OBJECTIVE: To compare mortality data obtained from randomized controlled trials for the 5 tumor necrosis factor-α (TNF-α) inhibitors used in the treatment of rheumatoid arthritis.

METHODS: A systematic review of articles published up to November 2014 was performed using electronic databases. We included randomized, controlled trials, with a follow-up period of at least 24 weeks, comparing TNF-α inhibitors to placebo or disease-modifying antirheumatic drugs. The primary outcome was the occurrence of all-cause mortality.

RESULTS: Twenty-three studies were selected. These articles included 6525 patients in the anti-TNF-α group and 3523 in the control group. The duration of patient follow-up ranged from 24 to 104 weeks. The risk of all-cause mortality in patients receiving TNF-α inhibitors was not significantly different from those receiving the comparator (odds ratio 1.32; 95% confidence interval, 0.76-2.29). Subgroup analyses with respect to the molecule used, the dose received, the use of TNF-α inhibitors as monotherapy or combination therapy, or the quality of the trial did not modify the findings.

CONCLUSION: This meta-analysis performed on a large number of patients and including the 5 TNF-α inhibitors currently available shows no increased risk of medium-term all-cause mortality in patients with rheumatoid arthritis.

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research was limited to English language and human clinical trials.

Inclusion Criteria
We defined the target population as adults with rheumatoid arthritis diagnosed according to the 1987 American College of Rheumatology criteria.\(^5\) Interventions included all 5 currently available TNF-\(\alpha\) inhibitors. Eligible comparators included placebo and conventional disease-modifying antirheumatic drugs (DMARDs). The primary outcome of this study was the occurrence of all-cause mortality defined on an intention-to-treat basis. To better reflect the drug effect on the potential risk of death, included studies have to report a minimum of 24 weeks of the study duration.

Methodological Quality
The articles that fulfilled the inclusion criteria underwent quality appraisal by using the Jadad scale.\(^6\)

Data Extraction
Two investigators (LP and JA) independently extracted data from articles using a customized form, available from the authors. Disagreements were resolved by consensus.

Statistical Analysis
We used the Mantel-Haenszel method for calculating the weighted summary odds ratio under the fixed-effect model. Next, the heterogeneity was incorporated to calculate summary odds ratios under the random-effects model (DerSimonian and Laird).\(^7\) Statistical heterogeneity was tested by Q-test (\(\chi^2\)) and \(I^2\) statistic calculation.\(^8\) All statistical tests and creation of forest plots were conducted with MedCalc software (v11.4.4; Ostend, Belgium). Additional subgroup analyses were planned to check whether they would substantially change the findings.

RESULTS

Included Studies
The results of the article selection process are reported in Figure 1. Among the 495 studies initially analyzed, 23 studies fulfilled our inclusion criteria (Table 1).\(^9\)\(^{-}\)\(^3\)\(^1\) The median study duration was 46 weeks (range: 24 to 104 weeks). This analysis included 10,048 patients: 6525 were treated with TNF-\(\alpha\) inhibitors show no increased risk of medium-term all-cause mortality.
• The type of molecule and the dose received do not modify this finding.

