Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial

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Objectives. In early and active RA despite MTX, continuous treatment with TNF blockers in combination with MTX is recommended. To compare this strategy with an initial combination of MTX and adalimumab (ADA) given for 3 months and then adjusted based on the disease activity status.

Methods. Prospective unblinded randomized multicentre controlled 1-year trial in which 65 patients with early (<6 months) and active disease activity score (DAS28ESR >5.1) RA were assigned to Group 1 (32 patients): MTX (0.3 mg/kg/week, maximum of 20 mg/week, without escalating dose regimen) or to Group 2 (33 patients): initial combination therapy with MTX (as in Group 1) and ADA (40 mg eow). In both groups, treatment was adjusted every 3 months. The aim was to achieve a low DAS (DAS28ESR <3.2).

Results. From Week 12 until Week 52, seven patients in Group 1 and 11 patients in Group 2 remained in low disease activity state while receiving MTX monotherapy ($P = 0.28$). The 1-year area under the curve (AUC) of DAS28 was lower in Group 2 owing to an initial better response. The total intake of anti-TNF-α and the mean increase in total modified Sharp score was similar in the two groups.

Conclusions. Initial combination of MTX and ADA and then an adjusted based on the disease activity status achieved a faster control of disease activity but did not increase the number of patients for whom anti-TNF-α treatment was not needed after 12 weeks nor a better subsequent clinical or radiological outcome than a 3-month delayed initiation of anti-TNF in patients with still active disease despite MTX.

Key words: Rheumatoid arthritis, Anti-TNF, Tight control.

Introduction

Our goals in RA are directed towards the suppression of signs and symptoms of synovitis, prevention of structural damage and maintenance of functionability. Patients with an early DMARD start for inflammatory arthritis do better in terms of function and progression than patients with a delayed start [1]. One hypothesis in RA treatment is that in the early course of the disease a window of opportunity may exist where therapeutic intervention has a disproportionate impact on outcome [2]. The concept that intensive interventions early in the course of persistent arthritis may profoundly affect long-term radiographic disease progression is supported by the results of the combination therapy in early RA (COBRA) trial and randomized controlled trials with TNF blockers in early RA [3–7]. The second concept is that a tight control of RA improves disease activity, radiographic disease progression, physical function and quality of life, as shown with conventional DMARD treatment in the Tight Control for Rheumatoid Arthritis (TICORA) and Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) studies [8, 9]. In the BeSt study, four different strategies all designed to obtain a low level of disease activity were compared: sequential substitution monotherapy, step-up add-on combination therapy, initial combination therapy with a short course of high-dose prednisone and initial combination therapy with the TNF antagonist infliximab [10]. Patients in the two combined therapy groups at 1 year achieved sustained low disease activity score (DAS) 44 and functional improvement more rapidly, but the clinical results at 1 year were the same, suggesting that any strategy is efficient if the objective is a tight control of the disease. However, patients in the two combined therapy groups at 1 year of follow-up had slower progression of structural damage than did the groups receiving sequential monotherapy or step-up combination therapy.

In clinical practice, MTX is the cornerstone therapy of early and active RA. In cases of persistent active disease, continuous treatment with TNF blockers is recommended in combination with MTX. GUEPARD, a French acronym for GUérir la PolyArthrite Rhumatoïde Débutante (cure early RA), is an open multicentre, randomized clinical trial which had two aims. The first was to determine if 3 months of adalimumab (ADA) in association with MTX could achieve and maintain low disease activity (DAS28 <3.2) in patients with early and active RA (<6 months, DAS28 >5.1) compared with MTX alone. The second was to determine, in patients who failed at 3 months to respond to initial strategy or relapsed after 3 months, whether disease activity-driven treatment with TNF-blockers was equally effective in controlling clinical manifestations and the progression of structural damage in both groups.

Patients and methods

Patients

Patients with early RA, as defined by the 1987 criteria of the American College of Rheumatology (ACR) (formerly the American Rheumatism Association), were recruited between May 2004 and May 2006 at 13 centres in France. Patients had a
maximum disease duration of 6 months, were at least 18 years of age, and had active disease defined as a DAS28ESR (DAS28) ≥ 5.1. They were screened for tuberculosis prior to receiving the study drug with a purified protein derivative and by chest radiography. Patients who were at high risk for tuberculosis were allowed to enroll in the study after chemoprophylaxis, as recommended in France [11].

