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## Comparison of in-office magnetic resonance imaging versus conventional radiography in detecting changes in erosions after one year of infliximab therapy in patients with rheumatoid arthritis

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**Abstract** The objective of this study was to compare standard hand radiographs with in-office 0.2T magnetic resonance imaging (MRI) in monitoring response to therapy in patients with rheumatoid arthritis (RA) who were receiving infliximab, to evaluate the frequency and location of erosions, and to determine if there were differences in outcome based on disease duration at baseline. Patients who satisfied the American College of Rheumatology criteria for RA and were receiving infliximab therapy were evaluated with a baseline and 1-year follow-up MRI. Magnetic resonance images were interpreted by two blinded, board-certified radiologists. Bone erosions were identified as well-defined defects extending through the cortical margin. The mean age of the 48 patients was 58.5 years. The median infliximab dosage was 4 mg/kg. Baseline data showed that 41 patients had abnormal MRIs. The mean time between the baseline and follow-up MRI examinations was 10.5 months. Follow-up MRI revealed regression in 11 patients. Thirty-one patients had both MRIs and radiographs. Magnetic resonance imaging was approximately twice as sensitive as radiography in detecting erosions at baseline. In-office MRI was useful in monitoring disease response after the initiation of infliximab treatment. Magnetic resonance imaging is potentially a very valuable diagnostic tool and prognostic indicator for use in patients with RA.

**Key words** Erosion · Infliximab · Magnetic resonance imaging · Radiography · Rheumatoid arthritis

### Introduction

Rheumatoid arthritis (RA) is a chronic disease leading to progressive joint damage and functional decline. Seventy-five percent of joint damage occurs within the first 5 years of onset of disease and continues throughout the course of the disease.<sup>1</sup> Consequently, diagnosis and treatment of early RA is crucial in slowing disease progression and preventing the disability associated with it.

The newest class of disease modifying antirheumatic drugs (DMARDs) target tumor necrosis factor alpha (TNF $\alpha$ ).<sup>2</sup> Infliximab, an anti-TNF $\alpha$  monoclonal antibody, has proven to be highly effective in the treatment of RA patients.<sup>3,4</sup> The United States Food and Drug Administration approved dosage of infliximab is 3 mg/kg at 0, 2, 6 weeks and then every 8 weeks thereafter. Infliximab should be given in combination with methotrexate. Monotherapy with infliximab is not indicated for the treatment of RA. There are currently no company-sponsored infliximab monotherapy trials for RA; however, monotherapy for other indications is being evaluated. For patients who had an incomplete response, the infliximab dosing may be adjusted up to 10 mg/kg or treating as often as every 4 weeks. Treatment with infliximab plus methotrexate has provided clinical benefit while inhibiting the progression of radiographic damage and preserving joint integrity in patients with active RA.<sup>5,6</sup> Nevertheless, it can sometimes be very difficult to determine the absolute benefit of this expensive form of therapy for individual patients.

Routine hand radiographs of patients with RA have been used to assess disease at baseline and to monitor disease progression after the initiation of therapy.<sup>7–9</sup> Studies have shown that magnetic resonance imaging (MRI) may be more sensitive than standard radiographs in detecting bone erosions and the change in bone erosions in response to therapy in early RA.<sup>10–13</sup> Thus, MRI can be beneficial in helping to determine the absolute benefit of therapy for individual patients.

The present study was undertaken in order to compare the value of standard hand radiographs versus in-office

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MRI evaluations in monitoring the response to therapy in patients with RA who were receiving infliximab. A second objective was to evaluate the frequency and location of erosions. A third objective was to use an in-office MRI system to evaluate changes in baseline and follow-up erosive status in patients with RA who were treated with infliximab to determine if there were differences in outcome based on disease duration at baseline.

## Materials and methods

### Study design and patients

In this retrospective chart review of a single rheumatology practice in the United States, patients who satisfied the American College of Rheumatology criteria for the diagnosis of RA<sup>14</sup> were evaluated at baseline and after approximately 1 year of therapy with infliximab. All patients had two MRI studies and some patients received both MRI and radiographic evaluations of disease progression. Baseline for each patient was defined as the time of the first MRI.