<table>
<thead>
<tr>
<th>CLINICAL SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis factor-(\alpha) inhibitors show no increased risk of medium-term all-cause mortality.</td>
</tr>
<tr>
<td>The type of molecule and the dose received do not modify this finding.</td>
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\(\text{Figure 1} \quad \text{Flow diagram of articles evaluated for inclusion and exclusion. RA = rheumatoid arthritis.}\)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Mean Disease Duration (Y)</th>
<th>n</th>
<th>Type</th>
<th>Placebo</th>
<th>TNF-α Inhibitor</th>
<th>Trial Duration (Wk)</th>
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<tr>
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<td>8.3</td>
<td>129</td>
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<td>Placebo</td>
<td>Golimumab 2-4 mg/kg/3 mo</td>
<td>257</td>
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<td>Emery et al, 2009</td>
<td>3.4</td>
<td>160</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Golimumab 50 or 100 mg/4 wk</td>
<td>318</td>
<td>24</td>
</tr>
<tr>
<td>Quinn et al, 2005</td>
<td>0.6</td>
<td>10</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Infliximab 3 mg/kg</td>
<td>10</td>
<td>54</td>
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<td>Placebo</td>
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<td>Placebo</td>
<td>Adalimumab 20 mg/wk or 40 mg/2 wk</td>
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<td>Adalimumab 40 mg/2 wk</td>
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<td>Placebo</td>
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<td>231</td>
<td>52</td>
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<td>Placebo</td>
<td>Etanercept 25 mg/2 wk</td>
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<td>127</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Certolizumab 200 mg or 400 mg/2 wk</td>
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<td>Fleischmann et al, 2009</td>
<td>9.6</td>
<td>109</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Certolizumab 400 mg/2 wk</td>
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<td>24</td>
</tr>
<tr>
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<td>6.2</td>
<td>199</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Certolizumab 200 or 400 mg/2 wk</td>
<td>783</td>
<td>52</td>
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<td>Placebo</td>
<td>Infliximab 3 mg/kg</td>
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<td>46</td>
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<td>88</td>
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<td>Placebo</td>
<td>Infliximab 3-10 mg/kg</td>
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<td>Kavarnaugh et al, 2013</td>
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<td>517</td>
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<td>76</td>
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<td>Breedveld et al, 2008</td>
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<td>9.4</td>
<td>87</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Adalimumab 20-40 mg or 80 mg/2 wk</td>
<td>265</td>
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<td>10.9</td>
<td>110</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Adalimumab 20-40 mg/wk or 2 wk</td>
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<td>Schiff et al, 2008</td>
<td>7.7</td>
<td>110</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Infliximab 3 mg/kg</td>
<td>165</td>
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<td>Leirisalo-Repo et al, 2013</td>
<td>0.3</td>
<td>49</td>
<td>Disease-modifying</td>
<td>Placebo</td>
<td>Infliximab 3 mg/kg</td>
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<td>104</td>
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<tr>
<td>Bejarano et al, 2008</td>
<td>0.7</td>
<td>73</td>
<td>Methotrexate</td>
<td>Placebo</td>
<td>Adalimumab Not reported</td>
<td>75</td>
<td>56</td>
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TNF = tumor necrosis factor.
<table>
<thead>
<tr>
<th>Reference</th>
<th>TNF-α Inhibitor</th>
<th>Dose of TNF-α Inhibitor</th>
<th>Placebo Dose of TNF-α Inhibitor</th>
<th>Deaths, n</th>
<th>Cause of Death</th>
<th>TNF-α Inhibitor</th>
<th>Dose</th>
</tr>
</thead>
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<td>2-4 mg/kg/3 mos</td>
<td>Placebo 2-4 mg/kg/3 mos</td>
<td>0</td>
<td>Myocardial infarction</td>
<td>Normal/high</td>
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<tr>
<td>Emery et al, 2009</td>
<td>Golimumab</td>
<td>50 or 100 mg/4 wk</td>
<td>Placebo 50 or 100 mg/4 wk</td>
<td>0</td>
<td>Suicide, cardiorespiratory arrest after surgery</td>
<td>Normal/high</td>
