasting and well-tolerated. Injections of small and large joints had similar effect in the long term. Even joints that were injected a second or a third time went into long-lasting remission. Thus, almost two-thirds of joints injected for the first time, half of joints injected for the second time, and one third of joints injected for the third time had not relapsed after one year (5). The on-demand use of intra-articular joint injections resulted in a low cumulated dose of glucocorticoids, corresponding to less than 1 mg of prednisolone daily. Patients who were negative for anti-CCP or had high

MRI synovitis scores had poorer results of joint injections (5).

As the treatment strategy of strict synovitis suppression was applied to both treatment arms throughout the 5 years of follow-up, the isolated impact of initial combination therapy could be studied. This was in contrast to most other long-term studies (i.e. more than 2 years of follow-up), in which the design was either open, or the treatment arms differed with respect to other factors, such as visit frequency or the use of concomitant prednisolone (19-22). The halting of erosive progression was observed in both treatment arms and therefore should be attributed to the strategy of tight control of inflammation rather than to initial mono- versus combination therapy.

The escalation of MTX represents the tradition at the turn of the century. A faster increase in MTX dose as recommended today as well as an earlier shift to triple therapy may have led to a faster clinical response. However, at one year, the average MTX dose in the CIMESTRA study was 20 mg/week. The addition of hydroxychlorochine from week 76 and onwards may have increased the potency of MTX, since co-administration of MTX with hydroxychlorochine has been reported to increase the bioavailability of MTX.

MRI bone marrow oedema was shown to be the best baseline predictor of radiographic progression after 2 years (4). At 5 years, it was still the strongest independent predictor, but anti-CCP positivity and baseline Sharp score also were independent predictors (3).

In conclusion, the CIMESTRA study showed that treatment with MTX aiming at suppression of synovitis with intra-articular betamethasone injections on demand over 5 years of follow-up of patients with early RA, led to halted radiographic progression and remission in the majority of patients. Addition of cyclosporine during the first 2 years did not improve long-term clinical and radiographic outcome.

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