After the initial titration, all patients received infusions of infliximab every 7 weeks for the duration of the study. Patients were also treated with methotrexate, nonsteroidal anti-inflammatory drugs, and steroids as necessary. The in-office MRI system in this study (MagneVu 1000, Carlsbad, CA, USA, self-shield low-field [0.2 Tesla scanner]) operates on standard 110-V power and occupies minimal office space.

### Assessments

Magnetic resonance and X-ray images were interpreted independently by two board-certified radiologists experienced in musculoskeletal imaging (S.N., D.R.) who were blinded to patients' clinical status, but not to the chronology of the examinations. Both radiologists read each image, and disagreements were resolved by consensus. Coronal 3D T1W (TR/TE = 100/24ms) and 3D STIR (TR/TE/TI = 100/24/50ms) sequences were acquired with the following imaging parameters: 1-cm-thick slab of 10 images at 1 mm thickness and no gap; field of view 4.9 × 7.5 cm; matrix 128 × 85; 2 acquisitions; echo train length = 4; series acquisition time = 8 min. Due to the small fixed field of view, examinations were targeted to visualize the second and third metacarpophalangeal (MCP) joints and to include as many of the carpal bones as possible. Between 85% and 100% of the target anatomy could routinely be imaged using these parameters. In one patient, the second and third metatarsophalangeal (MTP) joints were assessed.

Radiographs of the hand and wrist were performed in anterior/posterior, oblique, and lateral projections. All carpal bones and MCP joints were included.

Bone erosions were identified as well-defined marginal defects with cortical extension. The MRI signal characteristics for erosions were low signal intensity with respect to marrow fat on T1-weighted images and high signal intensity

on short tau inversion (STIR) images. Erosions were classified as small (<15% metacarpal head involvement), moderate (between 15% and 50% metacarpal head involvement), or large (≥50% metacarpal head involvement). "Regression" was defined as a significant (greater than 20%) change in size of erosion in at least one plane or a conspicuous change in T1 signal, and "stability" was defined as no significant (less than 20%) change in size of erosion or of its signal characteristics. The functional status of the patient at the 1-year follow-up assessment was rated independently by the physician and patient as improved, no change, or worse.

## Results

### Demographics

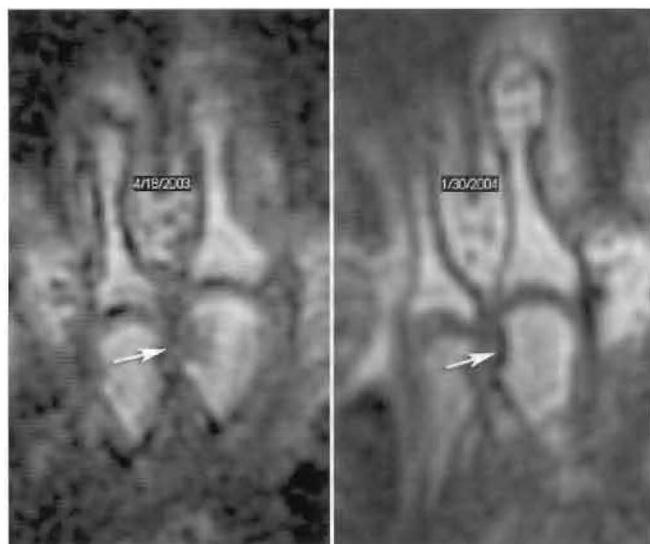
The charts of 48 patients, who were treated with i.v. infliximab during 2003 or 2004, were retrospectively reviewed. The mean (±SD) age of the patients was 58.5 ± 17.1 years (range, 16–86 years), and 18 patients were older than 65 years of age. The duration of RA was <1 year in 13 patients, <2 years in 7 patients, 3–5 years in 9 patients, and >5 years in 19 patients. Thirty-one of the 48 patients received both MRI and radiography and were included in evaluating the first objective, MRI versus standard radiography in monitoring the response to therapy with infliximab.

The median infliximab dosage was 4 mg/kg (range, 3–6 mg/kg). At the time of the first MRI, 43 patients were receiving combination therapy with infliximab and methotrexate (median dosage, 15 mg; range, 10–20 mg) and 40 patients were also receiving prednisone (median dosage, 10 mg; range, 1–20 mg). At the time of the second MRI, these numbers had decreased to 24 patients for both methotrexate and prednisone. At the time of the first MRI, 5 patients were receiving monotherapy with infliximab and this number increased to 13 patients at the time of the second MRI.