Exclusion criteria included previous treatment with MTX or biologics, concomitant treatment with an experimental drug, malignancy within the previous 10 years, cytopenia (haemoglobin <9 g/dl in men, 8.5 g/dl in women, leucocytes <3 × 10^9/L, platelets <150 × 10^9/L), a serum aspartate aminotransferase/alanine aminotransferase level more than 1.5 times the upper limit of normal, an estimated creatinine clearance level <50 ml/min, concurrent pregnancy and inadequate contraception. Patients who had chronic infectious disease, a major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 30 days or oral antibiotics within 14 days prior to screening were also excluded, as were patients with heart disease and multiple sclerosis. The study was approved by the ethics committee of Hôpital Cochin, Paris, and all participants provided written informed consent.

**Treatment allocation and intervention**

Patients who met the eligibility criteria were randomized (per centre) to receive MTX monotherapy (Group 1) or initial combination therapy with MTX and ADA (Group 2). The decision of whether to adjust medication was made every 3 months on the basis of the disease activity score in 28 joints (DAS28). If the patient did not achieve a low disease activity (DAS28 ≤ 3.2), the treating physician immediately adjusted therapy by proceeding to the next step in the allocated treatment group.

Patients assigned to initial monotherapy started with MTX (0.3 mg/kg/week, maximum of 20 mg/week, without escalating dose regimen). In the event of remission (DAS28 <2.6 for at least 6 months), MTX was tapered (2.5 mg/month) to a maintenance dose of 7.5 mg/week. If disease activity flared after tapering of MTX, the initial dose of MTX was reintroduced. Subsequent steps for patients with an insufficient response at Week 12 or thereafter were MTX and ADA (40 mg every other week), MTX and ADA (40 mg/week), MTX and etanercept (25 mg twice a week) and MTX and LEF.

The patients assigned to initial combination with ADA started with MTX (0.3 mg/kg/week, maximum of 20 mg/week, without escalating dose regimen) and ADA 40 mg every other week. If the DAS28 was <3.2 at Week 12, ADA was stopped. In the event of remission (DAS28 <2.6 for at least 6 months), MTX was tapered (2.5 mg/month) to a maintenance dose of 7.5 mg/week. If disease activity flared after tapering of MTX, the initial dose of MTX was reintroduced. In the event of relapse, patients restarted ADA 40 mg every other week for 12 weeks. If the DAS28 was >3.2 after 12 weeks, ADA was stopped. In the event of inefficacy (DAS28 >3.2 after 12 weeks of treatment), ADA was increased (40 mg/week) for 12 weeks. After 12 weeks of effective therapy, ADA was decreased (40 mg every other week) for 12 weeks and stopped if successful. In the event of failure on ADA 40 mg/week, etanercept (25 mg twice a week) was initiated for 12 weeks. If effective, etanercept was stopped and started again for 12 weeks if relapse occurred. If etanercept failed, LEF was initiated. If the treatment was unsuccessful after the initial 12 weeks, the same regimen was applied according to the protocol indicated above.

Patients were allowed to continue concomitant treatment with corticosteroids initiated before but not after inclusion (maximum daily dose of 10 mg of oral prednisone) and to take NSAIDs and simple analgesics. A single IA steroid injection was allowed during the trial. All patients received folic acid (20 mg 72 h after MTX therapy).

**Assessment of variables**

At baseline and every month the following variables were assessed: number of swollen joints (0–28), number of tender joints (0–28), visual analogue scale (VAS) score for pain (0–100 mm), VAS general well-being (0–100), VAS fatigue (0–100), VAS physician overall assessment (0–100), morning stiffness (minutes), ESR (millimetre per first hour) and CRP (milligram per litre). The French version of the HAQ was filled out at Weeks 0, 12, 24, 36 and 52 (0–3 = greatest functional disability). RF and anti-CCP status were defined at baseline. Radiographs of hands and feet were taken at baseline and at Week 52. Radiographs were independently scored by a trained assessor who was blinded to the patient’s identity, treatment centre and date according to the modified Sharp/vander Heijde score (SHS), with a range of 0–448. A patient was classified as having erosive disease if the erosion score was >1 [10].

