Double-blinded placebo-controlled trial measuring cartilage improvement in early Rheumatoid Arthritis under Adalimumab therapy using MRI

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Research article

Keywords: Early rheumatoid arthritis, Adalimumab, TNF-α-inhibitor, gadolinium-enhanced-MRI-of-cartilage (dGEMRIC), cartilage improvement

Posted Date: January 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-153294/v1

Abstract

Background: To compare the effect of Adalimumab (ADA) plus Methotrexate (MTX) versus MTX monotherapy in patients with therapy naïve early rheumatoid arthritis (eRA) on cartilage quality measured by glycosaminoglycan (GAG) content in cartilage using gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC).

Methods: Prospective double-blinded, randomized clinical trial of cartilage integrity in finger joints of eRA patients according to American College of Rheumatology/ European League Against Rheumatism. Patients were examined therapy-naïve, 12 and 24 weeks after initiation of Adalimumab+MTX or placebo+MTX with 3T-MRI, recording dGEMRIC values of metacarpophalangeal joints of index and middle finger.

Results: The study was prematurely terminated due to theoretical safety concerns regarding gadolinium deposition in the brain after MR contrast agent application. Instead of 30 planned patients, 10 patients could be included in the Adalimumab group (ADA+MTX: 6 females, 44.9y, range: 19-65), four in the control group (Placebo+MTX: 2 females, 46.7y, range: 24-64). Between treatment groups, cartilage composition did not change significantly (ADA+MTX: dGEMRIC mean change 85.8ms, range -156.2–346.5ms; Placebo+MTX: mean change-30.75ms, range-273.0–131.0ms; W=27, p=0.37). Neverthless a significant increase of the dGEMRIC values over time was observed in the Adalimumab group (median change 75.88 ms p=0.0117), but not in the placebo group (median change 9.50, p=0.878).

Conclusions: In patients with eRA, Adalimumab+MTX leads to a significant dGEMRIC improvement, indicating a possible reduction of cartilage damage in the finger joints. The level of significance for the difference of change in cartilage quality between groups, was not met, potentially due to lower than expected number of patients which could be recruited.

Trial registration: The cartilage in early Rheumatoid Arthritis (CAR-ERA)-Study was approved by the local ethics committee of the Heinrich-Heine University of Duesseldorf (reference number: MO-LKP-719) and was registered at clinicaltrials.gov under the number NCT02150473 / CAR-ERA 2013-004604-19 (EudraCT Number).

Background

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by enduring joint inflammation resulting in a specific pattern of cartilage and bone damage and ultimately loss of joint function (1). The chronic, progressive nature of the disease leads to physical limitation, reduced quality of life, and higher mortality rates (1, 2).

The pathomechanism of RA is not yet fully understood. However, inflammation of the synovial membrane, cytokine- and chemokine induced cell migration into the joint space, and consecutive cartilage damage and bone erosions, appear to play a key role in the progression and maintenance of the disease (3).

Early detection, accurate monitoring and a treat-to-target approach in the use of disease-modifying antirheumatic drugs (DMARDs) are components of a modern treatment strategy aimed at controlling

inflammation soon after diagnosis to prevent joint damage (4). In recent years, the treatment of RA has been revolutionized by the development of a new class of drugs, the biological agents, to which Adalimumab belongs (bDMARDs). Adalimumab is a globally approved TNF-α inhibitor recommended for the treatment of patients who do not achieve clinical remission with conventional DMARDs (including MTX) (5). In addition, it may be applied as a monotherapy for those who do not tolerate conventional DMARDs (6). The inhibition of bony structural damage in patients who received Adalimumab has been shown using conventional radiography (7).

MRI imaging is arguably more sensitive than conventional radiography in the detection of RA alterations (8). In particular, inflammation of the synovial membrane and bone marrow edema can be visualized. Bone marrow edema is even considered to be a prognostic indicator of erosions and joint destruction in the course of the disease (9).

In 2003, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group introduced the RA MRI score (RAMRIS) a highly reliable sum-score that reflects the severity of synovitis, bone marrow edema and erosions in the hand and wrist to determine the disease activity and to monitor therapy response (10). Cartilage changes do not directly contribute to the score, although cartilage changes appear to be important in monitoring RA and are even more closely associated with physical disability than bone damage (11), highlighting the potential benefit of closer monitoring strategies that focus on cartilage. Indirectly, however, cartilage damage was included in the RAMRIS in 2017 through joint space narrowing, which is a result of cartilage damage (12). As the sub-score only detects an advanced state of cartilage damage in which the cartilage thickness has already decreased, techniques to visualize early cartilage changes seem to be beneficial.

