ORIGINAL RESEARCH

# METHOFRACT, a methotrexate osteopathy multicentre cohort study

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## ABSTRACT

Methotrexate-induced osteopathy (MTX-IO) is a rare condition typically involving the lower limbs, especially tibia or foot fractures, among patients with well-controlled rheumatoid arthritis (RA) or psoriatic arthritis (PsA). This study aimed to identify the affected population, describe fracture characteristics and identify risk factors for poor clinical outcome. A multicentre retrospective study included patients with MTX-IO diagnosed by bone specialists or identified through French pharmacovigilance. The data collected included clinical presentation, imaging features, bone mineral density and biochemical markers. Between 2012 and 2024, 92 patients were included, predominantly postmenopausal women with seropositive RA. A history of major fractures was noted for 22% of the patients, and 56% presented osteoporosis at diagnosis. Fractures were most common in the tibial metaphysis (distal and proximal) (88%) and the foot bones (49%), with multiple fractures often present at diagnosis (76%), and frequently repeated fractures in the patients' recent histories (63%). Diagnosis was conducted using MRI of the painful sites (84%), but bone scintigraphy was also used (41 patients, 45%). Management involved methotrexate discontinuation in 79% of the cases. Fracture healing and pain relief were achieved in 77% of the cases, with a significant difference in outcomes between those who discontinued methotrexate (91%) versus those who continued (29%) (p<0.001). MTX-IO is a rare but significant condition, especially among postmenopausal women with RA or PsA. Early diagnoses via MRI or bone scintigraphy and the discontinuation of methotrexate are critical, as stopping the drug significantly improves outcomes and prevents further fractures.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ This is a little-known and little-studied subject, raised several years ago, with growing interest over recent years.
⇒ The need to discontinue methotrexate once the diagnosis has been made is fairly well known, although the data are scarce and often poorly known.

## INTRODUCTION

Methotrexate (MTX) is a widely used treatment for both localised and systemic conditions. It is the primary treatment for inflammatory rheumatic diseases (IRDs) involving the peripheral joints, such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA).[1 2] In addition to its role in managing inflammation, MTX is also useful in reducing the dose of corticosteroids used in IRDs. The doses used for these conditions are much lower (between 10 mg and 25 mg per week) than those used for cancers and leukaemia (1 g per dose). The mechanisms by which low doses of MTX exert an immune-modulatory and anti-inflammatory effect in IRD remain largely unknown.[3] Classic side effects, such as haematological or hepatic damage, are well known and are most often identified and partially remedied by the prescription of folic acid.[4]

Another side effect, MTX-related osteopathy, remains largely unknown to physicians. It was initially observed among patients receiving high doses of MTX for haematological treatment, particularly children with acute leukaemia.[5] This condition was characterised by a triad of osteoporosis, stress fractures and bone pain. The first case of osteopathy under MTX for PsA was only described a few years later.[6] In subsequent years, the role of MTX in bone damage was discussed, primarily because patients affected by it presented many other well-known risk factors for bone fragility, such

## WHAT THIS STUDY ADDS

⇒ This study evaluates real-world therapeutic alternatives after methotrexate discontinuation as a result of osteopathy.
⇒ It compares outcomes between patients who continued versus patients who discontinued methotrexate, reinforcing the clinical recommendation for withdrawal.
⇒ Data wasere collected using a European multicentre design, minimizingminimising bias from centre-specific diagnostic practices.
⇒ The study outlines a standardizedstandardised diagnostic approach, emphasizingemphasising the role of early imaging.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Methotrexate-induced osteopathy is a rare but serious complication among patients with chronic inflammatory diseases. This study emphasises the need for better recognition among clinicians prescribing methotrexate in the long term.
⇒ It demonstrates the limited sensitivity of standard X-ray and the diagnostic value of MRI or bone scintigraphy to confirm methotrexate-induced lesions.
⇒ This is the first study to detail therapeutic strategies following methotrexate withdrawal, offering practical guidance for on-going disease management.
⇒ Early discontinuation of methotrexate is crucial to prevent delayed healing, persistent pain and further fractures.

as corticosteroid use, postmenopausal status, chronic inflammation and osteoporosis.[7] Although the evidence at the time suggested that MTX did not exert a direct or measurable effect on bone mineral density (BMD),[8–10] the increasing number of reports of similar isolated cases in recent years has supported the existence of a specific entity. It is only recently that reviews of the literature have begun to compile the various cases, drawing attention to this issue.[7 11]

