Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study

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Objective: To determine the efficacy and safety of etanercept and etanercept plus sulfasalazine versus sulfasalazine in patients with rheumatoid arthritis (RA) despite sulfasalazine therapy.

Methods: Patients were randomly assigned to etanercept (25 mg twice weekly; sulfasalazine was discontinued at baseline), etanercept plus sulfasalazine (unchanged regimen of 2–3 g/day) or sulfasalazine in a double-blind, randomised, 2-year study in adult patients with active RA despite sulfasalazine therapy. Efficacy was assessed using the American College of Rheumatology criteria, disease activity scores (DAS) and patient-reported outcomes (PRO).

Results: Demographic variables and baseline disease characteristics were comparable among treatment groups; mean DAS 5.1, 5.2 and 5.1 for etanercept (n = 103), etanercept plus sulfasalazine (n = 101) and sulfasalazine (n = 50), respectively. Withdrawal due to lack of efficacy was highest with sulfasalazine (26% (52%) vs 6% (6%) for either etanercept group, p<0.001). Patients receiving etanercept or etanercept plus sulfasalazine had a more rapid initial response, which was sustained at 2 years, than those receiving sulfasalazine: mean DAS 2.8, 2.5 versus 4.5, respectively (p<0.05); ACR 20 response was achieved by 67%, 77% versus 34% of patients, respectively (p<0.01). Overall, PRO followed a similar pattern; a clinically significant improvement in health assessment questionnaire was achieved by 76%, 78% versus 40% of patients, respectively (p<0.01). Commonly reported adverse events occurring in the etanercept groups were injection site reactions and pharyngitis/tonsillitis (p<0.01).

Conclusion: Etanercept and etanercept plus sulfasalazine are efficacious for the long-term management of patients with RA. The addition of etanercept or substitution with etanercept should be considered as treatment options for patients not adequately responding to sulfasalazine.

PATIENTS AND METHODS

Study design and patients

This was a 2-year randomised, double-blind, double-dummy, multicentre study in patients with active RA who had an inadequate response to sulfasalazine.

Eligible patients were 18 years of age or older with disease duration of 20 years or less with active adult-onset RA (functional class I–III), defined as six or more swollen and 10 or more tender joints and one or more of the following: erythrocyte sedimentation rate (ESR; Westergren) ≥28 mm at the end of the first hour; serum C-reactive protein ≥20 mg/l and morning stiffness for 45 minutes or longer. Patients must have received stable doses of sulfasalazine (2–3 g daily) for 4 months or more before screening. Details of the exclusion/inclusion criteria have been published previously.10

This study was conducted in accordance with the International Conference on Harmonisation guidelines for good clinical practice in the European Community and the Declaration of Helsinki. Ethics committees of the participating centres approved the study protocol. Patients gave written informed consent before participating in the study.

Treatment

Patients were randomly assigned to one of three treatment groups (in a 2 : 1 : 2 ratio): etanercept (etanercept 25 mg by subcutaneous injection twice

Several options including disease-modifying anti-rheumatic drugs (DMARD), such as methotrexate and sulfasalazine and anti-tumour necrosis factor (TNF) agents such as etanercept, infliximab and adalimumab, are available for the treatment of patients with rheumatoid arthritis (RA). For patients with an inadequate response to DMARD therapy, one recommended therapeutic option is anti-TNF therapy either added to or as a replacement for the existing regimen.1,2

In clinical studies, anti-TNF agents are highly effective and generally well tolerated when added to existing treatment regimens for patients with active RA who do not respond to a DMARD such as methotrexate3,4 or sulfasalazine, another frequently prescribed DMARD. However, there are very few studies assessing the benefits and risks of adding an anti-TNF agent to existing sulfasalazine therapy for patients with RA inadequately responding to sulfasalazine.5–12 Combe et al9 previously reported on the 6-month interim results from the current study; the 6-month results showed that etanercept, in combination with or in place of sulfasalazine, resulted in substantial improvements in RA.10 Both etanercept regimens were well tolerated.10

This 2-year report provides data on the long-term therapeutic response including patient-reported outcomes (PRO) and safety of etanercept, added to or in place of sulfasalazine, versus sulfasalazine alone in patients with active RA, despite stable sulfasalazine therapy.