A sensitive method to visualize early cartilage changes is a compositional MR imaging technique called delayed Gadolinium-Enhanced MRI of the Cartilage (dGEMRIC). This highly reliable MRI technique indirectly enables the visualization of proteoglycans, which are one of the main components of healthy cartilage. In particular dGEMRIC enables the detection of proteoglycan loss after the application of gadolinium based contrast agent in the cartilage (13). dGEMRIC is a sensitive technique for cartilage changes and has the potential to predict joint space narrowing (14).

It has so far been shown that the molecular cartilage composition remains constant within 6 months by using MTX (15). But to the best of our knowledge it is not yet clear to what extent Adalimumab has an effect on cartilage quality. Therefore, the aim of this study was to monitor cartilage integrity under Adalimumab plus MTX versus MTX monotherapy in patients with early RA by using dGEMRIC.

Material And Methods

Study population

The study was conducted in line with the Declaration of Helsinki and approved by the local ethics committee of the Heinrich-Heine University of Duesseldorf (reference number: MO-LKP-719). Written informed consent was obtained from all individual participants. Fourteen patients with early RA fulfilling the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) 2010 classification criteria with a

disease duration ≥ 6 months prior to any DMARD including bDMARD were enrolled in this prospective double-blinded study. They were randomly assigned to one of the two groups and treated accordingly with Adalimumab plus MTX (10 patients, 6 females, mean age 44.9 years, range: 19-65 years) or MTX monotherapy plus placebo (4 patients, 2 females, mean age 46.7 years, range: 24-64 years). Patients were allocated to the two treatment arms, in a ratio of 2:1 by central block-randomization. The randomization list was generated by the local Coordination Centre for Clinical Studies using a validated system, which involves a pseudo-random number generator to ensure that the resulting treatment sequence will be both reproducible and non-predictable. To maintain blinding, the MTX monotherapy group was given appropriate subcutaneous placebo injections.

MR imaging

MRI of the dominantly affected hand was performed in all patients at baseline and 12 and 24 weeks after initiation of treatment with adalimumab plus MTX or MTX monotherapy, respectively. A 3T MRI system (Magnetom Skyra syngo; Siemens Healthineers, Erlangen, Germany) with a dedicated receive-only 16-channel hand coil (3T Tim Coil, Siemens Healthineers) was used. Subjects were imaged in prone position with the hand extended over the head and the palm facing down ('superman position').

For anatomical imaging, a coronal short tau inversion recovery (STIR) sequence of the hand and the wrist, T1-weighted turbo spin echo (TSE) sequence, a T1 VIBE and two T1 sequences with two different flip angles (8 and 26°) were acquired before injection of a contrast agent. Gadolinium-based MR contrast agent was applied intravenously (0.4 ml/kg body weight of Gd-DTPA2-, Magnevist; Schering). After contrast agent injection, a coronal VIBE, a TSE and a transversal SE-sequence with fat suppression were applied. The sequence parameters, presented in table 1, were selected according to a previous study and are adapted to the Magnetom Skyra syngo 3T-MRI (13). Cartilage integrity and the course of illness was monitored by evaluation of compositional MRI with dGEMRIC and cartilage thickness of MCP2 and MCP3 joints, as previous work has shown that MCP2 and MCP3 joints are more frequently affected (16). . To achieve high resolution images with thin sections and a small FOV the hand was placed in a dedicated 16 channel, high-resolution hand and wrist coil. According to previous studies, there was a delay of 40 minutes between the application of contrast agent and the dGEMRIC sequence (17). Three-dimensional dual-flip-angle gradient-echo sequence was used for T1 mapping (17). Flip angles were defined at 5° and 26°. Ten sagittal slices with a thickness of 2 mm and a FOV of 90 x 53.5 mm were positioned perpendicular to the joint spaces. Motion correction was applied to the MCP joint of each patient to reduce movement-related artifacts using STROKETOOL (Frechen, Germany) before image analysis (18)