Therefore, MTX-induced osteopathy seems to preferentially affect women with RA and PsA.[7 12] The underlying IRD at the time of diagnosis is often well controlled, and the pain described at diagnosis by patients is typically of a mechanical nature.[7] In the vast majority of cases, fractures affect the tibia and the lower limbs, often with a history of stress fractures in previous months or years, which were additive and potentially multiple. The fractures are metaphyseal, transverse and non-displaced and are often difficult to detect on X-ray.[7 11 12]

Treatment of MTX-induced osteopathy is not well established. Among all the therapeutic strategies considered, discontinuation of MTX has emerged as the only intervention that has consistently demonstrated a clear benefit in the healing process of fractures. In most cases, discontinuing MTX not only helps prevent further recurrences, but also significantly accelerates bone healing, making it the single most effective measure identified to date for promoting recovery.[7 12 13] Bisphosphonates have also been frequently used, with variable effects if MTX is not discontinued. Some groups have recommended the use of combined therapy comprising denosumab and teriparatide.[12]

The aim of this study was to compile case studies from the French Research and Information Group on Osteoporosis (GRIO), the leading authority on osteoporosis and bone disease management, in order to provide a more accurate description of a broad patient population affected by the disease, including information on treatment methods and clinical and radiological evolutions.

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## MATERIALS AND METHODS

### Study population

We conducted a multicentre retrospective study including all patients identified by a GRIO member presenting MTX-related osteopathy. All patients with suggestive clinical and/or imaging presentations and with current MTX treatment at the time of diagnosis were included.

As already described in the literature,[11 14] MTX-related osteopathy is diagnosed by the association between the occurrence of lower limb pain and the demonstration of concordant imaging features (on X-ray, MRI or bone scintigraphy)—mainly the occurrence of—atraumatic stress metaphyseal fractures or fractures of the bones of the foot among patients with active MTX treatment at diagnosis.

Patients not already included in this first step and identified by the French national pharmacovigilance database as having a condition suggestive of MTX-induced osteopathy were also included, after analysis of the medical file by the principal investigator (FR).

### Data collection

Baseline clinical information was collected, including demographic data (age at diagnosis, gender, body mass index (BMI) in kg/m², smoking and alcohol consumption, medical history and IRD activity at the time of diagnosis), as well as therapeutic data (weekly and cumulative MTX dose and route of administration, duration of MTX use, corticosteroid use at diagnosis and dose). The location of fractures at diagnosis and the location of previous fractures, if any, imaging conducted for diagnosis (X-ray, bone scintigraphy, PET-Scan, MRI) and BMD by dual energy X-ray absorptiometry (DXA) were also collected. BMD evaluations by DXA during follow-up were also collected if available. Results were expressed as T-scores (expressed as SDs). Biological data were collected, including standard markers used in bone diseases (calcium, phosphorus, magnesium, creatinine, C reactive protein (CRP), thyroid-stimulating hormone, 25 OH vitamin D and parathyroid hormone (PTH), liver function tests (alanine aminotransferase, aspartate amino-transferase, gamma-GT, alkaline phosphatase), blood cell count, electrophoresis of plasma protein, ferritin, albumin, carboxy-terminal collagen crosslinks. Therapeutic changes linked to MTX-induced osteopathy, including MTX interruption and/or the prescription of antiresorptive or anabolic agents, were also collected.

Regarding the terms of IRD treatment following the diagnosis of MTX-induced osteopathy, information was collected on treatments (conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs)) used or maintained in case of MTX discontinuation.

Concerning the evolution of fractures, the evolution shown on imaging was assessed if available. A favourable evolution of symptoms was defined as fracture healing on imaging, if available, with a decrease in bone oedema or clinical pain resolution.

### Statistical analysis

All analyses were performed using the SPSS V.16.0 software. Descriptive analysis was expressed as mean±SD. The $\chi^2$ test was used to assess associations between categorical variables. Correlation analyses were performed using Spearman's test. A p value<0.05 was considered significant.

## RESULTS

### General characteristics

Between 2012 and 2024, 76 patients were identified as affected by MTX-induced osteopathy. Diagnoses were established by a bone specialist in each centre. 31 other patients were identified from the French pharmacovigilance database, and their medical files were reassessed (to avoid duplications or other diagnoses) by the principal investigator (FR), enabling the inclusion of a further 16 patients, for a total of 92 patients.