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<td>Quinn et al, 2005</td>
<td>Infliximab</td>
<td>3 mg/kg</td>
<td>Placebo 3 mg/kg</td>
<td>0</td>
<td>Respiratory failure due to methotrexate, upper gastrointestinal bleed</td>
<td>Normal</td>
<td></td>
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<tr>
<td>St Clair et al, 2004</td>
<td>Infliximab</td>
<td>3 or 6 mg/kg</td>
<td>Placebo 3 or 6 mg/kg</td>
<td>2</td>
<td>Cardiac arrest, metastatic pancreatic cancer</td>
<td>Normal/high</td>
<td></td>
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<tr>
<td>Keystone et al, 2004</td>
<td>Adalimumab</td>
<td>20 mg/wk or 40 mg/2 wk</td>
<td>Placebo 20 mg/wk</td>
<td>0</td>
<td>Multiple fractures, urosepsis, complications of chemotherapy for lymphoma</td>
<td>Normal</td>
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<td>Furst et al, 2003</td>
<td>Adalimumab</td>
<td>40 mg/2 wk</td>
<td>Placebo 40 mg/2 wk</td>
<td>0</td>
<td>Necrotizing fascitis</td>
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<td>Smolen et al, 2013</td>
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<td>25 or 50 mg/wk</td>
<td>Placebo 25 or 50 mg/wk</td>
<td>0</td>
<td>Pulmonary embolism, septicemia</td>
<td>Low/normal</td>
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<td>Etanercept</td>
<td>25 mg 2/wk</td>
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<td>1</td>
<td>Pulmonary embolism</td>
<td>Normal</td>
<td></td>
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<td>Combe et al, 2006</td>
<td>Etanercept</td>
<td>25 mg 2/wk</td>
<td>Placebo 25 mg 2/wk</td>
<td>0</td>
<td>Stroke and pneumonia</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Smolen et al, 2009</td>
<td>Certolizumab</td>
<td>200 mg or 400 mg/2 wk</td>
<td>Placebo 200 mg or 400 mg/2 wk</td>
<td>0</td>
<td>Myocardial infarction, fracture and shock</td>
<td>Low/normal</td>
<td></td>
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<tr>
<td>Fleischmann et al, 2009</td>
<td>Certolizumab</td>
<td>400 mg/2 wk</td>
<td>Placebo 400 mg/2 wk</td>
<td>0</td>
<td>Myocardial infarction</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Keistone et al, 2008</td>
<td>Certolizumab</td>
<td>200 or 400 mg/2 wk</td>
<td>Placebo 200 or 400 mg/2 wk</td>
<td>1</td>
<td>Myocardial infarction</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Durez et al, 2007</td>
<td>Infliximab</td>
<td>3 mg/kg</td>
<td>Placebo 3 mg/kg</td>
<td>0</td>
<td>Septic shock, right ventricular failure, unknown cause, acute respiratory distress, two interstitial lung disease</td>
<td>Normal</td>
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<tr>
<td>Lipsky et al, 2000</td>
<td>Infliximab</td>
<td>3-10 mg/kg</td>
<td>Placebo 3-10 mg/kg</td>
<td>3</td>
<td>Sudden death</td>
<td>Normal/low/high</td>
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<td>Kavanaugh et al, 2013</td>
<td>Adalimumab</td>
<td>40 mg/2 wk</td>
<td>Placebo 40 mg/2 wk</td>
<td>1</td>
<td>Sudden death</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Van Vollenhoven et al, 2011</td>
<td>Adalimumab</td>
<td>40 mg/2 wk</td>
<td>Placebo 40 mg/2 wk</td>
<td>0</td>
<td>Complications of bowel obstruction</td>
<td>Normal</td>
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<tr>
<td>Choy et al, 2012</td>
<td>Certolizumab</td>
<td>400 mg/2 wk</td>
<td>Placebo 400 mg/2 wk</td>
<td>0</td>
<td>Pneumonia</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Breedveld et al, 2006</td>
<td>Adalimumab</td>
<td>40 mg/2 wk</td>
<td>Placebo 40 mg/2 wk</td>
<td>1</td>
<td>Ovarian cancer</td>
<td>Normal</td>
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<tr>
<td>Miyasaka et al, 2008</td>
<td>Adalimumab</td>
<td>20-40 mg or 80 mg/2 wk</td>
<td>Placebo 20-40 mg or 80 mg/2 wk</td>
<td>0</td>
<td>Interstitial lung disease, cerebral hemorrhage</td>
<td>Low/normal/high</td>
<td></td>
</tr>
<tr>
<td>van de Putte et al, 2004</td>
<td>Adalimumab</td>
<td>20-40 mg/wk or 2 wk</td>
<td>Placebo 20-40 mg/wk or 2 wk</td>
<td>1</td>
<td>Metastatic adenocarcinoma, cholangiocarcinoma, myocardial infarction</td>
<td>Low/normal/high</td>
<td></td>
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<td>Schiff et al, 2008</td>
<td>Infliximab</td>
<td>3 mg/kg</td>
<td>Placebo 3 mg/kg</td>
<td>0</td>
<td>Fibrosarcoma</td>
<td>Normal</td>
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<tr>
<td>Leirisalo-Repo et al, 2013</td>
<td>Infliximab</td>
<td>3 mg/kg</td>
<td>Placebo 3 mg/kg</td>
<td>0</td>
<td>Not reported</td>
<td>Normal</td>
<td></td>
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<td>Bejarano et al, 2008</td>
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<td>Not reported</td>
<td>Placebo Not reported</td>
<td>0</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