dGEMRIC was used as this highly reliable MRI technique indirectly enables the visualization of proteoglycans and therefore might show early cartilage changes (13). After the application of contrast agent, the negatively charged gadolinium diethylenetriamine pentaacetate anions (Gd-DTPA) enter the cartilage in an inverse relationship to the concentration of the negatively charged glycosaminoglycan side chains of the proteoglycans. A decrease in proteoglycan content in degenerated cartilage thus leads to an accumulation of paramagnetic gadolinium ions (19). This increased gadolinium concentration in turn leads to a shortened T1 relaxation time in MR imaging and thus to an increased signal in the T1-weighted sequences (20). With

dGEMRIC molecular cartilage changes in early RA could already be detected at a time when morphological changes were not yet visible (21, 22).

Image analysis

According to the OMERACT RAMRIS, MR images were analyzed in consensus by two radiologists trained in musculoskeletal imaging to evaluate sub-scores for synovitis, erosion and edema in the hand and the wrist (10). The radiologists were blinded to the patient data and the dGEMRIC values. Molecular imaging to visualize cartilage composition was performed using dGEMRIC on MCP2 and MCP3 joints. dGEMRIC is represented by the T1 map after injection of contrast agent. Two separate regions of interest (ROI) were placed in the phalangeal and metacarpal cartilage of the MCP joints. Gradient echo sequences with a flip angle of 8° served as anatomical reference for the algorithm by which the ROIs were automatically placed in each cartilage zone (23). Within these ROIs dGEMRIC values were recorded (T1 [in milliseconds]).

Statistical Analysis

Statistical analysis was performed using R (Version 3.6.0, 64-bit). The mean, median, 1st and 3rd quartile, minimum and maximum for dGEMRIC values were calculated as descriptive statistics (listed in table 2). Wilcoxon paired rank sum test was applied to compare dGEMRIC values of the MCP joints in patients treated with Adalimumab plus MTX and patients treated with MTX monotherapy to show whether Adalimumab affects a significant difference in cartilage composition after 6 months of therapy. P-values below 0.05 were considered to be significant.

Results

Adverse events

There were no serious adverse events in this study. Isolated adverse events were found in both treatment groups. Upper respiratory tract infection (ADA + MTX: 5 patients, placebo + MTX: 4 patients), urinary tract infection (ADA + MTX: 1 pat., placebo + MTX: 1 pat.) and abdominal pain (ADA + MTX: 1 pat., placebo + MTX: 1 pat.) were documented in both therapy groups within the 24-week treatment period. In the Adalimumab plus MTX therapy group, isolated events were additionally observed during the course of the treatment period: Elevated liver enzymes (3 pat.), myalgia of the tibia (2 pat.), cervical myalgia, high serum creatinine, hypertension, vaginal bleeding, rash at injection site, itching exanthema, xerosis cutis and hair loss. In addition, there was one allergic reaction to gadolinium.

Primary objective: Cartilage integrity (dGEMRIC)

There was no statistically significant change in cartilage composition between both treatment groups. Under Adalimumab, on average, there was a stronger increase in dGEMRIC values in MCP2 and MCP3 joints between baseline and 24-week follow-up than in the control group, but without statistical relevance (ADA plus MTX: dGEMRIC mean change 85.8 ms, range -156.2 – 346.5 ms; MTX monotherapy: dGEMRIC mean change -30.75 ms, range -273.0 – 131.0 ms; W = 27, p = 0.37) (figure 1). An example of dGEMRIC visualized cartilage of an early RA patient treated with Adalimumab plus MTX is shown in figure 2.

By considering the intermediate values after 12 weeks of therapy, a continuous increase in dGEMRIC values with strong statistical evidence over time was observed in the Adalimumab group (median change over 24 weeks: 75.88 ms, p=0.0117). In contrast to the Adalimumab group, only a minimal increase, but no significant dGEMRIC change over time could be observed in the placebo group (median change over 24 weeks: 9.50, p=0.878) (figure 3).

Due to increasingly serious concerns that gadolinium deposits may occur in the brain after application of linear MR contrast agent (24), this study was prematurely terminated. According to the power analysis, a total of 30 patients were originally planned for the study. Instead 10 patients could be included in the Adalimumab plus MTX group and four in the control group.

