Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial

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Summary

Background Biological agents offer good control of rheumatoid arthritis, but the long-term benefits of achieving low disease activity with a biological agent plus methotrexate or methotrexate alone are unclear. The OPTIMA trial assessed different treatment adjustment strategies in patients with early rheumatoid arthritis attaining (or not) stable low disease activity with adalimumab plus methotrexate or methotrexate monotherapy.

Methods This trial was done at 161 sites worldwide. Patients with early (<1 year duration) rheumatoid arthritis naïve to methotrexate were randomly allocated (by interactive voice response system, in a 1:1 ratio, block size four) to adalimumab (40 mg every other week) plus methotrexate (initiated at 7.5 mg/week, increased by 2.5 mg every 1–2 weeks to a maximum weekly dose of 20 mg by week 8) or placebo plus methotrexate for 26 weeks (period 1). Patients in the adalimumab plus methotrexate group who completed period 1 and achieved the stable low disease activity target (28-joint disease activity score with C-reactive protein [DAS28]<3.2 at weeks 22 and 26) were randomised to adalimumab-continuation or adalimumab-withdrawal for an additional 52 weeks (period 2). Patients achieving the target with initial methotrexate continued methotrexate-monotherapy. Inadequate responders were offered adalimumab plus methotrexate. All patients and investigators were masked to treatment allocation in period 1. During period 2, treatment reallocation of patients who achieved the target was masked to patients and investigators; patients who did not achieve the target remained masked to original randomisation, but were aware of the subsequent assignment. The primary endpoint was a composite measure of DAS28 of less than 3.2 at week 78 and radiographic non-progression from baseline to week 78, compared between adalimumab-continuation and methotrexate-monotherapy. Adverse events were monitored throughout period 2. This trial is registered with ClinicalTrials.gov, number NCT00420927.

Findings The study was done between Dec 28, 2006, and Aug 3, 2010. 1636 patients were assessed and 1032 were randomised in period 1 (515 to adalimumab plus methotrexate; 517 to placebo plus methotrexate). 466 patients in the adalimumab plus methotrexate group completed period 1; 207 achieved the stable low disease activity target, of whom 105 were rerandomised to adalimumab-continuation. 460 patients in the placebo plus methotrexate completed period 1; 112 achieved the stable low disease activity target and continued methotrexate-monotherapy. 73 of 105 (70%) patients in the adalimumab-continuation group and 61 of 112 (54%) patients in the methotrexate-monotherapy group achieved the primary endpoint at week 78 (mean difference 15% [95% CI 2–28%], p=0.0225). Patients achieving the stable low disease activity target on adalimumab plus methotrexate who withdrew adalimumab mostly maintained their good responses. Overall, 706 of 926 patients in period 2 had an adverse event, of which 52 were deemed serious; however, distribution of adverse events did not differ between groups.

Interpretation Treatment to a stable low disease activity target resulted in improved clinical, functional, and structural outcomes, with both adalimumab-continuation and methotrexate-monotherapy. However, a higher proportion of patients treated with initial adalimumab plus methotrexate achieved the low disease activity target compared with those initially treated with methotrexate alone. Outcomes were much the same whether adalimumab was continued or withdrawn in patients who initially responded to adalimumab plus methotrexate.

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Introduction Rheumatoid arthritis is characterised by an imbalance in the activities of inflammatory cytokines, such as tumour necrosis factor and interleukin 6, within the synovial tissue of affected joints. It occurs in an estimated 0·5–1·0% of the general population, with a higher prevalence in women than in men.1 Biological disease-modifying anti-rheumatic drugs, such as inhibitors of tumour necrosis factor, have greatly improved the treatment of patients with rheumatoid arthritis, and methotrexate remains the traditional anchor therapy. Timely initiation of biological therapy,2,3 with rapid


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attainment of a clinical target (eg, remission or low disease activity), minimises joint damage and preserves physical function. Nevertheless, information about the most effective use of biological agents, notably the best possible time to initiate and potential consequences of later withdrawal of these treatments, is unavailable. The European League Against Rheumatism (EULAR) recommends considering withdrawal of biological agents after attainment of a good clinical state, mainly on the basis of consensus findings. However, evidence from large controlled trials, in particular for patients with early disease, is scarce.