TNF = tumor necrosis factor.
inhibitors and 3523 were treated with placebo or conventional DMARDs.

**Primary Outcome: Mortality of Any Cause Upon TNF-α Inhibitors Compared with Controls**

During the study duration, 34/6525 (0.52%) deaths were observed in patients treated with TNF-α inhibitors, compared with 10/3523 (0.28%) deaths in those treated with conventional DMARDs/placebo (P = .113) ([Table 2](#)). Thus, the risk of death of any cause in patients receiving TNF-α inhibitors was not significantly different from those receiving the comparator (odds ratio [OR] 1.32; 95% confidence interval [CI], 0.76-2.29) ([Figure 2](#)). The results were consistent across trials (Q = 7.87, P = .99, I² < 25%).

Subgroup analysis within the type of comparator did not modify previously observed results. The OR of mortality of patients receiving TNF-α inhibitors used as monotherapy vs placebo was 1.04 (95% CI, 0.20-5.34), and the OR of mortality of patients receiving TNF-α inhibitors used in combination therapy vs conventional DMARDs was 1.36 (95% CI, 0.76-2.43).

**Secondary Analyses**

**Subgroup Analyses with Respect to Each Molecule.** Individually, each molecule analyzed separately did not show an increased risk of mortality of any cause ([Table 3](#)).

**Subgroup Analysis with Respect to the Dose of TNF-α Inhibitors.** To address the potential dose impact, we compared the mortality event rates according to TNF-α inhibitor dose (high dose, defined by a dose higher than usual TNF-α inhibitor dose as per package insert, vs usual dose). High dose of TNF-α inhibitors was not significantly associated with a significant increase in risk of mortality (OR 0.97; 95% CI, 0.26-3.54 vs 1.43; 95% CI, 0.79-2.59 for the usual dose).

**Table 3** Odds Ratio for All-cause Mortality According to the Molecule Used

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Adalimumab</th>
<th>Golimumab</th>
<th>Certolizumab</th>
<th>Infliximab</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis (OR, 95% CI)</td>
<td>1.32 (95% CI, 0.76-2.29)</td>
<td>2.17 (95% CI, 0.83-5.68)</td>
<td>2.02 (95% CI, 0.23-18.19)</td>
<td>1.19 (95% CI, 0.27-5.18)</td>
<td>0.70 (95% CI, 0.27-1.81)</td>
<td>1.28 (95% CI, 0.23-7.25)</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.
Subgroup Analysis with Respect to the Quality of Evidence. Most of our comparison analyses reached a high level of quality of evidence, with a mean Jadad score of 3.87 ± 1.01 (Table 1).9-31 We compared studies with a high quality (Jadad score >3) to those with a lower quality (Jadad score ≤3). The results did not appear to differ substantially. In high-quality studies, the OR for mortality of any cause was 1.60 (95% CI, 0.78-3.30), and in lower-quality studies, the OR was 0.99 (95% CI, 0.42-2.31).

To help address the potential impact of the calendar time, we also compared mortality according to calendar year of publication (before and after 2006). The summary ORs for mortality were both not significant for these 2 time periods (0.80; 95% CI, 0.37-1.76 before and 2.03; 95% CI, 0.91-4.52 after 2006).