**Clinical efficacy and radiographic progression**

Primary endpoint was the proportion of patients in low disease activity at Week 12 for whom anti-TNF-α was not introduced or reintroduced at 1 year. Secondary endpoints were the 1-year area under the curve (AUC) of DAS28, European League Against Rheumatism (EULAR) responders, ACR responders (20, 50 and 70%), the time to obtain low disease activity, the number of visits at which the patients had low disease activity, number of anti-TNF-α doses over the 1-year period, and functional assessment according to SF-36 (0–100), VAS physician overall assessment (0–100 mm), VAS general well-being (0–100), VAS fatigue (0–100), and HAQ (milligram per litre). The French version of the HAQ was filled out at Weeks 0, 12, 24, 36 and 52 (0–3 = greatest functional disability). RF and anti-CCP status were defined at baseline. Radiographs of hands and feet were taken at baseline and at Week 52. Radiographs were independently scored by a trained assessor who was blinded to the patient’s identity, treatment centre and date according to the modified Sharp/vander Heijde score (SHS), with a range of 0–448. A patient was classified as having erosive disease if the erosion score was >1 [10].

**Safety**

At each control visit, the following laboratory tests were performed: ESR, CRP, complete blood cell count, and serum levels of serum creatinine, uric acid, alkaline phosphatase, aspartate aminotransferase, γ-glutamyl transpeptidase and creatinine. The attending physician recorded all adverse events (AEs) and serious AEs (SAEs) and, if necessary, made treatment adjustments in accordance with the protocol. SAEs were defined as events that were fatal or life threatening or resulted in permanent or significant disability, malignancy, congenital anomalies or birth defects, or events that required or prolonged hospitalization. Serious infections were defined as infections requiring hospitalization or i.v. antibiotics. Criteria for dose adjustments or discontinuation of MTX use because of adverse events were established by the study protocol.

**Sample size calculation**

The sample size was originally calculated to provide a power of 80%, with a two-tailed α-level of 0.05 to detect a difference of 30% to maintain a low disease activity without anti-TNF in the two groups. We did not have robust enough data to estimate the delta and hypothesized an expected success of 20% in the MTX group and 50% in the combination group. We expected withdrawal rates of 10%. A total sample size of 88 patients (44/group) would have been needed if the hypothesized results had occurred.

**Statistical analysis**

All patients enrolled in the study were included in intent-to-treat analyses of efficacy and safety. The last observation carried forward approach was used to handle missing data. The AUCs were computed using a trapezoidal rule and then analysed by analysis of covariance adjusted to initial values. Survival curves were derived using the Kaplan–Meier method and were statistically tested by log rank test.

Differences between groups were tested using the Fisher test or one-way analysis of variance or logistic regression depending
on the variable tested. $P < 0.05$ were considered statistically significant.

**Results**

Sixty-five patients were included in the study between May 2004 and May 2006. The trial was prematurely interrupted owing to difficulties in recruiting patients. Sixty-five patients were randomly assigned to one of two treatment groups: 32 to initial monotherapy (Group 1), and 33 to initial combination therapy (Group 2). Eight patients dropped out (three patients in Group 1, and five patients in Group 2) (Fig. 1).

There were no statistically significant differences in the demographic and baseline disease characteristics between the two groups (Table 1). The study population consisted of patients with very early RA, with a median duration of symptoms of 4.4 months. All patients had active disease with a mean $\pm$ s.d. DAS28 of $6.23 \pm 0.82$, 34.4% of the patients had erosive disease at baseline, 73.8% were RF positive and 73.1% had anti-CCP antibodies. Ten patients in the two groups were on steroids.