We therefore designed the OPTIMA (Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab) trial to assess the clinical, radiographic, and functional outcomes of several therapeutic approaches in patients with early rheumatoid arthritis who had, or had not, initially achieved stable low disease activity. We tested the hypothesis that among patients who initially achieved a target of stable low disease activity, those receiving initial combination therapy with adalimumab plus methotrexate would have better clinical and radiographic outcomes than those receiving methotrexate alone. Additionally, we explored the hypothesis that therapeutic responses would be maintained after withdrawal of adalimumab in patients who initially responded to adalimumab plus methotrexate. In a post-hoc exploratory analysis, we assessed the effects of addition of adalimumab to the treatment regimens of patients who did not achieve stable low disease activity with initial placebo plus methotrexate.

**Methods**

**Study design and participants**

OPTIMA was a 78-week randomised, double-period, double-blind study, done at 161 sites (including academic hospitals and research centres, private practices, and rheumatology clinics) across Europe (n=71), North America (n=73), South America (n=5), Africa (n=6), Australia (n=3), and New Zealand (n=3). Eligible patients were aged 18 years or older with active rheumatoid arthritis (<1 year duration), according to 1987-revised American College of Rheumatology (ACR) classification criteria. Inclusion criteria enriched the population with patients with highly active disease who are likely to have poor outcomes and rapid, erosive damage. We excluded patients if they had previously received anti-tumour necrosis factor therapy, methotrexate or more than two disease-modifying antirheumatic drugs, or if they were immunocompromised, pregnant, or planning to become pregnant. Cotherapy with non-steroidal anti-inflammatory drugs, or prednisone or a prednisone equivalent (≤10 mg/day), could continue if maintained at a stable dose for 4 weeks or more before baseline. Each site’s institutional review board approved the protocol, and all patients provided written informed consent.

**Procedures**

For the first 26 weeks (period 1), patients were randomised in a 1:1 ratio to adalimumab (40 mg every other week) plus methotrexate (initiated at 7.5 mg/week and increased by 2.5 mg every 1–2 weeks to a maximum weekly dose of 20 mg by week 8) or placebo plus methotrexate. Patients who had, or had not, achieved a stable low disease activity target, defined for this analysis as 28-joint disease activity score (DAS28; based on number of swollen and tender joints, C-reactive protein concentration, and patients’ global assessment of disease activity) of less than 3.2 at weeks 22 and 26 were the focus of the strategic assignments in period 2 (weeks 26–78). Patients in the adalimumab plus methotrexate group reaching this target were rerandomised in a 1:1 ratio to adalimumab-continuation (40 mg every other week plus weekly methotrexate) or adalimumab-withdrawal (placebo every other week plus weekly methotrexate) during period 2; patients in the placebo plus methotrexate group achieving the target continued methotrexate-monotherapy (up to 20 mg weekly). In both groups, patients who did not attain stable low disease activity in period 1 received adalimumab (40 mg every other week) plus methotrexate (up to 20 mg weekly) in period 2; adalimumab-carry-on for patients originally in the adalimumab plus methotrexate group; adalimumab-rescue for those originally in the placebo plus methotrexate group.

Tapering of non-steroidal anti-inflammatory drugs or prednisone or prednisone equivalent could occur after week 26 if at least a 20% reduction from baseline in swollen and tender joints was recorded. Treatment compliance was monitored through dosing diaries, which were tracked against used and unused portions of dispensed drugs. There were no prespecified dose reductions in response to adverse events, with the exception of temporary interruptions in the event of surgery or serious infections necessitating administration of intravenous anti-infectives. Study drug treatment interruptions for more than 60 days necessitated study discontinuation.

The predefined primary endpoint was the proportion of patients with both low disease activity at week 78 and radiographic non-progression from baseline (week 0) to week 78, comparing continuation of adalimumab plus methotrexate with methotrexate-monotherapy in patients who had achieved stable low disease activity. As an important secondary analysis, we assessed the effects of continuation or withdrawal of adalimumab in patients who had achieved stable low disease activity with initial adalimumab plus methotrexate (adalimumab-continuation vs adalimumab-withdrawal) at week 78. Furthermore, we assessed adalimumab efficacy after an inadequate response to placebo plus methotrexate post hoc by comparing 26-week outcomes of addition of adalimumab to methotrexate (adalimumab-rescue, week 52 from baseline vs initial adalimumab plus methotrexate, week 26 from baseline).
A complete list of secondary outcomes is provided in the appendix. We used swollen and tender joint counts, physician’s and patient’s global assessments, C-reactive protein, and physical function (according to the health assessment questionnaire disability index [HAQ-DI]) to assess ACR20/50/70/90/100 response rates and composite measures of disease activity (DAS28, the simplified disease activity index [SDAI], and clinical disease activity index [CDAI]) over time and at week 78. For the purposes of this analysis we defined low disease activity as DAS28 of less than 3·2, SDAI of 11 or lower, or CDAI of 10 or lower; we defined remission as DAS28 of less than 3·2, SDAI of 11 or lower, or CDAI of 2·8 or lower.15 We assessed joint damage as change from baseline in radiographic non-progression (ΔTSS≤0·5) and normal function (HAQ-DI<0·5).