Discussion

An early start of a disease-modifying therapy and achieving early remission are two of the basic principles of the therapy concept for RA (4). Early treatment significantly improves the long-term outcome and is therefore an important principle of the EULAR recommendations (4). The treat-to-target (T2T) strategy has become almost universally established in order to make therapy more efficient (25). A clear therapeutic goal, usually remission, is pursued. If remission or at least low disease activity cannot be archived, the patient should be escalated according to EULAR guidelines at an early stage regarding the T2T concept (25). The introduction of biologic (b) and recently targeted synthetic (ts) DMARDs has opened up new therapeutic possibilities beyond conventional synthetic (cs) DMARD therapy, in particular for patients who have not responded to the conventional drugs or have responded only insufficiently (26).

In this double-blinded, placebo-controlled, randomized clinical trial, the effect of Adalimumab in combination with MTX vs. MTX monotherapy on joint cartilage integrity of MCP2 and MCP3 in patients with early RA was examined with compositional MRI of the cartilage by using dGEMRIC (27). To substantiate our results, further parameters describing disease activity were assessed, including cartilage thickness, the RAMRIS, specific bio- respectively serum cartilage markers and clinical and functional outcome. To the best of our knowledge this is the first randomized trial evaluating the effect on cartilage of Adalimumab therapy plus MTX versus MTX monotherapy using dGEMRIC and high-field MRI.

Our most important finding was that Adalimumab plus MTX therapy leads to a significant increase of dGEMRIC values over time. In contrast to the Adalimumab group, there was no significant increase of dGEMRIC values in the placebo group, which indicates that controlling inflammation with Adalimumab leads to an improvement of cartilage quality. These results are in line with Beals et al., who documented reduced cartilage damage under bDMARD therapy using Infliximab (28). But the results of this study thus point to an even clearer positive effect and indicate that even regeneration of cartilage composition seems to be possible under Adalimumab treatment. The slightly different results between our study and the results of Beals et al. could occur due to the different bDMARDs used or to the different cartilage measurement MRI techniques (DCE-MRI vs. dGEMRIC). Moreover, it has to be mentioned that the study populations differ since the CAR-ERA trial aimed at very early, therapy naïve RA patients. However, both studies support the notion of a positive effect of TNF-alpha inhibitors on cartilage integrity in RA. The results of this study are in contrast to the only further study that investigated the effect of bDMARDs on cartilage using dGEMRIC. Tiderius et al. investigated

knee joints in 7 chronic RA patients and found cartilage deterioration after 22 weeks (29). A possible explanation is that patients with early – not established - RA respond better to bDMARDs than patients at a chronic stage of the disease, which in turn supports the current treatment principle of early and T2T therapy. Another potential explanation is a varying response in different joints. This theory can be supported by findings that point out a difference of cartilage regeneration between knee and ankle joints. Kuettner and Cole showed that in response to damage, knee chondrocytes synthesize proteoglycans at a lower rate than in ankle cartilage chondrocytes, which suggests a lower capacity for repair and regeneration (30). As expected, the results of Kuettner and Cole indicated an increased degree of cartilage surface disorder with increasing body weight. In our cohort, however, there were no significant differences with respect to body weight.

Recently, the suitability of MRI for therapy monitoring was critically questioned based on the control parameter bone edema. A superiority could not be demonstrated for the MRI-guided treat-to-target group compared to the conventionally guided group (31). In this study, the focus was explicitly placed on the compositional cartilage quality measurable with dGEMRIC, since compositional cartilage imaging is expected to be able to detect cartilage damage at an early stage (14), which in turn may be a sign of progressive RA (12). Therefore, we consider MRI to be a valuable diagnostic tool. However, cartilage changes may be a more sensitive control parameter than bone marrow edema.

This study had several strengths. It is a double-blinded, placebo-controlled, randomized clinical trial and the first published report of compositional MRI's ability to point out cartilage regeneration in RA. This is significant since the exclusion of the assessment of cartilage in previous clinical trials was an obstacle to the acceptance of MRI as a substitute for radiography (32). However, the use of MRI is preferable as previous studies have shown that cartilage loss is at least as relevant to long-term outcome as bone erosion (32). One of the further strengths of this study at once is the use of the dGEMRIC for cartilage visualization. Until recently, the MRI technique dGEMRIC was considered the reference standard to evaluate extracellular matrix components of hyaline cartilage (17). For dGEMRIC the application of gadolinium-based contrast agent is obligatory. Due to new indications of gadolinium ablation in the brain and a subsequent recommendation of the European Medicines Agency (EMA) to discontinue the use of linear contrast agents based on gadolinium, subject safety was prioritized, and the study was stopped prematurely (24). A limitation therefore arises due to the discontinuation of the study in the unequal group size and in the relatively small number of control subjects. Despite a reduced number of subjects, the results, which were collected until the end of the study, are highly valuable.