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Extended report

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Safety assessments were based on reports of adverse events and

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of death, hospitalisation or cancer. An infection was a serious

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treatment groups using

Statistical analysis

The ACR 20, ACR 50 and ACR 70 response rates were analysed

were applied to the HAQ disability index at week 104 were compared

To determine whether PRO closely reflected clinical improve-

weekend plus placebo); sulfasalazine (sulfasalazine 2, 2.5, or 3 g
daily plus placebo) or combination (etanercept plus sulfasala-
zine) therapy. Patients in the etanercept group discontinued

Safety assessments were based on reports of adverse events and

Safety assessments were based on reports of adverse events and laboratory determinations. An event was considered to be a treatment-emergent adverse event (TEAE) if it occurred during the study or if the severity or frequency of a preexisting event increased during the study. A serious adverse event (SAE) included any event resulting in death, hospitalisation or cancer. An infection was a serious infection if reported as an SAE.

Testing for antinuclear, anti-double-stranded DNA, anti-
etanercept and anti-cardiolipin antibodies was performed at screening and at specified visits.

The incidence of malignancies in this study was compared with the incidence estimated from the US National Cancer Institute’s (NCI) surveillance, epidemiology, and end results (SEER) database. The age and sex-specific incidence rates for cancer from the SEER database were applied to the exposure in this study.

Figure 1  Percentage of patients remaining in the study versus time (in weeks). Based on the log-rank test, the p values for the comparisons of the time to discontinuation are <0.001 (sulfasalazine versus etanercept), <0.001 (sulfasalazine versus combination), and 0.06 (etanercept versus combination).

Clinical assessment

Response to therapy was assessed at baseline and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 68, 80, 92 and 104. The primary efficacy endpoint, the percentage of patients achieving 20% or greater improvement, as defined by American College of Rheumatology (ACR) 20 criteria, at week 24, was reported previously.

Key efficacy assessments included ACR response rates (ACR 20, ACR 50 and ACR 70), disease activity score (DAS) and morning stiffness in minutes. Assessments were based on ACR criteria and DAS as previously reported.

PRO measures included the health assessment questionnaire (HAQ) disability index, EQ-5D visual analogue scale (VAS), patient global assessment of overall RA activity (PGAD) and patient general health assessment (GHVAS). The PGAD is recorded on an 11-point numeric rating scale in which a score of 0 means no disease activity and a score of 10 means extreme disease activity. For the GHVAS, patients responded to the question “How do you feel concerning your arthritis?” by marking the appropriate position on a 100-mm VAS ranging from “very well” to “extremely bad.” For both PGAD and GHVAS, lower scores imply better health.

To determine whether PRO closely reflected clinical improvements, the study examined the relationship between changes in health status measures or disability and changes in disease activity. Pearson correlation analysis was performed between the four PRO measures (HAQ, EQ-5D VAS, PGAD and GHVAS) and a measure of disease activity, DAS.

Figure 2  Mean disease activity score (DAS) over time (in weeks; last-observation-carried-forward, modified intent-to-treat analysis). $^*$ Etanercept plus sulfasalazine; $\bullet$ etanercept; $\blacksquare$ sulfasalazine.

Statistical analysis

The ACR 20, ACR 50 and ACR 70 response rates were analysed using the Mantel–Haenszel $\chi^2$ test, stratified by study centre. Changes from baseline in components of the ACR and PRO (HAQ disability index, EQ-5D, GHVAS and PGAD) were analysed with a two-way analysis of covariance with treatments and centre as factors and the baseline as a covariate. Efficacy analyses were based on a modified intent-to-treat population, including patients who received any test article and provided efficacy data at baseline and at any subsequent visit.