Adverse events in period 1 have been described previously.16 We monitored treatment-emergent adverse events throughout the study and defined them during period 2 by an onset date on or after the first dose of study drug in period 2 and up to 70 days after the last dose. The investigator assessed adverse events for severity (mild, moderate, severe) and relation to study drug (probably related, possibly related, probably not related, not related). The number and percentages of patients with adverse events and events per 100 patient-years are reported by treatment group.

Randomisation and masking

Patients were centrally randomised in blocks of four by interactive voice response system on the basis of information supplied by the investigator. All patients and investigators were masked to treatment allocation in period 1. During period 2, treatment reallocation of patients who achieved the target was also masked to patients and investigators; patients who did not achieve the target remained masked to original randomisation, as did their physicians, but patients and physicians were aware of the subsequent assignment to adalimumab plus methotrexate in period 2.

Statistical analysis

The sample size calculation is shown in the appendix. Unless otherwise indicated, analyses were by intention-to-treat, including all patients who received at least one dose of study drug in period 2. We assessed the primary endpoint using non-responder imputation (NRI) as per the statistical analysis plan and we tested for homogeneity across investigative sites using the Breslow-Day test.16 We used NRI or last observation carried forward (LOCF), or both, for additional clinical outcomes; LOCF was used for functional outcomes. We used the Markov Chain Monte Carlo method to impute missing radiographic data ten times (multiple imputation).17 According to the protocol, period 2 treatment allocation was decided at the week 26 visit (ie, before the availability of week 26 C-reactive protein value). To calculate week 26 DAS28, the C-reactive protein value from the previous visit (ie, week 22) was carried forward, resulting in possible misclassification of some patients in period 2. To account for these misclassifications among adalimumab-continuation and adalimumab-withdrawal comparisons, we present a post-hoc sensitivity analysis, limited to those patients having verified low disease activity at week 26.

We analysed categorical efficacy variables using Pearson’s χ² test; assessments of DAS28, SDAI, CDAI, HAQ-DI, and TSS scores were based on an ANCOVA model, adjusting for baseline measurements of these scores. All statistical tests were two-sided. Secondary efficacy variables were not ranked; no statistical multiplicity adjustment was done. Statistical analyses were prepared using SAS (version 9.1 or later).

This trial is registered with ClinicalTrials.gov, number NCT00420927.

Role of the funding source

OPTIMA was designed and the data were analysed by the sponsor, AbBiVie, in collaboration with the principal investigators (JSS and AK). AbBiVie participated in the interpretation of data, review, and approval of the report. An initial draft of the report was prepared under the authors’ guidance by a professional medical writer, employed by the sponsor. Two employees of the sponsor helped to write subsequent drafts. All authors participated in collection and interpretation of the data, contributed substantially to report drafts, and agreed to submit the report for publication. All authors had full access to the data and vouch for accuracy and completeness of the data and analyses.

Results

The study was done between Dec 28, 2006, and Aug 3, 2010. 1032 patients were enrolled, with 515 being assigned to adalimumab plus methotrexate and 517 to placebo plus methotrexate (figure 1). 466 patients in the adalimumab plus methotrexate group completed period 1, of whom 207 (44%) satisfied the stable low disease activity target; 105 were rerandomised to adalimumab-continuation and 102 to adalimumab-withdrawal. 460 participants in the placebo plus methotrexate group completed period 1, of whom 112 (24%) satisfied the target and continued to receive methotrexate-monotherapy; those who did not (348 of 460, 76%) received open-label adalimumab plus methotrexate (adalimumab-rescue). Overall, 792 of 926 (86%) patients completed period 2. The primary frequencies of, and reasons for, discontinuation during period 2 were much the same among all groups (figure 1).