Further limitations of this study include manually selected ROIs for dGEMRIC measurement in the MCP finger joints instead of automatically algorithm-based ROIs. Due to the small size of the MCP joint and the resulting low contrast, automated cartilage recognition is not yet reliable enough to be used in this study. Manual evaluation by an experienced radiologist was therefore preferred, despite the possible human interference factor. For future studies, the increased automated evaluation of clinical image data should be pursued.

Conclusion

In conclusion, this study demonstrates that there is a trend to cartilage regeneration under Adalimumab plus MTX versus MTX monotherapy after 24 weeks in early RA patients. The results indicate that Adalimumab can

improve cartilage impairment as a very early sign of inflammation in early RA and inhibits the initiation of joint damage. MRI is a valuable tool for assessing inflammation to detect early cartilage damage in RA.

Abbreviations

ACR	American College of Rheumatology
ADA	Adalimumab
DCE-MRI	dynamic contrast enhanced MRI
dGEMRIC	delayed gadolinium-enhanced magnetic resonance imaging of cartilage
DMARDs	disease-modifying antirheumatic drugs
bDMARDs	biological DMARDs
cs DMARD	conventional synthetic DMARD
ts DMARDs	targeted synthetic DMARDs
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
GAG	glycosaminoglycan
Gd-DTPA	gadolinium diethylenetriamine pentaacetate anions
MTX	Methotrexate
MRI	magnetic resonance imaging.
RA	rheumatoid arthritis
RAMRIS	RA MRI score
eRA	early rheumatoid arthritis
STIR	short tau inversion recovery
TSE	turbo spin echo
OMERACT	Outcome Measures in Rheumatology Clinical Trials

Declarations

- Ethics approval and consent to participate: The study was conducted in line with the Declaration of Helsinki and approved by the local ethics committee of the Heinrich-Heine University of Duesseldorf

(reference number: MO-LKP-719). Written informed consent was obtained from all individual participants.

- Consent for publication: Not applicable
- Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- Competing interests: The authors declare that they have no competing interests
- Funding: AbbVie Deutschland GmbH & Co. KG; Max-Planck-Ring 2; 65205 Wiesbaden provides the study medication and finances the study. DBA was supported by a research grant of the Medical Faculty of the University Dusseldorf.
- Authors' contributions: design of the study (BO, OS, PS), data acquisition (OS, JR, PS, SV, CS, AML), data analysis and interpretation (RB, CS, MF, DBA), manuscript draft (MF), manuscript revision (BO, CS, DBA, PS, GA, MS)
- Acknowledgements: The authors thank Erika Rädisch for assistance with the MRI measurements.

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Tables

Table 1. Detailed sequence parameters

Sequence/ Parameter	STIR without contrast agent	T1 TSE without contrast agent	T1 VIBE without contrast agent	T1 FLIP without contrast agent	T1 VIBE with contrast agent	T1 TSE with contrast agent	T1 SE fs with contrast agent	T1 with contrast agent
orientation	coronal	coronal	coronal	coronal	coronal	coronal	transversal	sagittal
TE/TR [ms/ms]	31 / 5560	27 / 862	5.8 / 1.9	5.8 / 1.9	5.8 / 1.9	27 / 862	16 / 702	4.56 / 15
Flip angle [°]	120	150	8	8 + 26	8	150	90	5 + 26
Slice thickness [mm]	2,5	2,5	3	3	3	2,5	2,5	2
FoV [mm x mm]	130 x 130	140 x 140	140 x 140	140 x 140	140 x 140	140 x 140	120 x 120	90 x 53.5
Number of images	1	1	1	2	1	1	1	2
Basic resolution	448	512	128	128	128	512	384	384
Number of acquired slices	17	17	10	10	10	17	20	10