**Clinical outcomes**

From Week 12 until Week 52, 7 patients in Group 1 and 11 patients in Group 2 remained in low DAS while receiving MTX monotherapy ($P = 0.28$). MTX was decreased in 6/7 patients in Group 1 and in 4/11 patients in Group 2. The 1-year AUC of DAS was lower in Group 2 [164.6 (149.2–180.0)] vs Group 1 [186.7 (171.1–202.4); $P = 0.049$] owing to an initial better response [AUC W0–W12: 49.2 (45.5–52.9) vs 62.0 (58.3–65.8), $P < 0.0001$; AUC W12–W52: 126 (115–136) vs 113 (102–124); $P = 0.11$] (Fig. 2). Among the variables of DAS, the initial combination therapy resulted in statistically lower median AUC in the first 12 weeks compared with monotherapy for tender joint count ($P = 0.0071$), swollen joint count ($P = 0.0004$) and ESR ($P = 0.0014$) but not for patient's global assessment.

![Fig. 1. Patient disposition during the 1-year follow-up period.](image-url)

**Table 1. Baseline demographic and disease characteristics**

<table>
<thead>
<tr>
<th></th>
<th>MTX $n=32$</th>
<th>MTX ADA $n=33$</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean $\pm$ s.d., years</td>
<td>49.3 $\pm$ 15.2</td>
<td>46.3 $\pm$ 16.3</td>
<td>0.44</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>26 (81.25)</td>
<td>26 (78.79)</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptom duration, median (IQR), months</td>
<td>4.4 (3.3–5.1)</td>
<td>4.4 (2.5–5.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>IgM RF positive, n (%)</td>
<td>24 (77.4)</td>
<td>21 (70.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>Anti-CCP positive, n (%)</td>
<td>22 (78.6)</td>
<td>16 (66.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Pain (VAS 0–100), mean $\pm$ s.d.</td>
<td>57.3 $\pm$ 24.6</td>
<td>62.5 $\pm$ 18.9</td>
<td>0.35</td>
</tr>
<tr>
<td>Fatigue (VAS 0–100), mean $\pm$ s.d.</td>
<td>64.7 $\pm$ 21.9</td>
<td>71.45 $\pm$ 14.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Physician global assessment (VAS 0–100), mean $\pm$ s.d.</td>
<td>58.0 $\pm$ 26.1</td>
<td>56.9 $\pm$ 21.8</td>
<td>0.85</td>
</tr>
<tr>
<td>Tender joint count, mean $\pm$ s.d.</td>
<td>66.09 $\pm$ 18.2</td>
<td>69.12 $\pm$ 17.16</td>
<td>0.44</td>
</tr>
<tr>
<td>Swollen joint count, mean $\pm$ s.d.</td>
<td>14.1 $\pm$ 6.4</td>
<td>13.8 $\pm$ 7.1</td>
<td>0.87</td>
</tr>
<tr>
<td>ESR, mean $\pm$ s.d., mg/l</td>
<td>10.8 $\pm$ 5.3</td>
<td>9.5 $\pm$ 4.5</td>
<td>0.26</td>
</tr>
<tr>
<td>CRP, mean $\pm$ s.d., mg/l</td>
<td>35.1 $\pm$ 23.8</td>
<td>39.4 $\pm$ 20.9</td>
<td>0.45</td>
</tr>
<tr>
<td>DAS28ESR, mean $\pm$ s.d.</td>
<td>32.8 $\pm$ 4.0</td>
<td>24.7 $\pm$ 24.7</td>
<td>0.93</td>
</tr>
<tr>
<td>DAS28CRP, mean $\pm$ s.d.</td>
<td>6.15 $\pm$ 0.88</td>
<td>6.31 $\pm$ 0.78</td>
<td>0.44</td>
</tr>
<tr>
<td>HAQ score, 0–3 scale, mean $\pm$ s.d.</td>
<td>5.85 $\pm$ 0.91</td>
<td>5.80 $\pm$ 0.83</td>
<td>0.84</td>
</tr>
<tr>
<td>JSN score, 0–168 scale, mean $\pm$ s.d.</td>
<td>1.41 $\pm$ 0.74</td>
<td>1.69 $\pm$ 0.59</td>
<td>0.10</td>
</tr>
<tr>
<td>Total SHS, 0–448 scale, mean $\pm$ s.d.</td>
<td>7.5 $\pm$ 21.3</td>
<td>2.4 $\pm$ 4.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Erosion score, 0–280 scale, mean $\pm$ s.d.</td>
<td>3.9 $\pm$ 12.4</td>
<td>1.2 $\pm$ 2.1</td>
<td>0.21</td>
</tr>
<tr>
<td>JSN score, 0–168 scale, mean $\pm$ s.d.</td>
<td>3.6 $\pm$ 9.2</td>
<td>1.3 $\pm$ 3.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Erosions on hand/foot radiograph, n (%)</td>
<td>12 (37.5)</td>
<td>10 (31.25)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