At baseline (week 0), patients had about 4 months of active disease and several risk factors for aggressive rheumatoid arthritis (table 1), with more than 60%...
having evidence of erosive joint damage. Patients who did not reach the stable low disease activity target in period 1 had significantly higher levels of disease activity and disability at baseline than those who met the target (table 1). Disease activity was lower at the onset of period 2 across all treatment groups than at baseline.

A signifi cantly higher proportion of patients who had attained stable low disease activity at weeks 22 and 26 achieved the primary composite endpoint (DAS28 <3·2 at week 78 and ΔTSS≤0·5 from baseline to week 78) with adalimumab-continuation (73 of 105, 70%) than with methotrexate-monotherapy (61 of 112, 54%; mean difference 15% [95% CI 2–28%], p=0·0225; appendix). This advantage persisted in a post-hoc multiple regression analysis (adjusted odds ratio 2·18 [95% CI 1·19–4·01], p=0·0121) and across investigative sites (p=0·3816 for differences between sites). In both groups, the clinical responses achieved at week 26 were mostly maintained to week 78 (figure 2; appendix).

Although signifi cantly more patients in the adalimumab-continuation group achieved higher levels of clinical response at week 78 using both LOCF (figure 2A–G; appendix) and NRI (appendix), we identified only small increases in radiographic progression with continued methotrexate-monotherapy over 78 weeks (figure 2H), which were not statistically different from changes identifi ed with adalimumab-continuation at week 78 (p=0·5065; post-hoc analysis of number needed to treat to prevent a 1 unit increase in TSS in one patient=15). Nevertheless, a somewhat higher proportion of patients in the adalimumab-continuation group (92 of 103, 89%) did not progress radiographically (ΔTSS≤0·5) compared with those in the methotrexate-monotherapy group (85 of 109, 78%, p=0·0185; appendix). In line with these radiographic fi ndings, week 78
functional improvements were much the same between adalimumab-continuation and methotrexate-monotherapy (HAQ-DI<0·5: 70 of 105 [67%] with adalimumab-continuation and 72 of 112 [64%] with methotrexate-monotherapy, p=0·7127; mean HAQ-DI: 0·35 [SD 0·52] with adalimumab-continuation and 0·39 [0·49] with methotrexate-monotherapy, p=0·5894). Thus, attainment of stable low disease activity within 6 months leads to robust outcomes irrespective of treatment type; however, importantly, nearly twice as many patients initiated with adalimumab plus methotrexate reached the low disease activity target compared with those initiated with placebo plus methotrexate.10 Adalimumab-withdrawal was associated with small and clinically insignificant mean increases in disease activity and HAQ-DI from week 26 to 78, which were not identified for adalimumab-continuation (appendix). Nevertheless, most patients who withdrew adalimumab sustained their clinical responses up to week 78 (figure 2A–C; appendix), although we identified a (non-significant) numerical

<p>| Table 1: Demographics, previous and concomitant therapies, and disease characteristics |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
<th>Adalimumab-withdrawal (n=102)</th>
<th>Adalimumab-continuation (n=105)</th>
<th>Adalimumab-carry-on (n=259)</th>
<th>Methotrexate-monotherapy (n=112)</th>
<th>Adalimumab-rescue (n=348)</th>
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<tbody>
<tr>
<td>Demographics</td>
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<td>Week 26</td>
<td>Baseline</td>
<td>Week 26</td>
<td>Baseline</td>
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<tr>
<td>Women</td>
<td>74 (72.5%)</td>
<td>77 (73.3%)</td>
<td>197 (76.1%)</td>
<td>75 (67.0%)</td>
<td>266 (76.4%)</td>
<td>77 (73.3%)</td>
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<tr>
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<td>94 (89.5%)</td>
<td>220 (88.8%)</td>
<td>104 (92.9%)</td>
<td>313 (89.9%)</td>
<td>94 (89.5%)</td>
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<tr>
<td>Age (years)</td>
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<td>49.5 (15.3)</td>
<td>50.4 (13.9)</td>
<td>48.5 (12.9)</td>
<td>50.7 (13.9)</td>
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<tr>
<td>Rheumatoid arthritis duration (months)</td>
<td>3.9 (3.3)</td>
<td>3.9 (2.9)</td>
<td>3.9 (3.2)</td>
<td>4.0 (2.6)</td>
<td>4.1 (3.2)</td>
<td>3.9 (2.9)</td>
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</tbody>
</table>