### Magnetic resonance imaging results

A total of 83 baseline examinations were performed on the 48 patients. One patient had MRI imaging of bilateral second and third MTP joints. Thirty-four out of the remaining 47 patients had bilateral evaluations of the carpal bones and second and third MCP joints. Thirteen patients had a unilateral MRI exam at baseline.

Baseline MRI showed the following results: (1) of the 83 studies, 64 were abnormal in 41 patients; (2) 7 patients had no MRI abnormalities; (3) 45 examinations out of the 83 were positive for MCP erosions in 34 patients; (4) 36 out of 83 studies were positive for carpal bone erosions in 24 patients; and (5) 1 patient showed erosion in an MTP joint. The mean time between the baseline and follow-up MRI examinations was 10.5 ± 4.1 months (median, 11 months; range, 5–19 months). Follow-up MRI showed regression of 9 MCP joint erosions, 8 carpal bone erosions, and 1 MTP



**Fig. 1.** Magnetic resonance images showing regression of the erosion in the second metatarsophalangeal joint (arrows)

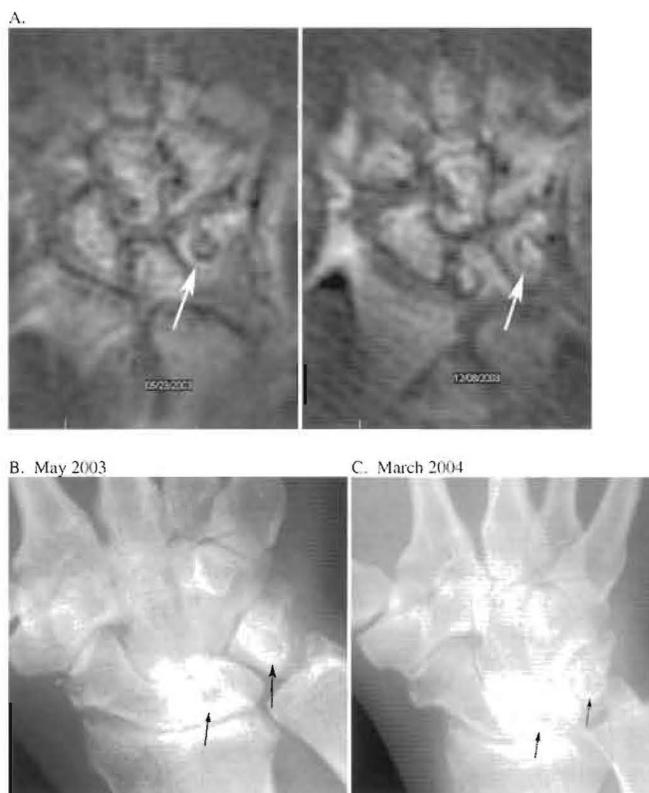
joint erosion for a total of 18 joint regressions in 11 patients. Thus, MRI evidence of erosion regression was detected with similar frequency in MCP joints and in the carpus. Magnetic resonance imaging evidence of regression of an erosion in the second MTP joint is shown in Fig. 1. Thirty-four patients showed no deterioration or progression of disease. Finally, 4 examinations (3 MCP, 1 carpal) showed progression in size or number in 3 patients.

Of the 35 bilateral examinations, 13 patients had bilateral erosions and 6 patients had unilateral erosions. Also, 25 patients with MCP joint erosions did not have carpal bone erosions, compared with only 16 patients with carpal bone erosions who also had no MCP joint erosions. If only MCP joints had been evaluated, 13 patients had unilateral erosions. If only wrists had been evaluated, 12 patients had unilateral erosions.

Treatment was associated with stability of erosive disease in 70.8% of the patients and with a reversal of the original documented erosive findings in 22.9%. Progression of RA occurred in only 6.3% of the patients. Patients from both populations of disease duration ( $\leq 5$  years [ $n = 29$ ] and  $> 5$  years [ $n = 19$ ]) showed MRI responsiveness to therapy with regression of erosions (19% for both groups) or disease stability (77% for  $\leq 5$  years and 74% for  $> 5$  years).