Patient characteristics are summarised in table 1. The patients were mainly female (86/92, 93%), with post-menopausal status (86/86, 100%). 27 patients (29%) had a history of osteoporotic fractures, including 20 major osteoporotic fractures (vertebral fracture, proximal or distal femoral fracture, proximal humeral fracture, pelvis fracture) (22%). The underlying IRD was RA (70/92, 76%) and mainly seropositive (68/92, 74%). Other diagnoses included psoriasis and PsA (6/92), inflammatory undifferentiated rheumatism (5/92), spondyloarthritis with peripheral involvement (5/92), calcium pyrophosphate deposition disease (1/92), multiple sclerosis (1/92), systemic sclerosis (1/92), dermatomyositis (1/92), eosinophilic fasciitis (1/92) and rheumatic immune-related adverse events (1/92). At diagnosis, IRD was often in remission (76/92, 83%) or with low disease activity (10/92, 11%) despite absence (58/92, 63%) or low doses (≤ 5 mg/day) (18/92, 20%) of prednisone.

Data on DMARDs were available for 84 patients. At diagnosis, for IRD treatment, 28 patients received another treatment associated with MTX: csDMARDs (hydroxychloroquine, n=1), bDMARDs (n=25 (abatacept (n=6), adalimumab (n=7), etanercept (n=5), rituximab (n=2), golimumab (n=1), sarilumab (n=1), tocilizumab (n=2), certolizumab pegol (n=1)) or with tsDMARDs (n=3).

**Table 1** General demographic and therapeutic data

| **General characteristics (n=92)** | |
|---|---|
| Women, *n (%)* | 86 (93) |
| Body mass index, *kg/m² mean±SD* | 25.1±4.1 |
| Risk factors of osteoporosis | |
| Menopause, *n (%)* | 86 (100) |
| Medical history of fracture, *n (%)* | 27 (29) |
| Medical history of major fracture, *n (%)* | 20 (22) |
| Medical history of hip fracture in a first-degree relative, *n (%)* | 4 (5) |
| History of smoking, *n (%)* | 28 (34) |
| Alcohol consumption, *n (%)* | 5 (6) |
| Corticosteroids use at diagnosis, *n (%)* | 34 (37) |
| Underlying rheumatic disease | |
| Seropositive rheumatoid arthritis, *n (%)* | 68 (74) |
| Seronegative rheumatoid arthritis, *n (%)* | 2 (2) |
| Psoriatic arthritis, *n (%)* | 5 (7) |
| Other, *n (%)* | 16 (17) |
| Underlying rheumatic treatment at diagnosis (n=84) | |
| Methotrexate alone, *n (%)* | 56 (67) |
| Association with bDMARD, n (%) | 25 (29) |
| Association with tsDMARD, n (%) | 3 (4) |
| MTX treatment | |
| Duration at diagnosis in months, *mean±SD* | 123±74 |
| Dose at diagnosis (mg), *mean±SD* | 18.3±5.1 |
| Oral administration, *n (%)* | 27 (29%) |
| Subcutaneous administration, *n (%)* | 55 (71%) |

bDMARD, biological disease-modifying anti-rheumatic drug; MTX, methotrexate; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

BMD was available at diagnosis for 78 patients: 44 patients (56%) had at least one T-score ≤−2.5 SD. 42 patients had already received treatment for osteoporosis (six patients with teriparatide and 36 patients with antiresorptive treatment, mainly bisphosphonates).

### Biological evaluation at diagnosis

Biological tests were carried out in order to eliminate secondary causes of osteoporosis (online supplemental table). Calcium and phosphate evaluations were available for 82 patients and were in the normal range for 79 and 81 patients, respectively (with abnormalities limited to mild hypocalcaemia or hypophosphataemia); 25 OH vitamin D and PTH were normal for 77% and 89% of patients, respectively (two mild increases of PTH without low associated 25 OH vitamin D levels or hypercalcaemia). In these two patients, a morphological examination was conducted to eliminate primary hyperparathyroidism. CRP was <5 mg/L for 93% of patients (74/80 patients) in accordance with the overall stability of the