The proportions of patients with clinically meaningful changes in the HAQ disability index at week 104 were compared between treatment groups using $\chi^2$ analyses. Pearson correlation analyses were used to assess correlations between DAS and PRO over 104 weeks. The last-observation-carried-forward (LOCF) approach was used to account for missing data points. LOCF imputation was also applied to patients who discontinued for unsatisfactory response. Adverse events were summarised and compared among treatment groups, using $\chi^2$ or Fisher’s exact test. The sample sizes, 100 for the etanercept-alone group and sulfasalazine plus etanercept group versus 50 for the sulfasalazine-alone group, gave approximately 90% power to detect pairwise differences in the ACR 20 response of 33% versus 66% between the monotherapies.

RESULTS

Efficacy

Of the 260 patients who were randomly assigned in the study, 254 patients received one or more test articles (etanercept 103,
The population was predominantly white, female, and had a mean age of 51 years (consistent with the typical RA population). As previously reported, there were no significant differences among the groups in the baseline characteristics with the exception of the percentage of patients receiving previous corticosteroids and the mean number of previous DMARDs.

A total of 96 patients discontinued the study: 38 receiving etanercept, 34 receiving sulfasalazine and 24 receiving combination therapy. Overall, a significantly greater number of the patients who continued on sulfasalazine monotherapy (68%) withdrew from the study compared with those receiving etanercept, either as combination (24%) or replacement (37%) therapy ($p<0.001$); the difference between etanercept and the combination was also significant ($p<0.05$). The most common primary reason for discontinuation, lack of efficacy, led to a significantly higher number of withdrawals in patients receiving sulfasalazine (52%) compared with those receiving either etanercept regimen (6% for each; $p<0.001$). Discontinuations because of adverse events were not significantly different among the groups (8%, 19% and 10%, for the sulfasalazine, etanercept and combination groups, respectively) and there was no trend in the types of adverse events that led to discontinuation in any of the groups.

Times to discontinuation were estimated using the Kaplan–Meier method (fig 1); the combination group had the longest times to discontinuation. Based on the log-rank test, the differences among the three groups were statistically significant ($p<0.001$ for sulfasalazine vs etanercept or combination and $p=0.06$ for etanercept vs the combination).

Disease activity, as assessed by mean DAS, was significantly lower in the groups receiving etanercept than in the group receiving sulfasalazine from week 2 to week 104 ($p<0.01$, fig 2). Significantly lower mean DAS values were observed during weeks 68–104 for the combination group compared with the etanercept-alone group ($p<0.05$). A significantly higher proportion of patients receiving the combination or etanercept had a low level of disease activity (as assessed by DAS $<2.4$) compared with those receiving sulfasalazine after 6 months, which was maintained throughout the 2 years ($p<0.01$); at 2 years, 57.0% of patients receiving combination, 45.6% receiving etanercept and 4.0% receiving sulfasalazine. Likewise, the proportion of patients achieving ACR 20, 50 and 70 responses was significantly lower in the sulfasalazine group compared with the etanercept or combination groups ($p<0.05$ for sulfasalazine vs etanercept).

sulfasalazine 50 and combination 101). The population was predominantly white, female, and had a mean age of 51 years (consistent with the typical RA population). As previously reported, there were no significant differences among the groups in the baseline characteristics with the exception of the percentage of patients receiving previous corticosteroids and the mean number of previous DMARDs. A total of 96 patients discontinued the study: 38 receiving etanercept, 34 receiving sulfasalazine and 24 receiving combination therapy. Overall, a significantly greater number of the patients who continued on sulfasalazine monotherapy (68%) withdrew from the study compared with those receiving etanercept, either as combination (24%) or replacement (37%) therapy ($p<0.001$); the difference between etanercept and the combination was also significant ($p<0.05$). The most common primary reason for discontinuation, lack of efficacy, led to a significantly higher number of withdrawals in patients receiving sulfasalazine (52%) compared with those receiving either etanercept regimen (6% for each; $p<0.001$). Discontinuations because of adverse events were not significantly different among the groups (8%, 19% and 10%, for the sulfasalazine, etanercept and combination groups, respectively) and there was no trend in the types of adverse events that led to discontinuation in any of the groups.