#### X-ray results

Thirty-one patients received both MRI and radiography evaluations. Disease duration was  $\leq 5$  years in 18 patients and  $> 5$  years in 13 patients. Twenty-two patients had bilateral studies and 9 had unilateral hand images, resulting in a total of 53 examinations at baseline. Baseline erosion status of the 31 patients who received both MRI and radiography is shown in Table 1. Table 2 illustrates the erosion status of those 31 patients after approximately 1 year of follow-up. Using MRI as the comparator and the data in



**Fig. 2.** Comparison of magnetic resonance (MR) images (A) and radiographs (B,C) from the same patient. The MR images show the erosion has "filled in" with fat-intensity (increased T1-weighted) signal suggesting regression (white arrows), while the radiographs show stable lunate and triquetral erosions (black arrows)

**Table 1.** Baseline erosion status in patients who received both X-ray and magnetic resonance imaging (MRI) examinations ( $n = 31$  patients; 53 exams)

Joints evaluated	X-ray: no. of exams (no. of patients)		MRI: no. of exams (no. of patients)	
	Positive	Negative	Positive	Negative
MCP	19 (12)	34 (19)	30 (23)	23 (8)
Carpus	16 (11)	37 (20)	26 (19)	27 (12)

MCP, metacarpophalangeal

**Table 2.** Erosion status at 1-year follow-up in patients who received both X-ray and MRI examinations ( $n = 31$  patients, 53 exams)

Erosion status	X-ray: no. of exams (no. of patients)	MRI: no. of exams (no. of patients)
No change	52 (30)	40 (22)
Progression	0	1 (1)
Regression	1 (1)	12 (8)

Table 1, the sensitivity of radiography in detecting erosions was 63% in the MCP joints and 61.5% in the carpus. Figure 2 shows MR images and radiographs from the same patient. The MR images show regression of erosions while the radiographs show stable erosions. McNemar's test comparing in-office MRI versus plain radiograph in detecting bone

erosions suggested that the observed difference in results was statistically significant ( $P = 0.0037$ ).

Another comparison of radiography and MRI results looked at the data for all of the joints imaged after treatment with infliximab. Five erosions seen with X-ray were in areas not imaged with MRI, 3 erosions were visible on X-ray retrospectively after viewing the MRI image, and 2 erosions were visible on MRI retrospectively after seeing the X-rays. One X-ray showed regression of an erosion that was also observed with MRI.

Using the data for all of the individual joints in the 31 patients, the sensitivities for X-ray relative to MRI for MCP joints and carpal bones are approximately 53%–56% (Table 3). When patients were divided into those recently diagnosed ( $\leq 5$  years;  $n = 18$ ) and patients with long-standing disease ( $> 5$  years;  $n = 13$ ), there were no statistically significant differences in the frequency or accuracy of detection of erosions between the two groups.

#### Functional status

Forty-three of the patients (89.6%) had improved functional status as assessed by both the physician and patient (Table 4). The only disagreement between the physician and patient assessment was that the three patients who were described as showing deterioration by the physician rated themselves as having no change.

## Discussion

We found that in-office MRI was approximately twice as sensitive as radiography in detecting erosions at baseline. In this patient series, the distribution of erosions was similar in MCP joints and carpal bones. Magnetic resonance imaging evidence of erosion regression was detected with similar frequency in the MCP joints and in the carpus.

**Table 3.** Statistical comparison of X-ray imaging of all of the joints in patients ( $n = 31$ ) relative to the MRI results in the same patients

Statistic (%)	MCP joints (108 joints)	Wrists (46 wrists)
Sensitivity	55.8	52.9
Specificity	95.4	93.1
Positive predictive value	88.9	81.8
Negative predictive value	76.5	77.1

Finally, our results suggest that erosion regression occurred with treatment, regardless of disease duration.