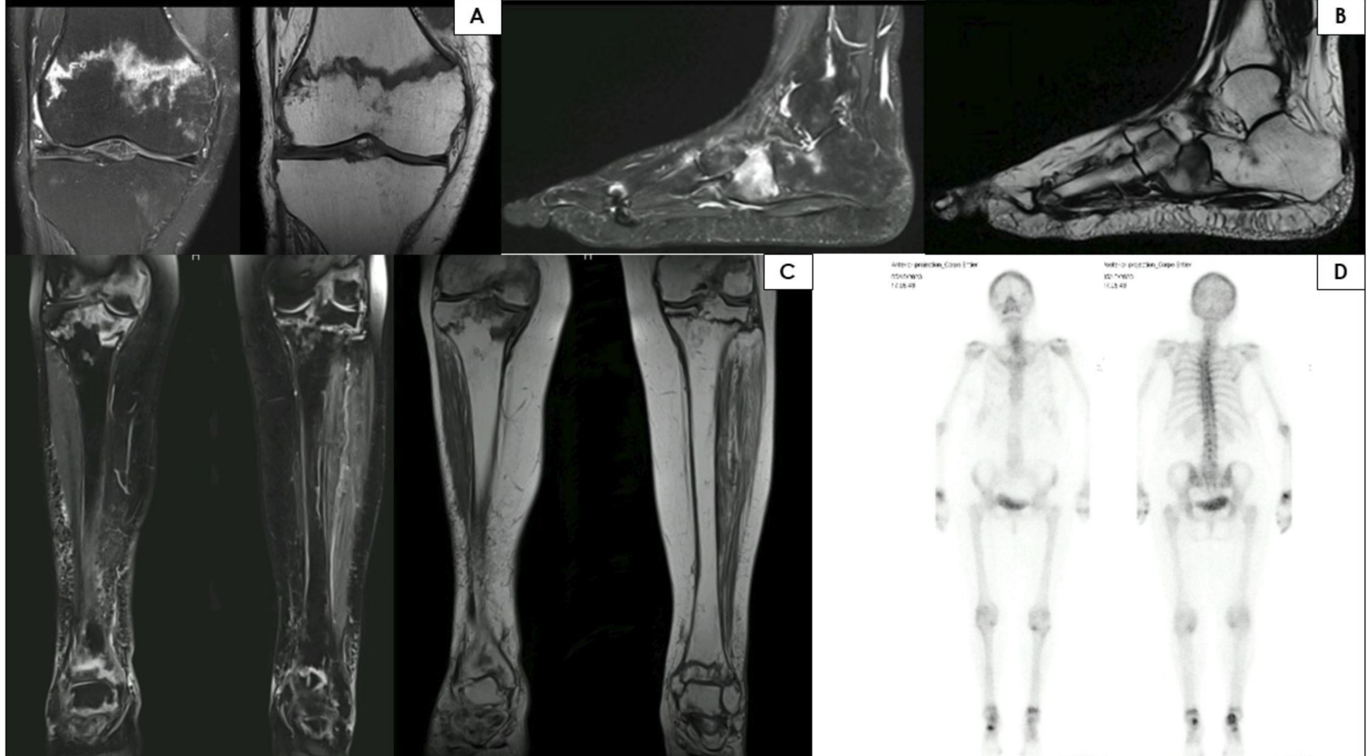


**Figure 1** Standard fracture aspect and location in methotrexate osteopathy. (A) Transversal fracture of the femoral distal metaphysis (T1 on the right and T2 weighted MRI on the left); (B) fracture of the lateral cuneiform (T1 on the right and T2 weighted MRI on the left); (C) association of bilateral transversal fracture of the proximal and distal tibial metaphysis (T1 on the right and T2 weighted MRI on the left), (D) bone scintigraphy aspect with fracture of distal and proximal tibial metaphysis.

underlying IRD. No biological abnormality was identified as the cause of the bone lesions by the investigators.

### MTX administration

The main results are summarised in table 1. MTX was used at standard rheumatological doses for each patient included. The mean dose was 18.3 mg/week (±5.1), with a cumulative dose of 8.5 g (± 5.4) and a mean duration of treatment of 123 months (±74). Oral administration was used for 27/92 (29%), while subcutaneous administration was used for 65/92 patients (71%). If we consider possible MTX doses higher than 0.3 mg/kg/week, 27 patients (34%) had a high MTX dose for inflammatory condition.

### Fracture characteristics

The characteristic presentation and location of the fracture lesions are presented in figure 1. The main locations were the lower limbs, with two main locations: the tibia and the tarsal-metatarsal bones. 81 patients (88%) had tibial involvement; 45 patients had a history of fractures or active fractures on the feet at diagnosis (49%), often with a diagnosis of 'stress fractures'. Another main feature was the existence of multiple fractures, often bilateral. In our cohort, 76% of patients (70/92) had multiple fractures at diagnosis. These fractures reoccurred over time for 63% of the patients (58/92), with frequent delay in diagnosis and a clinical history lasting several years. Even if this information was difficult to obtain retrospectively, delayed fracture consolidation was noted for eight patients.