Data are n (%) or mean (SD). p values are baseline comparisons across groups. CRP=C-reactive protein. DMARD=disease-modifying anti-rheumatic drug. DAS28=28-joint count disease activity score with CRP. SDAI=simplified disease activity index. TSS=modified total Sharp score. HAQ-DI=health assessment questionnaire disability index. * Differences at baseline between the five treatment groups by ANOVA or χ². ** Differences at baseline between the five treatment groups by ANOVA or χ².
Figure 2: Clinical and radiographic outcomes in patients who achieved the target of DAS of less than 3.2 at weeks 22 and 26

The proportions of patients who achieved (A) 20%, (B) 50%, and (C) 70% improvement in ACR response criteria, (D–F) low disease activity and remission by DAS28, and (G–H) low disease activity and remission by SDAI, up to week 78.

(H) Mean change from baseline to week 78 in TSS. Bars are 95% CIs. 44% (207 of 466) of patients randomised to adalimumab plus methotrexate and 24% (112 of 460) of those randomised to placebo plus methotrexate, achieved stable low disease activity. ACR=American College of Rheumatology. DAS28=28-joint disease activity score with C-reactive protein. SDAI=simplified disease activity index. ΔTSS=change in modified total Sharp score. *p<0.0001; †p<0.05; ‡p<0.001; §p<0.05; ¶p<0.001 comparing adalimumab-continuation with methotrexate-monotherapy (last observation carried forward analyses); exact p values provided in appendix; all other comparisons are non-significant.
advantage in ACR response for adalimumab-continuation. A significantly higher proportion of patients who continued, rather than withdrew, adalimumab maintained DAS28 states at week 78 for both DAS28 of less than 3·2 (96 of 105 [91%] vs 82 of 101 [81%], p=0·0361) and DAS28 of less than 2·6 (90 of 105 [86%] vs 67 of 101 [66%], p=0·0014; figure 2D–E). However, much the same proportions of patients in both groups achieved SDAI low disease activity (97 of 105 [92%] for adalimumab-continuation vs 85 of 101 [84%] for adalimumab-withdrawal; p=0·0659) or remission (65 of 105 [62%] vs 51 of 101 [50%}; p=0·0988) at week 78 (figure 2F–G), although significant differences between the intention-to-treat adalimumab-continuation and adalimumab-withdrawal populations were apparent during period 2 (figure 2G). Similar clinical outcomes were obtained when the data were analysed by NRI (appendix). The functional improvements identified at week 26 were maintained with adalimumab-withdrawal and were much the same as those identified with adalimumab-continuation, as mentioned previously; with adalimumab-withdrawal, 72 of 102 (71%) patients exhibited normal function, and mean HAQ-DI was 0·38 (SD 0·58) at week 78.

Despite randomisation, significant differences in the proportions with low disease activity were apparent between the adalimumab-continuation and adalimumab-withdrawal groups at the beginning of period 2, with a lower proportion of participants in the adalimumab-withdrawal group starting with low disease activity at week 26 (94 of 102 [92%] vs 104 of 105 [99%], p=0·0416; figure 2D).

A post-hoc sensitivity analysis assessing only those patients with confirmed stable low disease activity at weeks 22 and 26 showed that 95 of 103 (92%) patients in the adalimumab-continuation group and 75 of 90 (83%) patients in the adalimumab-withdrawal group had main-
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was maintained in most participants who withdrew (51%; p=0.0926). Thus, although the degree of response indicating continuing improvement, were identified with as baseline, substantial ACR20/50/70 responses, increased up to week 78 (figure 3). Resetting week 26 for 26 weeks during period 1, and these improvements occurring between weeks 26 and 52 in the adalimumab-continued combination therapy.

Naive patients who received adalimumab plus methotrexate, period 1), and similar percentages of patients attained the assessed definitions of low disease activity or remission (figure 3B). The significance of serious infections was 3.9% with adalimumab-rescue up to week 78 (appendix).