With value defined as the ability to determine both therapeutic choices as well as adjustments during the course of RA, our study shows the utility of an in-office MRI system to monitor patients' responses to treatment. The low field strength 0.2T MRI system we used has several advantages over conventional MRI systems. Conventional whole-body MRI units are relatively expensive, inconvenient, and may be an unpleasant experience for some patients.<sup>15</sup> In fact, 5% of patients are unable to complete the MRI exam because of claustrophobia.<sup>15</sup> In contrast, low-field strength MRI machines are significantly less expensive, allow patients to insert only their limb into the magnet, thus eliminating claustrophobia, and provide greater patient comfort. Low-field strength portable MRI also provides the possibility of office-based imaging because it has no special air-conditioning requirements, is relatively light, mounted on wheels, and has no need for external radio frequency or magnetic field shielding.<sup>10</sup>

Our results agree with other studies that show that MRI is more sensitive than radiography in detecting disease, including studies using low-field strength systems like ours.<sup>10–13</sup> In a study conducted in 132 patients with RA, low-field strength MR (0.2T) imaging of wrist and MCP joints detected bone erosions in 125 (95%) patients versus 78 (59%) for radiography ( $P < 0.05$ ).<sup>10</sup> Thus, low-field strength MRI, like conventional MRI, is more sensitive than radiography in detecting bone erosions.

Another argument in favor of the superiority of MRI over radiography is that the most commonly recognized mechanism for bone erosions in RA assumes that the initial event is inflammation extending from the synovium into the bone at the synovial–cortical interface.<sup>16–18</sup> Thus, in the earliest phases of the erosion process, soft tissue changes of inflammation should be present before focal loss of bone calcium. Thus, theoretically, MRI should detect changes of cellular infiltrate or marrow edema before X-ray techniques can detect calcium loss, an assumption consistent with the literature.<sup>10–13</sup>

In addition to being superior to radiography in sensitivity, low field MRI provides comparable sensitivity in detecting bone erosions to that of conventional high field MRI. In a study by Ejlberg et al., MRI of the wrist and of the second through fifth MCP joints was performed on a low-field MRI (0.2T) unit and a high-field MRI (1.0T) unit in 37 patients with RA and 28 healthy controls.<sup>19</sup> With high-field MRI as the standard reference, the sensitivity, specificity, and accuracy of low-field MRI for bone erosions were

**Table 4.** Comparison of physician and patient assessments of functional status and MRI assessments after 1 year of treatment with infliximab ( $n = 48$ )

Category	Functional status as assessed by		MRI, $n$ (%)
	Physician, $n$ (%)	Patient, $n$ (%)	
Improvement	43 (89.6)	43 (89.6)	11 (22.9)
No change	2 (4.2)	5 (10.4)	34 (70.8)
Deterioration	3 (6.3)	0 (0)	3 (6.3)

94%, 93%, and 94%, respectively ( $P < 0.005$ ).<sup>19</sup> This study demonstrates that low-field dedicated extremity MRI provides similar results in detecting bone erosions as conventional MRI.

Even though our retrospective study was not designed to measure the effectiveness of treatment with infliximab, we did notice functional improvement and stability of erosive disease. These results are consistent with other studies that showed that treatment with infliximab can slow the progression of disease in patients with RA,<sup>5,6,20,21</sup> however, these studies used radiographs to assess disease progression. Two studies have been published recently about the benefit of using MRI to assess the effect of treatment with infliximab in patients with RA. In a report by Quinn et al.,<sup>22</sup> 20 patients with RA were studied in a 12-month randomized, double-blind, placebo-controlled trial of combination therapy with infliximab plus methotrexate. Because MRIs are more sensitive than radiographs, fewer patients were required for the study than if X-rays were used to assess disease progression. Combination therapy produced a significant reduction in MRI evidence of synovitis and erosions. In a study conducted in 16 patients with refractory RA, MRI was used to quantify the degree of hand synovitis.<sup>23</sup> Clinical, laboratory, and MR imaging results provided evidence of improvement after 1 year of treatment with infliximab plus methotrexate.

The increased sensitivity of in-office MRI versus radiography in detecting erosions at baseline has implications with regards to the choice of therapy offered to RA patients. Because erosions can be detected earlier, patients may be offered more aggressive therapy earlier in the course of their disease. In contrast to standard radiographs, we found that MRI was also useful in monitoring disease response within 12 months after the initiation of infliximab, in both early and long-standing RA. The appearance of joint regression with infliximab provides objective evidence for a beneficial effect of this expensive pharmacotherapy. At the same time, we found that the value of X-rays was very limited over a 12-month period. The shrinking of erosions observed with MRI is direct evidence that the erosive process has stopped, and this is more sensitive than relying on the failure of new erosions to develop on radiographs. Being able to detect small structural changes (i.e., either progression or regression of erosions) could be valuable in patient management by signaling the need for adjustment of dosage regimen, the discontinuation of ineffective therapies, or by providing justification for remaining on an expensive therapy.<sup>24</sup> Another implication is that, even though the distribution of erosions was similar in MCP joints and carpal bones, for a higher yield, it would appear to be more beneficial to measure simultaneously for erosions in both the carpal bones and two MCP joints.