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Disease remission was significantly higher with the etanercept groups compared with the sulfasalazine group (p < 0.01). Treatment response as assessed by ACR 20 was achieved by a significantly higher percentage of patients receiving etanercept, added to or in place of sulfasalazine, compared with those receiving sulfasalazine (p < 0.01 compared with sulfasalazine alone). Similarly, significantly higher proportions of patients receiving etanercept or the combination achieved EQ-5D VAS scores above population norms at week 104 compared with those receiving sulfasalazine (p < 0.01 compared with sulfasalazine alone).

Further analyses revealed that changes in disease activity from baseline to 104 weeks correlated with changes in disability as measured by the HAQ disability index and with changes in health status measures. Pearson correlations between the change from baseline in DAS and HAQ (0.57), PGAD (0.69), EQ-5D VAS (−0.61), or GHVAS (0.67) were all significant (p < 0.001).

Safety

The pattern of adverse events reported during the 2 years of the study was not different from that reported during the first 6 months of the study.19 There were no significant differences between the combination and either monotherapy groups in the overall incidence of non-infectious adverse events (Table 1). However, there were significantly more treatment-emergent infections in patients receiving etanercept than in those receiving sulfasalazine (p < 0.001).

Treatment-emergent infections per patient-year were significantly higher with etanercept (1.72) than with etanercept and sulfasalazine (1.11) or with sulfasalazine (0.86; p < 0.001 overall). There were significant differences between the etanercept group and both the sulfasalazine and combination groups (p < 0.001). Medically important infections occurred in more patients receiving etanercept (11; 10.7%) than in those receiving combination (5; 5%, p not significant) or sulfasalazine (0; p < 0.05). After 352 days receiving combination therapy, one patient was hospitalised and withdrawn from the study and

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**Figure 5** Health status at baseline and week 104 for patients with rheumatoid arthritis receiving etanercept, sulfasalazine, or combination therapy as measured by least squares means for EQ-5D, patient general health assessment (GHVAS) and global assessment of overall rheumatoid arthritis activity (PGAD) (last-observation-carried-forward analysis). (A) EQ-5D; (B) GHVAS; (C) PGAD.
treated with antituberculous drugs following a histological determination of tuberculous lymphadenitis.

There was no clustering of SAE. In the 2 years of the study, 23 patients receiving the combination, 27 receiving etanercept and two receiving sulfasalazine had one or more SAE. Non-infectious SAE were significantly greater in patients receiving the combination group, two (1.9%) in the etanercept group and none in the sulfasalazine group. Across all treatment groups, no subjects developed any NCI grade 3 or 4 WBC abnormalities. No patients withdrew from the study because of this laboratory parameter.

At all scheduled visits, patients receiving the combination had a significantly greater reduction in white blood cell (WBC) counts (mean change from baseline) than those receiving sulfasalazine alone (p = 0.001). In contrast, there was no significant difference in this laboratory parameter between the etanercept and sulfasalazine groups. Across all treatment groups, no subjects developed any NCI grade 3 or 4 WBC abnormalities, except for one subject who had a transient grade 1 WBC abnormality that normalised. All mean WBC counts were within normal limits at all visits.

Leucopenia was reported as a TEAE in eight (7.9%) patients in the combination group, two (1.9%) in the etanercept group and none in the sulfasalazine group (p = 0.01). None of the events of leucopenia were associated with NCI grade 3 or 4 WBC abnormalities, except for one subject who had a transient grade 4 WBC abnormality that normalised. All mean WBC counts were within normal limits at all visits.