In a post-hoc exploratory analysis, clinical improvements occurring between weeks 26 and 52 in the adalimumab-rescue group were much the same as those of methotrexate-naive patients who received adalimumab plus methotrexate for 26 weeks during period 1, and these improvements increased up to week 78 (figure 3). Resetting week 26 as baseline, substantial ACR20/50/70 responses, indicating continuing improvement, were identified with adalimumab-rescue up to week 78 (appendix). Similarly, mean DAS28 values were much the same after the first 26 weeks of adalimumab plus methotrexate treatment (3.27 [SD 1.27] for adalimumab-rescue; 3.32 [1.44] for adalimumab plus methotrexate, period 1), and similar percentages of patients attained the assessed definitions of low disease activity or remission (figure 3B). The significant radiographic progression (mean ΔTSS 1.2 [SD 4.22]) occurring during the initial 26 weeks of placebo plus methotrexate therapy was, on average, halted after adalimumab addition (mean ΔTSS 0.1 from week 26 to 78; appendix), and the risk of high damage accrual (ΔTSS≥1.5 in 26 weeks, 28 of 332 [8%] for adalimumab-rescue vs 77 of 348 [22%] for placebo plus methotrexate) was restricted to the first 26 weeks. Moreover, about the same proportions in each group had normal function after 26 weeks of adalimumab treatment (125 of 348 [36%] for adalimumab-rescue vs 226 of 513 [44%] for adalimumab plus methotrexate, period 1); mean HAQ-DI for adalimumab-rescue was 0.79 (SD 0.61) and 0.72 (SD 0.68) for adalimumab plus methotrexate, period 1. Functional improvements after the addition of adalimumab were sustained with adalimumab-rescue up to week 78 (appendix).

Overall, 706 of 926 patients in period 2 had an adverse event, of which 82 were deemed serious. The frequencies of, and discontinuations attributable to, adverse events were generally much the same across treatment groups during period 2 (table 2), and event profiles were consistent with those known for adalimumab (appendix). Adverse event rates per 100 patient-years were somewhat higher in the adalimumab-carry-on and adalimumab-rescue groups than in the other groups (appendix). The frequency of serious infections was 3.9% with adalimumab-withdrawal and 5.7% with adalimumab-continuation versus 1.5–2.3% for the other groups; however, no clear pattern based on exposure to adalimumab was evident. Frequencies of malignancies were much the same among groups (appendix). One patient in the adalimumab-carry-on group and two patients in the adalimumab-rescue group died after stopping study drug (adalimumab-carry-on: 56-year-old man whose cause of death was listed as a possible cerebrovascular accident 66 days after stopping treatment; adalimumab-rescue: 78-year-old woman died of pulmonary aspergillosis 36 days after stopping treatment, and 68-year-old woman died from pneumonia 9 days after stopping treatment).

**Discussion**

Among patients who satisfied the stable low disease activity target at week 26, continued adalimumab plus methotrexate resulted in a significantly higher proportion achieving the composite endpoint of DAS28 of less than 2.6 at week 78 (87% vs 77% of patients in the adalimumab-withdrawal and adalimumab-cont"
than 3.2 with radiographic non-progression at week 78 compared with continued methotrexate monotherapy. Nevertheless, overall progression rates were modest and statistically much the same among responder populations. The differences between combination therapy and methotrexate monotherapy during the first 26 weeks accounted for the bulk of the treatment effect, since both groups maintained good clinical, radiographic, and functional outcomes between weeks 26 and 78, showing that attainment of stable low disease activity within 6 months of treatment onset conveys good subsequent outcomes irrespective of the type of treatment.

Importantly, induction of stable low disease activity within 6 months with adalimumab plus methotrexate combination therapy followed by withdrawal of adalimumab might constitute a novel treatment strategy for patients with early disease. From a post-hoc sensitivity analysis assessing only those patients with confirmed stable low disease activity at weeks 22 and 26, loss of response after adalimumab withdrawal appeared minimal, and most patients were able to maintain low disease activity without significant radiographic consequences for 1 year. However, since the induction phase employing adalimumab plus methotrexate conveyed nearly twice as many stable low disease activity outcomes at week 26 as did methotrexate monotherapy, substantial proportions of patients seemed to have benefited from induction with combination therapy. Nevertheless, an estimated one in 11 patients might have benefited from further treatment adjustment (eg, addition of disease-modifying antirheumatic drugs or glucocorticoids, or resumption of adalimumab) after adalimumab withdrawal. The fact that withdrawal of the biological agent did not result in a significant loss in the proportion of responders shows that initial short-term combination therapy followed by methotrexate monotherapy induces proportionally larger and greater sustained improvements than does initiation with methotrexate monotherapy. These findings contrast with studies of patients with more long-standing or methotrexate-resistant disease who had disease flare-up and more pronounced radiographic progression after withdrawal of inhibitors of tumour necrosis factor.24–28 Early intervention with adalimumab plus methotrexate in this study might have occurred during a window of opportunity enabling successful adalimumab withdrawal. The benefits afforded by such an induction-maintenance strategy might represent a shift in the present framework of management of early rheumatoid arthritis (panel 7). Longer-term follow-up is needed to establish whether the sustained outcomes identified for 1 year are maintained in this chronic disease.