Using MRI to track the progression of RA in patients is associated with several problems. Firstly, there may be a lack of specificity with the erosions observed by MRI. When MR imaging of wrist and MCP joints was performed on 28 healthy volunteers, bone erosion-like changes were found in 2.2% of MCP joints and 1.7% of wrist joint bones.<sup>25</sup> Although some of these erosions may reflect subclinical

arthritis, the significance of bone erosion-like changes in healthy volunteers is not known. Secondly, the validity of MRI for indicating bone lesions has not been completely established because radiography directly detects bone calcium loss and bone does not give a signal on MRI. Instead, the erosions observed in MR images are due to differences in soft tissue characteristics. However, data from ultrasonography-guided biopsies<sup>26</sup> and miniarthroscopy<sup>27</sup> suggest that MRI erosions do represent actual bone damage. Thirdly, not all erosions detected by MRI are followed by the development of radiographic erosions. For example, in one study conducted in 42 patients with RA, only 25% of erosions seen on MRI at baseline had progressed to radiographic erosions by the 1-year follow-up.<sup>28</sup> In spite of these conceptual difficulties, erosion regression observed by MRI is an indication that the erosive process has stopped.<sup>15</sup>

Based on clinical experience from this study and previous anecdotal evidence, we observed that erosions heal in a manner similar to other bone pathology. For example, following removal of orthopedic hardware, the typical MRI changes observed include the medullary cavity "filling in" with fat-intensity signal. Similar signal changes are observed with healing bone erosions. Thus, despite the lack of histological evidence from the literature, we believe that these changes represent a "lipoma-like" process rather than restoration of healthy bone. Nevertheless, we have assumed that the principle of T1 shortening associated with "healing bone" is also associated with what we believe are regressing erosions. Furthermore, we evaluated the size of erosion based upon its depth from the cortex in two planes (using percentage). We did not attempt to evaluate the true volume of erosion. In all cases, the erosions identified were imaged in their entirety, and therefore there was no difficulty assigning the depth of the erosion. An advantage of the in-office MRI system is the ability to obtain a 3D slab with 1-mm-thick T1W images and no gap. We believe the relative size of erosion can be accurately assessed by carefully comparing each image with the prior study. To minimize the effect of slight differences in positioning, we only reported changes in erosions that were at least 20% in size.

In assessing the significance of our results, the limitations of our study must be kept in mind. This was a retrospective, open-label study, and the MRI and functional status assessments were qualitative. The lack of a standardized follow-up time is not important because this retrospective study looked at patient who had more than two MRI studies and were being treated with infliximab in a clinic setting. However, the goal of our study was to follow the treatment of patients with RA using techniques that are common practice in clinics. Further work is needed to confirm these results using quantitative assessments of functional status and MRI evaluations.

There are some limitations in our study with respect to the in-office MRI system. Because the MagneVu does not always image an entire bone, it is possible (if not likely) that we did not image erosions that would have been detected on an MRI using a larger field of view and slab depth. We anticipate other MRI units, such as the Esaote C-Scan,

would provide an even greater sensitivity than we found in this study.<sup>29</sup> The MagneVu system is limited in its field of view, which in a typical exam of the hand allows visualization of two MCP joints. A typical exam of the wrist will visualize most of the carpal bones.

This study provides evidence in a group of 48 patients that MRI is potentially a valuable diagnostic tool and prognostic indicator for patients with RA. In-office MRI demonstrates subtle changes in erosion morphology in RA patients at the time of diagnosis and in response to therapy. Although the distribution of erosions was similar in MCP joints and carpal bones, a higher yield is obtained by screening for erosions in both the carpus and two MCP joints. Regardless of disease duration, some patients exhibited erosion regression or stability with treatment.

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