Malignancy was diagnosed in two patients receiving etanercept; all events were resolved during the study. The incidence of malignancy observed in this study was compared with the expected incidence based on the US SEER programme. The observed number (1.0) of malignancies in etanercept or combination-treated patients during the entire study was lower than the expected numbers (2.7) based on SEER, which excludes non-melanoma skin cancers.

The second reported death was a patient with interstitial pneumonitis, who had a history of smoking, coronary obstructive pulmonary disease and childhood pneumonia.

No patients developed systemic lupus erythematosus or a lupus-like syndrome, glomerulonephritis, pleuritis, peritonitis, or seizure. There were no reports of central demyelinating diseases in this study. Occurrences of auto-antibodies were not significantly different among groups at baseline and at the last visit.

## DISCUSSION

The results from this 2-year double-blind, randomised study in patients with active RA despite sulfasalazine therapy provide further evidence that etanercept, either alone or when added to existing DMARD therapy, has a favourable long-term safety and efficacy profile. The addition of or switching to etanercept resulted in a rapid and sustained improvement of all clinical efficacy endpoints compared with sulfasalazine alone. The efficacy results were similar in both etanercept groups, indicating that patients inadequately responding to sulfasalazine would benefit by either the addition of etanercept to their existing (sulfasalazine) treatment or by switching from sulfasalazine to etanercept. Treatment with etanercept, sulfasalazine, or

### Table 1 Number (%) of patients with the most common TEAE (≥10% in any treatment group)

<table>
<thead>
<tr>
<th>Body system TEAE</th>
<th>Etanercept (n = 103)</th>
<th>Etanercept + sulfasalazine (n = 101)</th>
<th>Sulfasalazine (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-infectious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE (excluding infection)</td>
<td>90 (87.4)</td>
<td>80 (79.2)</td>
<td>32 (64.0)*</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>34 (33.0)</td>
<td>21 (20.8)</td>
<td>2 (4.0)*†</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (10.7)</td>
<td>25 (24.9)†</td>
<td>4 (8.0)‡</td>
</tr>
<tr>
<td>Back pain</td>
<td>9 (8.7)</td>
<td>20 (19.8)†</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (6.8)</td>
<td>19 (18.8)†</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>16 (15.5)</td>
<td>17 (16.8)</td>
<td>2 (4.0)†‡</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (4.9)</td>
<td>16 (15.8)†</td>
<td>2 (4.0)‡</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (14.6)</td>
<td>8 (7.9)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14 (13.6)</td>
<td>12 (11.9)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (13.6)</td>
<td>12 (11.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>9 (8.7)</td>
<td>14 (13.9)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (7.8)</td>
<td>14 (13.9)</td>
<td>7 (14.0)</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>10 (9.7)</td>
<td>12 (11.9)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Diarhoea</td>
<td>11 (10.7)</td>
<td>6 (5.9)</td>
<td>0.0*</td>
</tr>
<tr>
<td>Cough increased</td>
<td>7 (6.8)</td>
<td>12 (11.9)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>4 (3.9)</td>
<td>11 (10.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td><strong>Infectious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE infection</td>
<td>76 (73.8)</td>
<td>60 (59.4)†</td>
<td>21 (42.0) *</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>29 (28.2)</td>
<td>29 (28.7)</td>
<td>10 (20.0)</td>
</tr>
<tr>
<td>Pharyngitis/laryngitis</td>
<td>24 (23.3)</td>
<td>10 (9.9)</td>
<td>3 (6.0)‡</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>21 (20.4)</td>
<td>12 (11.9)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>18 (17.5)</td>
<td>12 (11.9)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Gingival/dental infection</td>
<td>7 (6.8)</td>
<td>12 (11.9)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>12 (11.7)</td>
<td>3 (3.0)†</td>
<td>0.0*</td>
</tr>
<tr>
<td>Miscellaneous skin infections§</td>
<td>19 (18.4)</td>
<td>12 (11.9)</td>
<td>0.0*‡</td>
</tr>
</tbody>
</table>