Initial imaging used for diagnosis was mainly X-ray (84/90, 93%), with the need in all cases for a more precise assessment by MRI (76/90, 84%) or bone scintigraphy (41/90, 46%). Positron emission tomography scan was much less widely used (5/90, 6%). Only five patients underwent solely bone scintigraphy for diagnosis, and in the vast majority of cases, MRI and/or Tomodensitometry (TDM) of the painful location were implemented (n=36). In the case of an ultrasound assessment (n=6), joint effusion was noted in some cases, most often with a mechanical joint fluid count (n=6, with white blood cell count <1000/mm$^3$ for five).

### Treatments used

As reported in the literature, the first therapeutic option in a large proportion of cases is MTX discontinuation (70/91, 77%). If we focus on additional treatment, four patients received teriparatide in monotherapy, and six patients in combination or association (five patients received teriparatide after antiresorptive treatment (bisphosphonates and denosumab), and one patient was given denosumab-teriparatide combined therapy). 40 patients received at least one antiresorptive treatment (bisphosphonates (n=33) or denosumab (n=7)) after diagnosis. As already noted, in our work, 42 patients had

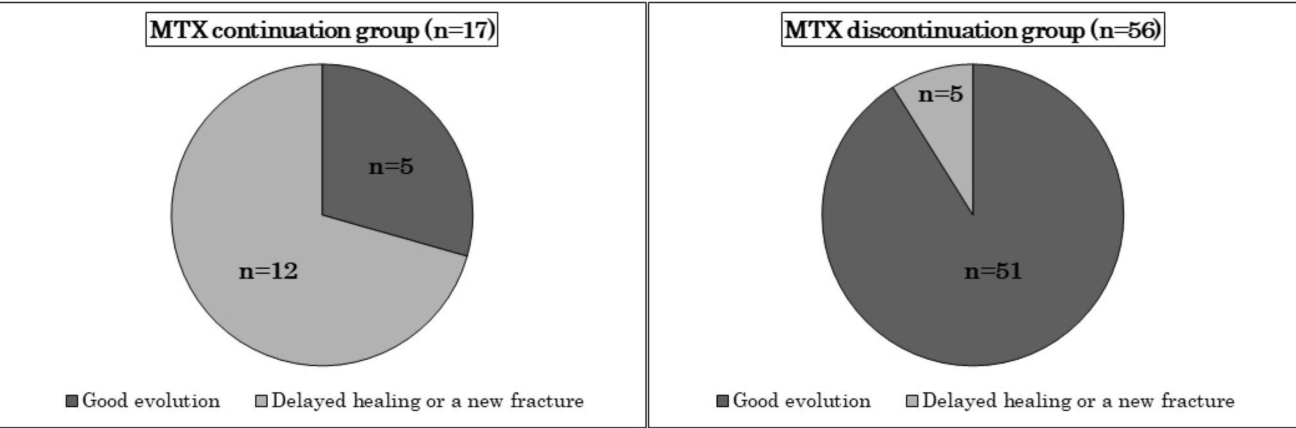


**Figure 2** Comparison of evolution according to MTX management. Poor evolution was defined as persistent pain, recurrent fractures or delayed healing. MTX, methotrexate.

already received anti-osteoporotic treatment before diagnosis.

Concerning IRD treatment (data available for 82 patients), in case of MTX discontinuation (n=61), 29 patients had no MTX replacement (discontinuation of all treatments or bDMARDs and tsDMARDs monotherapy). For others, the predominant choice (20 patients) was to switch to another csDMARD (leflunomide or sulfasalazine), while 11 patients were placed under bDMARDs (n=10) or tsDMARDs (n=1).

### Comparison of clinical evolution according to MTX management

The main results are summarised in figure 2. Clinical evolution was evaluated at 6 months for a total of 73 patients.

For all patients, poor clinical outcomes—defined as persistent pain, recurrent fractures or delayed healing—were reported for 17 patients (21%), while 79% of the patients experienced a favourable course.

Concerning evolution according to MTX management, the patients without MTX discontinuation experienced poor evolution in the vast majority of cases (12/17 patients, 71% (eight patients with recurrent fractures and four patients with delayed healing), compared with five patients (9%, three patients with recurrent fractures and two patients with delayed healing) in the MTX discontinuation group ($p<0.001$). Therefore, patients with MTX discontinuation experienced a favourable evolution, 91% (compared with 29% in the MTX continuation group, $p<0.001$). MTX continuation was inversely correlated with favourable evolution (rho=−0.603, $p<0.001$).