JSN: joint space narrowing; IQR: interquartile range.
Among the other variables assessed, morning stiffness \((P = 0.028)\) and physician overall assessment \((P = 0.0017)\) improved significantly in the initial combination therapy in the first 12 weeks, but there were no differences for pain \((P = 0.19)\), fatigue \((P = 0.20)\) or CRP \((P = 0.12)\). There was no difference in any of the variables between Week 12 and Week 52. The percentage of patients with a good EULAR response (i.e. DAS <3.2 and a fall in score from baseline by >1.2) and in remission (DAS <2.6) was higher at Week 12 in the group treated with ADA and MTX: 63.6 vs 25\% \((P = 0.0014)\) and 36.4 vs 12.5\% \((P = 0.0223)\), respectively (Fig. 2). There were no statistically significant differences at Week 52: 63.6 vs 65.6\% \((P = 0.98)\) and 39.4 vs 59.4\% \((P = 0.15)\), respectively (Fig. 2). Patients treated with MTX and ADA demonstrated a significantly greater clinical response at 12 weeks, as measured by ACR20 (84 vs 50\%), ACR50 (66 vs 27\%) and ACR70 (44 vs 19\%) (Fig. 3). However, there were no statistically significant differences in ACR response at 52 weeks between the two groups: 85 vs 81\% for an ACR20 response, 67 vs 68\% for an ACR50 response and 42 vs 58\% for an ACR70 response (Fig. 4). The time to obtain low disease activity was shorter in the group on MTX and ADA \([12 (8.3–12.6)\) weeks vs \(19.6 (16.9–26.0)\) weeks; \(P = 0.049)\]. However, the number of visits in which the patients had low disease activity did not differ between the two groups \([Group 1: 10.4 (7.6–13.3), Group 2: 13.4 (10.6–16.2); P = 0.11)\]. Four patients in Group 1 and two patients in Group 2 needed to switch to etanercept but the total consumption of anti-TNF-\(\alpha\) agents (number of doses) was similar in the two groups \([ADA Group 1: 11.7 \pm 10.6, Group 2: 15.9 \pm 10.9; P = 0.12; etanercept Group 1: 4.2 \pm 12.2, Group 2: 2.1 \pm 9; P = 0.43)\).

**Improvement in physical function**

HAQ scores improved from baseline to Week 12 in the two groups, MTX alone \((-0.51; 95\% CI -0.30, -0.72)\) and MTX and ADA \((-0.82; 95\% CI -0.52, -1.11)\), but without statistically significant inter-group difference; \(P = 0.26\). At 52 weeks, improvement did not reach statistical significance between the two groups \([-0.93 (95\% CI -0.69, -1.17), -1.02 (95\% CI -0.81, -1.24); P = 0.79]\) or in terms of SF-36 physical and mental components (data not shown).
Radiological outcomes

Radiographs obtained at baseline and at 1 year of follow-up were available for 29 patients in Group 1 and for 27 patients in Group 2. The progression of structural damage was not statistically different between the two groups. The mean change in total modified Sharp score from baseline was 1.8 ± 4.7 and 1.9 ± 4 at Week 52 in Groups 1 and 2, respectively (P = 0.18). The separate analysis of the erosion and joint space narrowing scores showed no differences between the two groups at 52 weeks (data not shown). There were 16 patients without radiological progression in Group 1 and 14 in Group 2 (P = 0.41).