Table 2. dGEMRIC-values at baseline (T0) and change in dGEMRIC-values after 24 weeks (T3) compared to baseline

pooled MCP2 and MCP3 dGEMRIC values		Adalimumab		Placebo
	T0	Δ (T3 - T0)	T0	Δ (T3 - T0)
Min.	390.0	-156.20	380.2	-273.00
1st Qu.	428.5	31.62	473.2	-97.88
Median	513.0	75.88	616.0	9.50
Mean	523.7	85.78	585.5	-30.75
3rd Qu.	614.8	141.60	676.2	76.62
Max.	647.8	346.50	803.2	131.00

Figures

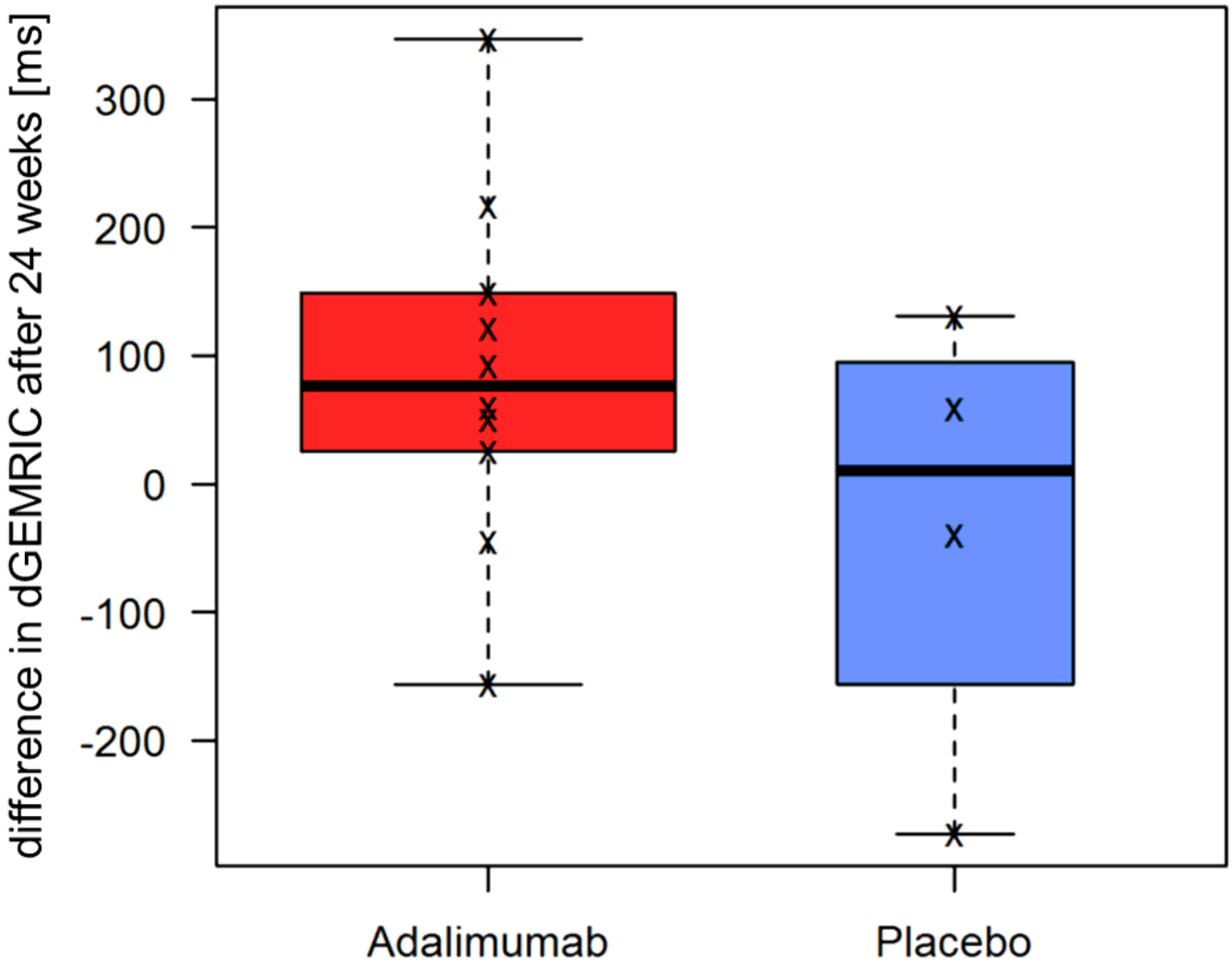

Figure 1

Change in cartilage quality in both treatment arms. Figure 1 shows the difference in delayed Gadolinium-enhanced MR Imaging of Cartilage (dGEMRIC) values in ms between baseline and 24-week follow-up in both treatment groups. There is a greater but not significant GAG gain, which indicates a slight improvement in cartilage quality under Adalimumab plus Methotrexate (MTX) compared to MTX monotherapy.