Comparisons between the population maintaining MTX (n=17) and the population discontinuing MTX (n=56) are summarised in table 2. The general characteristics are similar between the groups, especially for age, BMI, medical history of major fractures and densitometric osteoporosis. Concerning MTX use, the only significant difference was the duration of MTX use at diagnosis, which was longer in the MTX continuation group than in the MTX discontinuation group (160 ±88 vs 113 ± 71 ($p<0,05$)). The proportion of patients using corticosteroids was larger, but not significantly different, in the MTX discontinuation group than in the MTX continuation group (25 patients (45%) vs three patients (18%)).

### Comparison of patients' characteristics according to fracture evolution

Comparisons between patients with favourable fracture evolution (n=57) and those with a less favourable or unfavourable evolution (delayed fracture healing/new fractures) (n=16) are summarised in table 3.

The general characteristics were similar between the groups, especially age, BMI, medical history of major fractures and densitometric osteoporosis. Concerning MTX use, MTX duration, dose at diagnosis or cumulative dose, they were not associated with a poor evolution. The use or the dose of corticosteroids at diagnosis was not associated with poor evolution. The only main significant difference between the groups was linked to MTX continuation/discontinuation ($p<0001$).

## DISCUSSION

MTX-induced osteopathy is a rare condition characterised by bone pain and the occurrence of specific spontaneous fractures, which differ from those associated with classic osteoporosis.[7 11] Despite the presence of multiple risk factors for osteoporosis (eg, menopausal status, corticosteroid use, RA), MTX-induced osteopathy appears to have specific characteristics.

To our knowledge, ours is one of the largest multicentre cohorts of MTX-induced osteopathy cases. This study highlights the specific clinical presentation of this condition, which is characterised by stress fractures in the lower limbs, primarily affecting the tibia (88% of cases). Although X-rays are most commonly used for diagnosis (93%), MRI (84%) and bone scintigraphy (46%) are also frequently used. The study pinpoints the importance of discontinuing MTX treatment, as a significant proportion of patients experience a poor outcome if MTX is continued after the identification of MTX-induced

**Table 2** General demographic and therapeutic data

| | MTX continuation group (n=17) | MTX discontinuation group (n=56) | P value |
|---|---|---|---|
| General characteristics | | | |
| Age, *mean±SD* | 64±11 | 68±9 | NS |
| BMI, kg/m$^2$, mean±SD | 26±3 | 25±4 | NS |
| T-score, lumbar site, *mean±SD* | −1.7±1.2 | −1.8±1.1 | NS |
| T-score, total hip, *mean±SD* | −1.9±0.6 | −2.2±0,9 | NS |
| T-score, femoral neck, *mean±SD* | −2.2±0.7 | −2.4±0.9 | NS |
| Densitometric osteoporosis *n (%)* | 10 (59%) | 32 (56%) | NS |
| Medical history of major fracture *n (%)* | 3 (18%) | 12 (21%) | NS |
| History of antiosteoporotic treatment, *n (%)* | 7 (41%) | 25 (45%) | NS |
| MTX treatment | | | |
| Duration at diagnosis in months, *mean±SD* | 160±88 | 113±71 | <0.05 |
| Dose at diagnosis (mg), *mean±SD* | 16.5±6 | 19.3±4 | NS |
| Cumulative dose (g) at diagnosis, *mean±SD* | 9.7±6.2 | 8.2±5.6 | NS |
| Oral administration, *n (%)* | 7 (41%) | 12 (21%) | NS |
| Subcutaneous administration, *n (%)* | 10 (59%) | 44 (79%) | NS |
| Corticosteroid treatment | | | |
| Corticosteroid use, *n (%)* | 3 (18%) | 25 (45%) | NS |
| Corticosteroid dose (mg), *mean±SD* | 1.5±4.0 | 3±4.5 | NS |
| MTX-Induced osteopathy management | | | |
| Antiosteoporotic treatment, *n (%)* | 11 (65%) | 29 (52%) | NS |
| Antiresorptive treatment alone, *n (%)* | 8 (47 %) | 24 (43%) | NS |
| Teriparatide alone, *n (%)* | 0 (0%) | 4 (7%) | NS |
| Sequential or concomitant combo therapy, *n (%)* | 3 (18%) | 1 (2%) | <0.05 |

BMI, body mass index; MTX, methotrexate.

osteopathy (71%). In our study, the MTX dose at diagnosis, the cumulative dose and the duration of MTX treatment were not associated with poor outcome.