Fisher’s exact pairwise comparisons: *p < 0.05 etanercept versus sulfasalazine; †p < 0.05 etanercept versus combination and §p < 0.05 combination versus sulfasalazine. §The types of skin infections included commonly reported events such as acne, phlebitis, fungal infections and nail disorders. TEAE, treatment-emergent adverse event.
the combination did not result in any unexpected safety findings. The combination of etanercept and sulfasalazine was not associated with greater toxicity than either therapy alone.

Modifications to a less than adequate treatment regimen, such as the addition of another agent or substitution of a “failing” drug with another agent, are a standard approach. Clinical studies in patients with RA have shown that adding or substituting an anti-TNF agent to the existing methotrexate therapy \(^5\) \(^7\) \(^9\) \(^10\) \(^20\) results in a significant improvement in the therapeutic response. The addition of an anti-TNF agent to (or in place of) inadequate sulfasalazine has not been extensively evaluated in clinical trials. In the only other placebo-controlled trial in RA patients not adequately treated with sulfasalazine, adalimumab was added to the existing treatment. \(^9\) \(^12\) In that study, patients receiving the combination showed a greater degree of improvement than those receiving sulfasalazine alone. However, modest sample sizes (sulfasalazine alone, n = 33; sulfasalazine plus adalimumab, n = 29) make it difficult to compare the efficacy results among the treatment arms. In a larger open-label study evaluating adalimumab alone and in the combination did not result in any unexpected safety findings. The combination of etanercept and sulfasalazine was not associated with greater toxicity than either therapy alone.

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The use of anti-TNF agents has also been associated with the increased frequency of autoantibodies, which could result in autoimmune diseases such as systemic lupus erythematosus. \(^27\) \(^29\) Although the number of patients who tested positive for anti-dsDNA increased by the end of our study, there were no relevant clinical symptoms associated with the positive autoantibody test results in any of the treatment groups.

Leucopenia, neutropenia, thrombocytopenia and pancytopenia have also been reported in patients receiving anti-TNF therapies. In this study, the incidence of leucopenia was greater in the combination group (7.9%) than in the etanercept group (1.9%) or the sulfasalazine group (0%), but between-group differences were not statistically significant. Investigators categorised the severity of all eight events in the combination group as mild; none of the TEAE of leucopenia were associated with NCI grade 3 or 4 values of neutrophils or with other NCI grade 3 or 4 laboratory abnormalities. No patients withdrew from the study because of leucopenia. The lower WBC counts thus did not seem to be clinically relevant. Furthermore, there were no reports of aplastic anaemia or pancytopenia.

This study shows that the addition of etanercept to sulfasalazine, a DMARD other than methotrexate, can provide significant long-term improvement in efficacy. In particular, it shows that etanercept provides benefit when added to or switched with sulfasalazine in patients who show an inadequate response to sulfasalazine. The reported findings are especially relevant in view of the recent reports regarding monotherapy failures, which discourage the choice of both methotrexate plus sulfasalazine and leflunomide plus sulfasalazine combination therapy. \(^30\) \(^31\) Generally, combination treatment was not associated with an increased incidence of adverse events. Etanercept either alone or added to existing sulfasalazine therapy is associated with a favourable risk benefit profile, thus broadening the range of options for the treatment of patients with active RA.

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Patient consent: Obtained.

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REFERENCES

Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study

B Combe, C Codreanu, U Fiocco, M Gaubitz, P P Geusens, T K Kvien, K Pavelka, P N Sambrook, J S Smolen, R Khandker, A Singh, J Wajdula, S Fatenejad and for the Etanercept European Investigators Network *

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