AE

Malignancy was diagnosed in two patients, both of whom were in the MTX and ADA group. One patient had ovarian carcinoma diagnosed at Week 12, and the other had pancreatic cancer diagnosed at Week 20. In these two cases, a diagnosis of paraneoplastic rheumatism could not have been ruled out. The patient with ovarian cancer had RF and anti-CCP antibodies, but rapidly developed palmar fasciitis. The second patient had no autoantibodies or erosions. Owing to the rapid appearance of neoplasia, it is unlikely that the treatment was responsible. Three other patients in Group 2 had SAEs: one had hepatitis (Week 6), the other had MTX pneumonia (Week 6) and the last had acoustic neuroma (Week 10). In Group 1, five patients were hospitalized for the following reasons: one for vasculitis with revision of diagnosis to Sharp syndrome (Week 6), one for hepatitis secondary to MTX (Week 4), one for a hip prosthesis operation (Week 12), one for weight loss (Week 36) and one for haemophysis (Week 32).

Discussion

In a strategy of tight control of disease activity, although MTX-anti-TNF combination therapy, given initially and then as required, produced a faster response it did not achieve a better subsequent (1 year) clinical or radiological outcome than a 3-month delayed initiation of anti-TNF in patients who still had active disease despite MTX therapy. Nor did it decrease the number of patients who still required anti-TNF at 1 year. Both strategies resulted in a similar 1-year dose of anti-TNF intake.

As in the BeSt study, at Week 12, more patients treated with initial combination achieved clinical improvement than patients assigned to sequential monotherapy or to step-up add-on combination therapy, who started with 15 mg/week MTX. However, the initial combination did not decrease the number of patients who still required anti-TNF at 1 year. This could be due to the small size of our patient sample. Another explanation could be the too brief initial duration of anti-TNF therapy. In the fourth group of the BeSt study, patients with active early RA were initially treated with infliximab (3 mg/kg) in combination with MTX (25 mg/week). DAS was measured every 3 months. In patients with persistent low disease activity (DAS ≤ 2.4) for at least 6 months, infliximab dosage was tapered and the therapy finally discontinued. With this protocol, 56% (67/120) of patients had persistent low disease activity and discontinued infliximab after a median of 9.9 months with a median MTX dosage of 10 mg/week after 2 years [12, 13]. As in the BeSt study, a large proportion of patients would be overtreated if all those with early RA were to start with initial combination therapy. However, this proportion was lower in our study (21%) than that observed in Groups 1 and 2 of the BeSt study, in which 40% of the patients had a sustained adequate suppression of disease activity with MTX monotherapy. In the SWEfOT trial, 144 of 487 (30%) patients with early RA who started on MTX at up to 20 mg/week achieved a low disease activity state at 3–4 months. These patients continued to have very good clinical responses throughout the first year, since 75% had low disease activity state at 1 year and only 12% needed their DMARD to be modified [14]. Thus, an initial good response to MTX, as observed in the BeSt, SWEfOT and GUEPARD trials, defines a subpopulation of early RA with an excellent 1-year clinical prognosis.

In our study, patients with initial combination therapy did not have slower progression of structural damage than the groups receiving initial monotherapy. This could be explained by the large number of patients who received an anti-TNF drug during the 1-year study. Anti-TNFs have conclusively demonstrated their ability to slow down structural damage in RA, even in non-clinical responders [15, 16]. In the post hoc analysis of the BeSt study patients who started initial MTX plus infliximab were compared with 67 patients who started MTX plus infliximab treatment after failing on three or more traditional DMARDs. Patients who started initial MTX infliximab had less progression of radiographic damage. However, unlike in our study, the introduction was delayed by 13 months (12–17 months) [17].

In a strategy of tight control, treatment of early and active RA could be initial MTX, since delayed initiation of anti-TNF after failure of initial high-dose MTX has no harmful clinical or structural damage at 1 year. In cases of MTX failure, the introduction of anti-TNF seems reasonable, since anti-TNFs are more effective than sequential monotherapy or step-up add-on combination therapy [17, 18]. At what point combination therapy of anti-TNF and MTX should be introduced remains to be determined.

Rheumatology key messages

- Initiating MTX treatment in combination with anti-TNF agents is not justified.
- When there is persistent activity despite MTX treatment, anti-TNF therapy can be deferred for 3 months.
- Tight control of disease activity is effective.

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References