Understanding the pathophysiology of MTX-induced osteopathy remains challenging. In vitro and in vivo data suggest that MTX decreases bone formation by reducing osteoblast activation and differentiation[15,16] and inhibition of the Wnt/β-catenin pathway (through an increase in Dickkopf1 and secreted frizzled-related protein 1).[17] MTX also induces osteocyte apoptosis.[18,19] With regard to bone resorption, MTX appears to increase osteoclast activation and activity by raising the level of the receptor activator of nuclear factor kappa-B ligand.[20,21] Pathological studies on bone tissue in MTX-induced osteopathy are scarce, but they have suggested an increase in local bone remodelling, with an increase in osteoclast numbers and surfaces and a decrease in osteoblast numbers and surfaces on bone biopsies.[11]

As in previous reports, this study demonstrated that fractures in the lower limbs (particularly the tibia and the feet) were more prevalent than those observed in postmenopausal osteoporosis. This finding is consistent with a recent study.[14] In our study, the conclusions were similar, with tibial involvement in 88% of cases and foot involvement in 49% of cases. This study also highlighted specific features of MTX-induced osteopathy, such as differences in fracture characteristics, stress fractures without bone deformities and the need for an MRI scan for diagnosis. MRI was used in 84% of our cases, highlighting a typical metaphyseal (proximal and distal) fracture pattern, characterised by extensive bone oedema. This aspect was considered typical and comparable to cases reported in the literature on the use of MTX in rheumatology[7,11,12] but also in haematology.[5,22] In our work, even if the X-rays were always available, MRI (84%) and/or bone scintigraphy (46%) were mainly used for diagnosis, as already described in the literature.[7]

In support of the role of MTX in the development of this osteopathy, it can be noted that discontinuing MTX was associated with an absence of fracture recurrence in both haematological[5,23] and rheumatological cases.[7,12] Although our work was not designed to draw definitive conclusions, it was in accordance with the literature for clinical evolution in cases of MTX continuation.[7,12] In our study, the vast majority of patients (12/17, 71%) who continued MTX experienced unfavourable progression,

**Table 3** Comparison between favourable and unfavourable evolution of fracture

| | Favourable evolution of fracture (n=57) | Delay of fracture healing or fracture recurrence (n=16) | P value |
|---|---|---|---|
| General characteristics | | | |
| Age, *mean±SD* | 67±10 | 65±10 | NS |
| BMI, kg/m$^2$, mean±SD | 25±4 | 24±4 | NS |
| T-score, lumbar site, *mean±SD* | −1.7±1.1 | −2.2±1.1 | NS |
| T-score, total hip, *mean±SD* | −2.1±0.9 | −2.2±0,5 | NS |
| T-score, femoral neck, *mean±SD* | −2.3±0.9 | −2.5±0.9 | NS |
| Densitometric osteoporosis, *n (%)* | 28 (49%) | 9 (56%) | NS |
| Medical history major fracture, *n (%)* | 11 (19%) | 4 (25%) | NS |
| History antiosteoporotic treatment, *n (%)* | 26 (46%) | 6 (38%) | NS |
| MTX treatment | | | |
| Duration at diagnosis in months, *mean±SD* | 120±77 | 141±81 | NS |
| Dose at diagnosis (mg), *mean ± SD* | 19.0 ± 6 | 17.5 ±6 | NS |
| Cumulative dose (g) at diagnosis, *mean±SD* | 8.6±5.8 | 8.6±5.7 | NS |
| Oral administration, *n (%)* | 16 (28%) | 3 (19%) | NS |
| Subcutaneous administration, *n (%)* | 41 (72%) | 13 (81%) | NS |
| Corticosteroid treatment | | | |
| Corticosteroid use, *n (%)* | 25 (44%) | 3 (19%) | NS |
| Corticosteroid dose (mg), *mean±SD* | 1.6±4.0 | 2.9±4.5 | NS |
| MTX-Induced osteopathy management | | | |
| MTX discontinuation, *n (%)* | 52 (91%) | 4 (25%) | p<0.001 |
| Antiosteoporotic treatment, *n (%)* | 28 (49%) | 12 (75%) | NS |
| Antiresorptive treatment alone, *n (%)* | 24 (42%) | 8 (50%) | NS |
| Teriparatide alone, *n (%)* | 3 (5%) | 1 (6%) | NS |
| Sequential or concomitant combined therapy, *n (%)* | 1 (2%) | 3 (19%) | p<0.001 |

Unfavourable evolution was defined as persistent pain, recurrent fractures or delayed healing.
BMI, body mass index; MTX, methotrexate.