Long-term disease control was much the same whether methotrexate-naive patients initially received adalimumab plus methotrexate or adalimumab was added after incomplete disease control after 6 months of methotrexate monotherapy. Importantly, adalimumab halted further radiographic progression in these patients. Furthermore, the stringent ACR-EULAR index-based remission criteria using SDAI22 were fulfilled in about the same proportions of patients in this comparison. All these results support existing treatment recommendations,1,8 provide important insights into the optimum treatment approach with traditional and biological agents,3,28 and suggest that stable low disease activity or remission, and, if this target is not attained, adding an inhibitor of tumour necrosis factor in patients with poor prognostic markers. The recommendations also propose withdrawal of the biological agent when a good clinical state has been achieved; however, that specific point was not based on evidence, because no double-blind, placebo-controlled trials had addressed this important issue.8 Also, these recommendations do not advocate the use of biological agents as part of an initial disease-modifying antirheumatic drug therapy, assuming that rapid addition of a biological agent in insufficient responders to methotrexate would provide much the same benefit as using combination treatment with a biological agent from the start. The EULAR recommendations were based on systematic literature reviews, although because a paucity of relevant evidence, many items were solely derived from expert opinion. Since the time of publication, data from a double-blind, randomised, controlled clinical trial24 in patients with established rheumatoid arthritis have shown that withdrawing an inhibitor of tumour necrosis factor mostly results in reactivation of disease. However, several uncontrolled or observational studies have suggested that, in patients with early rheumatoid arthritis, withdrawal of the biological agent might be possible to an extent greater than in established rheumatoid arthritis. For example, after reaching low disease activity or remission upon initial treatment with a biological agent in combination with methotrexate, there might be maintenance of the good initial response even after the biological agent has been withdrawn. These data have been recently reviewed,4 therefore, no additional systematic review was done for the present study. Importantly, the possibility for withdrawal of inhibitors of tumour necrosis factor in comparison with their continuation has not been assessed in a large randomised controlled trial in patients with early rheumatoid arthritis until now. This question constitutes a major focus of the present study.

Interpretation
The results of our double-blind, randomised, placebo-controlled trial suggest that in most patients with early (<1 year disease duration) rheumatoid arthritis who have achieved a stable low disease activity with a 6 month course of therapy with adalimumab plus methotrexate, the good response will be maintained clinically, functionally, and structurally even when adalimumab is withdrawn. This finding suggests that a short course of an induction therapy using a biological agent in combination with methotrexate might be sufficient to allow maintenance of low disease activity or remission upon continuation of methotrexate only. This outcome has great implications for care of patients and economic aspects of treatment of rheumatoid arthritis with expensive biological agents, and could lead to changes in existing treatment frameworks. Moreover, we showed that in early rheumatoid arthritis, introduction of a biological agent after an insufficient response to methotrexate is a reasonable strategy. Thus, in our study, addition of adalimumab in patients who did not achieve stable low disease activity after 6 months’ treatment with methotrexate monotherapy conveyed much the same results at the end of the subsequent year of follow-up as using combination therapy from the very beginning. This finding provides evidence that a treat-to-target approach early in the disease course can result in excellent outcomes in rheumatoid arthritis even if initial therapy with a traditional synthetic disease-modifying antirheumatic drug has resulted in an insufficient clinical, functional, and structural response.
disease activity might be an appropriate treatment target for achieving optimum long-term therapeutic outcomes in many patients with early rheumatoid arthritis.