**DISCUSSION**

A recent meta-analysis has underlined the higher risk of overall serious adverse events in certolizumab pegol-treated patients and the significant increase in the risk of serious infections in patients on adalimumab, certolizumab pegol, and infliximab, which might suggest a potential higher risk of mortality.1 This hypothesis has not been confirmed in our meta-analysis, which covered the same time period and compared the 5 currently available TNF-α inhibitors for the risk of mortality, an undisputed hard endpoint. Indeed, the use of TNF-α inhibitors is not associated in our study with an increased risk of medium-term mortality.

Several registries have suggested a reduction of the risk of mortality in patients with rheumatoid arthritis treated with TNF-α inhibitors.32-34 Several factors may explain this discrepancy, especially the exclusion of highly selected patients in randomized controlled trials compared with unselected patients in registries, and the longer time of drug exposure in the latter. This may suggest that registries may be more adequate to address the impact of TNF-α inhibitors on overall mortality. However, our results are consistent with data extracted from the British Society for Rheumatology Biologics Registers and with the meta-analysis of Leombruno.35

Strengths of our meta-analysis are its large sample size, an indirect comparison among the 5 available molecules, the presence of a control group obtained through a process of randomization, the quality of data extracted from a majority of high-quality randomized controlled trials, and the absence of heterogeneity among included trials. Limitations of our meta-analysis included the generalization of our results and the absence of long-term exposition on TNF-α inhibitors. Insufficient data were provided to perform a subgroup analysis according to the duration of use of TNF-α inhibitors. Moreover, effect of TNF-α inhibitors on mortality may occur after discontinuation of these drugs, and this aspect could not be assessed in our meta-analysis.

In conclusion, this meta-analysis shows that treatment with TNF-α inhibitors is not associated with a higher risk of medium-term mortality of any cause in patients with rheumatoid arthritis. These results are reassuring for this duration, given that these therapies are highly effective at controlling symptoms and reducing disability and damage. Further studies are warranted to assess the long-term effect of TNF-α inhibitors on mortality.

**References**


**APPENDIX**

Supplementary references accompanying this article can be found in the online version at [http://dx.doi.org/10.1016/j.amjmed.2015.07.020](http://dx.doi.org/10.1016/j.amjmed.2015.07.020).
Appendix 1: References of included studies

mumb, a new human anti-tumor necrosis factor α antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-
week efficacy and safety results of a phase III randomized, double-blind,

2. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor α monoclonal antibody, injected subcutaneously every four weeks in
methotrexate-naive patients with active rheumatoid arthritis: Twenty-
four-week results of a phase III, multicenter, randomized, double-
blind, placebo-controlled study of golimumab before methotrexate as
2009;60(8):2272-2283.

3. Quinn MA, Conaghan PG, O’Connor PJ, Karim Z, Greenstein A,
Brown A, et al. Very early treatment with infliximab in addition to
methotrexate in early, poor-prognosis rheumatoid arthritis reduces
magnetic resonance imaging evidence of synovitis and damage, with
sustained benefit after infliximab withdrawal: Results from a twelve-
month randomized, double-blind, placebo-controlled trial. Arthritis

4. St. Clair EW, van der Heijde DMFM, Smolen JS, Maini RN,
Bathon JM, Emery P, et al. Combination of infliximab and metho-
trexate therapy for early rheumatoid arthritis: A randomized, controlled

5. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y,
Teoh LS, et al. Radiographic, clinical, and functional outcomes of
treatment with adalimumab (a human anti-tumor necrosis factor
monoclonal antibody) in patients with active rheumatoid arthritis
receiving concomitant methotrexate therapy: A randomized, placebo-

6. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA,
Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis
factor-alpha monoclonal antibody, and concomitant standard anti-
rheumatic therapy for the treatment of rheumatoid arthritis: results of
STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis).

7. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazone-Palazuelos F,
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