compared with five patients (9%) in the MTX discontinuation group. Focusing on patients with a poor outcome, only the continuation of MTX treatment appeared to be related to this observation. The same observations have been reported recently.[13] Another hallmark of the clinical evolution was the rapid resolution of pain (within a few weeks). This recent study reinforced the finding that continuing MTX use in cases of specific osteopathy could be harmful and increase the risk of recurrence. The second part of the article focused on the potentially higher risk of major osteoporotic fractures associated with continuing MTX use, a phenomenon that was not observed in our study. However, the conclusion of the article regarding the increased risk of major osteoporotic fractures still warrants careful consideration, particularly in populations at continued risk of osteoporotic fractures regardless of MTX exposure. To our knowledge, there have been no reports in the literature (nor in our study) evaluating the reduction of MTX doses rather than discontinuing them altogether, in order to limit toxicity while maintaining their efficacy in treating rheumatism.

In addition to discontinuing MTX, a large proportion of patients received osteoporosis treatment. Based on the data for underlying pathophysiology and histomorphometric characteristics, some groups have suggested a combination therapy with denosumab and teriparatide.[11 12] In our study, antiresorptive treatments (such as bisphosphonates or denosumab) were the most commonly chosen additional treatments, but they did not improve bone damage in the case of MTX continuation. Only one patient in our study received combined therapy consisting of teriparatide, denosumab and MTX discontinuation, leading to an improvement in their symptoms.

Regarding IRD, the vast majority of patients in our study presented with RA. At diagnosis, the disease was often in remission or with low disease activity. Corticosteroid use was minimal at the time of diagnosis, reflecting low disease activity. In our study, the average dose of prednisone was 7.8 mg±7.1, which is higher than that reported in the literature (3.2 mg±1.2[11]), but some patients did not have corticosteroids at all (58/92, 63%) and others only received low doses (≤ 5 mg/day) (18/92, 20%) of

prednisone in our population. When it was necessary, the main choice in our work was to introduce other csDMARDs after MTX or to discontinue all treatments. In cases where bDMARDs were used in combination with MTX at the time of diagnosis, the most common decision was to continue bDMARDs or tsDMARDs in monotherapy. Although a recent study has assessed concomitant treatments at diagnosis,[13] to our knowledge, our study is the first to report the therapeutic choices made after discontinuation of MTX, particularly in terms of substitution treatments.

Our study presents some strong points. It was a multicentre, binational large study, with cases identified by a bone specialist after exclusion of other classic causes of bone fragility and using a pharmacovigilance database. It was one of the largest cohorts on this topic with the inclusion of 92 patients (including pharmacovigilance database identification). It is also the first study evaluating therapeutic choices after MTX discontinuation. However, our study also presents some weaknesses. It was a retrospective study with a possible bias, without a standardised evaluation, mainly concerning pain duration after MTX discontinuation. Given the design of our work, we cannot conclude on the efficacy of associated specific bone therapy on fracture evolution. In addition, as previously described in various studies on this topic, the patients presented multiple risk factors for bone fragility, including prolonged corticosteroid therapy, which can play a role in bone phenotypes.

Clinicians should bear in mind that the benefits of using MTX far outweigh the risk of developing this osteopathy in most cases. Even if this condition remains rare, reports of MTX-induced osteopathy seem to be more frequent, reflecting a progressive improvement in knowledge on the subject and better screening of suspected cases. The other possibility is that, since MTX has been used in rheumatological indications since the 1980s, the recent increase in cases could reflect its broader use in recent years (raising the question of a potential individual susceptibility to developing this type of osteopathy producing a dose- and time-dependent effect). In any case, the discontinuation of MTX seems essential to improve symptoms in identified cases, generally with rapid improvement (a few weeks) after discontinuation. The main advantage of improving knowledge of this condition is the avoidance of diagnostic delay and the scope to instate therapeutic changes. Although fatigue/insufficient fractures in these characteristic locations among patients treated with MTX should not necessarily point to the possibility of this condition, clinicians should bear its existence in mind, particularly in the event of recurrence or delayed healing or in case of multiple locations. This work reinforces the need to identify patients at risk and underlines the importance of performing imaging (bone scintigraphy or MRI of the painful areas) in case of diagnostic suspicion. Further studies are needed to gain a deeper understanding of the mechanisms involved in the development of MTX-induced osteopathy in order to better identify individuals at risk. Similarly, the prospective evaluation of osteo-forming treatment initiated at the time of diagnosis is warranted, as this approach could offer a promising pathway to accelerated healing.

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