Although these results are in accordance with other studies,16–18 which have shown that treating patients early in the course of disease leads to improved outcomes, the strategy to begin treatment with an inhibitor of tumour necrosis factor in patients who did not obtain stable low disease activity by week 26 with methotrexate monotherapy had not been previously tested in a group of patients whose disease duration at study initiation was only about 4 months. These results are also in line with data from some studies of patients with long-standing and active disease despite extended periods of methotrexate therapy19,20 and the improved efficacy of strategic treatment approaches with or without biological agents.21–25 However, these findings contrast with those from patients with early rheumatoid arthritis receiving inhibitors of tumour necrosis factor only after 1 or 2 years of methotrexate, strategies that were associated with poorer structural outcomes.26–29 Thus, delays in treatment intensification beyond 6 months in methotrexate-treated patients who did not achieve low disease activity might be associated with significant long-term effects on joint damage and physical function. Notwithstanding the potential new framework of short-term induction therapy discussed previously, this finding provides reassurance that application of the existing EULAR recommendations, which suggest therapy initiation in patients with early rheumatoid arthritis with methotrexate monotherapy followed by the addition of a biological in patients with poor prognostic markers at 6 months, lead to clinical outcomes that are not surpassed by initial biological therapy. Thus, sequential, timely intensification of therapy is highly effective.

We noted no clear pattern in the frequency of adverse events during period 2 on the basis of different exposures to adalimumab plus methotrexate and methotrexate alone, and the adverse events for adalimumab were consistent with its known safety profile.14 Although more deaths were recorded with adalimumab plus methotrexate treatment during period 1 than with placebo plus methotrexate,15 this pattern was not identified in period 2.

Our study has some limitations. Patients who failed to attain the stable low disease activity target received open-label adalimumab; however, patients and assessors remained masked to period 1 treatment, and therefore the insights gained seem pertinent and helpful, especially since radiographic assessments were masked. Increased proportions of responders might have been identified had the protocol allowed for escalation of methotrexate beyond 20 mg weekly, since higher doses typically provide better disease control, although more tolerability issues might have been noted. The addition of glucocorticoids in the placebo plus methotrexate group might have increased the attainment of low disease activity, as in several other studies,12,13,15 however, tapering of glucocorticoids has been associated with reactivation of disease activity.19 Other treatment methods, such as step-up combination therapy with traditional synthetic disease modifying antirheumatic drugs, are recognised options when methotrexate monotherapy fails.14,26 However, the EULAR recommends this option mainly for patients who do not have traditional risk factors,26 a population not studied in OPTIMA. Follow-up beyond 78 weeks will be needed to fully appraise the efficacy of biological withdrawal. Results from this population of patients with early, aggressive disease might not necessarily be applicable to patients with long-standing disease. The manner in which patients were rerandomised after 26 weeks was associated with misclassification of some patients during period 2, but misclassifications were accounted for in a post-hoc sensitivity analysis.

Several questions were not addressed in OPTIMA: whether disease control can be recaptured by adalimumab reinstition in patients who have disease flare-ups after adalimumab withdrawal; whether patients starting adalimumab after a 6 month delay can withdraw adalimumab after 6 months of treatment as successfully as those initially starting adalimumab plus methotrexate therapy; whether results might have been affected by the target selected, specifically low disease activity versus stringent remission; and whether methotrexate can be withdrawn or reduced in patients attaining stable low disease activity with methotrexate monotherapy or who maintained low disease activity after adalimumab withdrawal. Notably, in open-label studies, good outcomes are noted upon reintroduction of inhibitors of tumour necrosis factor in patients who had disease flare-ups after their withdrawal.21

Contributors
All authors contributed to collection and interpretation of data, contributed substantially to drafts of the report, and agreed to submit the report for publication. All authors had full access to the data and vouch for accuracy and completeness of the data and analyses.

Conflicts of interest
JSS has received grant fees, research fees, consulting fees, or other remuneration from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Centocor-Janssen, GlaxoSmithKline, Lilly, Pfizer (Wyeth), MSD (Scherling-Plough), Novo-Nordisk, Roche, Sandoz, and UCB. PE has provided paid expert advice and has done trials for AbbVie, Merck, Pfizer, Roche, UCB, Celgene, Centocor-Janssen, Amgen, AstraZeneca, Bristol-Myers Squibb, Lilly, and Novartis. RFvV has served as a consultant for, or received grant or research support from, AbbVie, GlaxoSmithKline, Merck, Pfizer, Roche, and UCB. RF has received research grants and consulting fees or other remuneration from Amgen, Pfizer, Roche, UCB, and Bristol-Myers Squibb. PD has served on speaker’s bureaus for BMS, BG, HK, and VA are shareholders and employees of AbbVie. LR is a former employee of AbbVie. AK has received grant fees, research fees, or provided paid expert advice to AbbVie, Amgen, Astra-Zeneca, Bristol-Myers Squibb, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB.

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