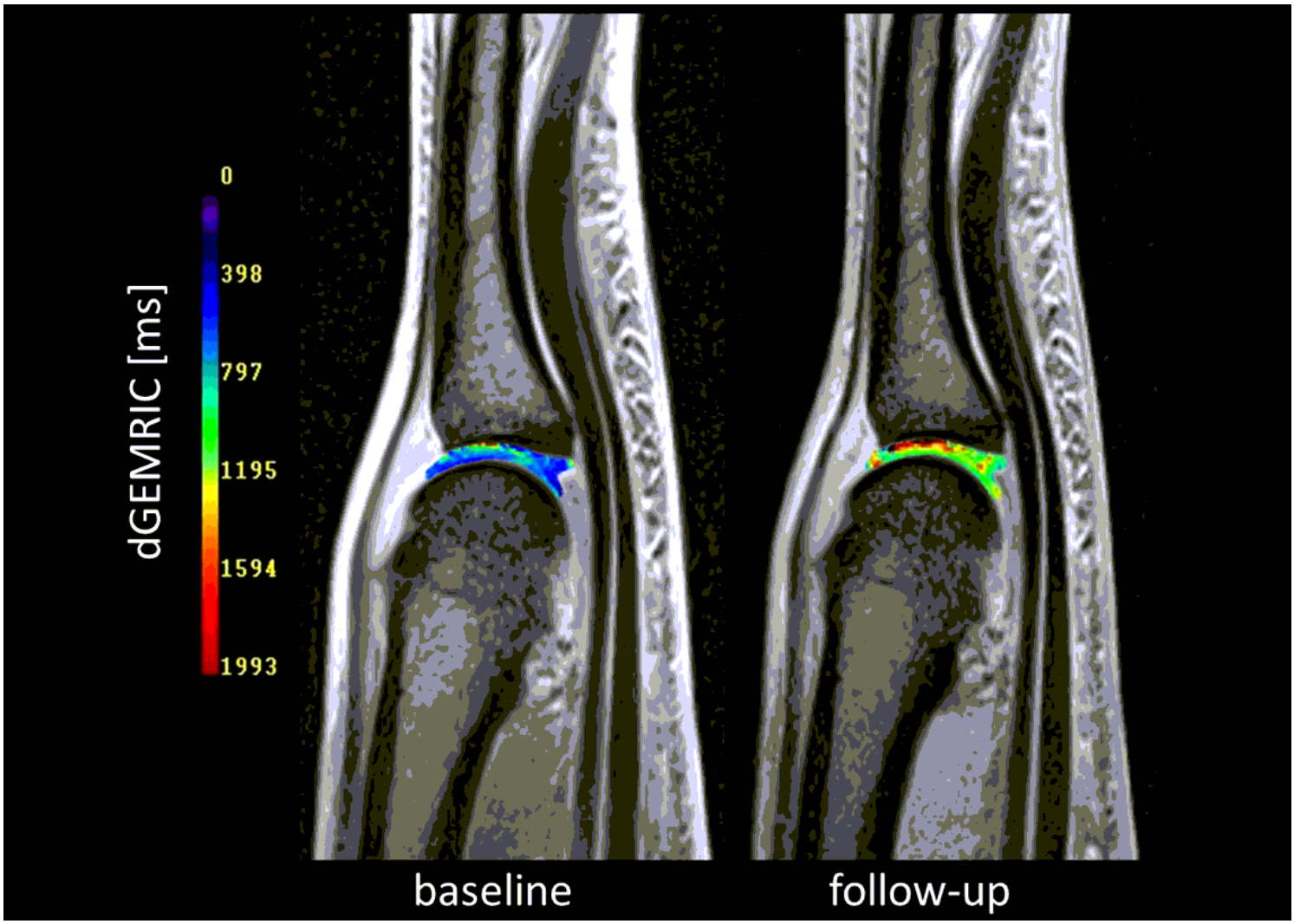

Figure 2

Cartilage composition of the MCP3 joint at baseline and after therapy. Fusion of morphological images with dGEMRIC maps demonstrating cartilage composition of the MCP3 joint at baseline and after 24 weeks of Adalimumab plus MTX therapy (follow-up). Blue indicates cartilage damage and red indicates healthy cartilage. After therapy dGEMRIC values have increased (change from blue to green), indicating cartilage regeneration.

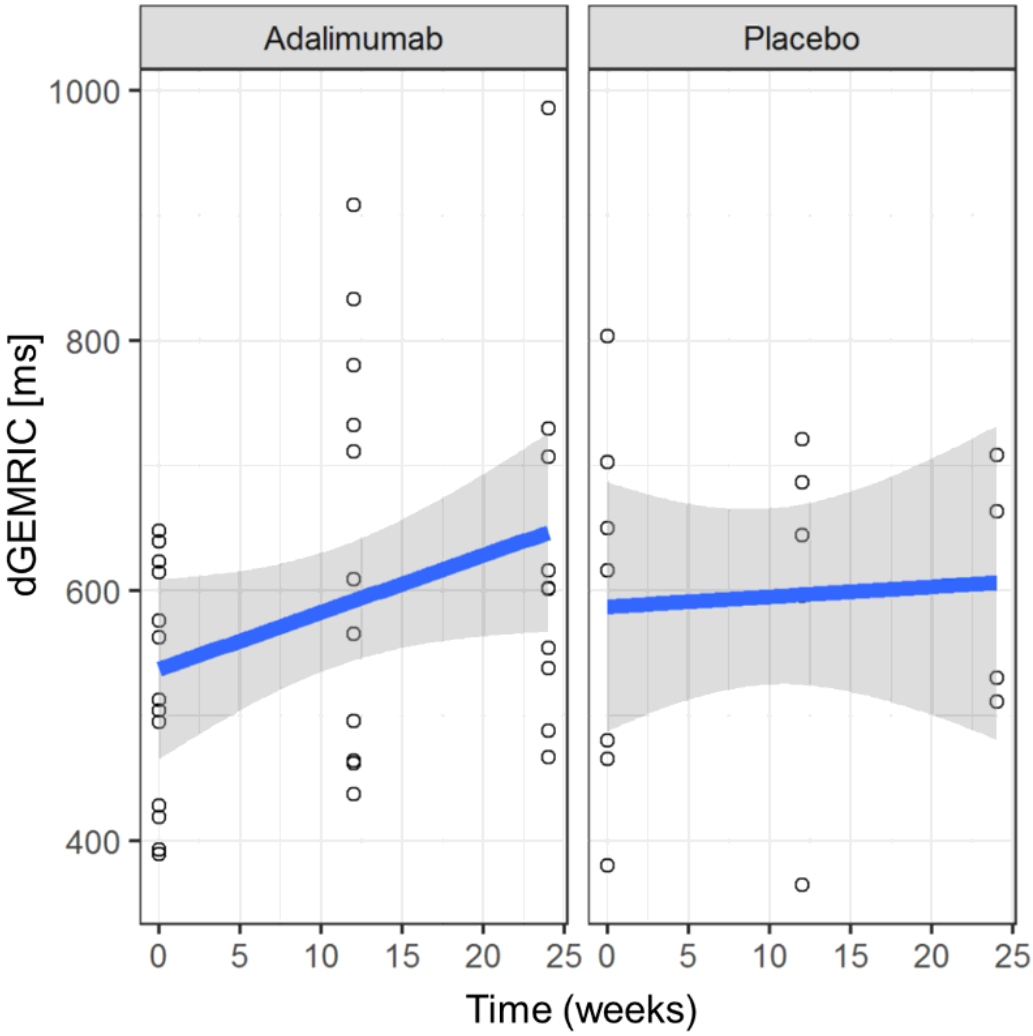

Figure 3

Change in cartilage quality over time. Change in dGEMRIC values in ms for both treatment groups over time with consideration of intermediate results (baseline, 12-weeks- and 24-weeks follow-up). There is strong statistical evidence of an increase in dGEMRIC values over time ($p = 0.0117$), whereas the placebo group shows only a slight increase without statistical evidence ($p = 0.878$).