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REVIEW

Optimal dose of etanercept in the treatment of rheumatoid arthritis

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Abstract: Etanercept (ETN) is one of a number of biological therapies targeting the proinflammatory cytokine tumor necrosis factor-alpha that have demonstrated efficacy in the management of rheumatoid arthritis (RA). As experience has grown, a number of different treatment strategies have been investigated to ascertain the optimal conditions for use of ETN in RA and maximize the clinical gains from therapy. These have included the use of higher- and lower-dose treatment regimens, ETN as a monotherapy or in combination with other nonbiologic disease-modifying antirheumatic drugs, the use of ETN in very early clinical disease, and intraarticular ETN administration for resistant synovitis. Recent trials have focused on phased dose reduction or withdrawal of ETN in patients achieving low disease activity states or clinical remission. This review summarizes existing data regarding the optimal timing of ETN initiation and dosing regimens and also evaluates more recent evidence regarding dose-reduction strategies that offer the possibility of biologic-free remission in RA.

Keywords: rheumatoid arthritis, etanercept, biologics, antirheumatic agents, monoclonal antibodies, anti-TNF

Introduction

Rheumatoid arthritis (RA) is a multisystem, chronic, inflammatory disease associated with progressive joint destruction, deformity, and loss of function. Affected individuals experience significant morbidity, disability,[1] and excess cardiovascular mortality[2] compared with the general population. To prevent joint damage and consequent disability, a "treat to target" approach aiming for early disease remission through the early use of disease-modifying antirheumatic drugs (DMARDs) and biologic therapies has been proposed.[3] Because of the chronic nature of RA, medications are often required for many years, making the long-term efficacy, tolerability, and cost of therapeutic agents important factors to consider when making treatment decisions.

Tumor necrosis factor (TNF) has been identified as a key cytokine in the pathogenesis of RA.[4] Etanercept (ETN; Enbrel®; Immunex, Seattle, WA, USA), a genetically engineered protein consisting of two molecules of the extracellular domain of the TNF receptor 2 (p75) and the Fc portion of immunoglobulin G 1, which binds to and inactivates TNF,[5,6] was approved by the US Food and Drug Administration for the treatment of RA in 1998.

What dose of ETN should be used?

ETN is currently licensed at a dose of 50 mg/week after a number of dose-ranging trials. Moreland et al compared placebo, ETN 10 mg twice weekly (ETN20), and ETN

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25 mg twice weekly (ETN50)[7] in patients with long-standing RA and an inadequate response to DMARDs. Although both treatment arms were significantly better than placebo, ETN50 was significantly more efficacious than ETN20, as measured by American College of Rheumatology[8] 20%, 50%, and 70% improvement criteria (ACR 20/50/70), with a greater proportion of patients achieving ACR50 at 6 months (40% versus [vs] 24%; P=0.032). The superior efficacy of ETN50 over ETN20 was confirmed by Bathon et al the following year.[9]

Subsequently, Keystone et al demonstrated equivalent clinical efficacy between 25 mg twice-weekly and 50 mg once-weekly dosing of ETN, thereby improving the convenience of ETN for patients by reducing the frequency of treatment administration.[10]

Two studies have investigated whether higher doses of ETN are more effective than the standard dose. In a 12-week study, patients who were suboptimal responders to methotrexate (MTX) and ETN50 once weekly were randomized to ETN50 twice weekly (ETN100) plus MTX, or ETN50 once weekly plus MTX. At week 12, there was no statistically significant difference in ACR20/50/70 responses between the two treatment groups (ACR50, 13% vs 8%). The incidence of serious adverse events including serious infections was higher with ETN100, although this difference was not statistically significant.[11] In a smaller, 24-week study of ETN monotherapy after DMARD failure, Johnsen et al compared ETN100 against ETN50. Again, there was no significant difference in clinical efficacy between the two groups (ACR50, 38% vs 37%), but there was a significantly higher incidence of upper respiratory tract infections in the ETN100 treatment group (26% vs 4%; P=0.027).[12]

Is ETN monotherapy better than MTX monotherapy?

Although MTX is effective in slowing the progression of joint destruction and preserving function in early RA,[13] ETN has a faster onset of action, leading investigators to assess its superiority to MTX as initial therapy for RA. Three studies have compared ETN monotherapy with MTX monotherapy for RA (Table 1).

The Enbrel ERA (early rheumatoid arthritis) trial compared the efficacy of ETN50 monotherapy (25 mg bi-weekly [biw]) with MTX monotherapy in patients with early RA.[9] During the first 4 months of therapy, ETN achieved significantly greater ACR20/50/70 response rates compared with MTX, but after 6 months, ETN was not significantly better than MTX. At a 2-year follow-up, only the ACR20 was significantly different between ETN and MTX (72% and 59%, respectively; P=0.005),[14] although ETN demonstrated better outcomes than MTX, as measured by Health Assessment Questionnaire Disability Index (HAQ-DI) score (≥0.5 improvement in HAQ, 55% vs 37%; P<0.001). The proportion of patients with radiographic nonprogression (as measured by ≤0.5 units of change from baseline) in Total Sharp Score (TSS) at 6, 12, and 24 months was also significantly greater for ETN.

Similar findings were reported by the Trial of Etanercept and Methotrexate with Radiographic and Patient Outcomes (TEMPO).[15] Comparing the ETN50 monotherapy (25 mg biw) and MTX monotherapy arms, there was no statistically significant difference in the ACR20/50/70 response at the 52-week endpoint (ACR50, 48% vs 43%) or at the subsequent 2- and 3-year follow-up.[16,17]

Hu et al[18] demonstrated that 50 mg weekly Yisaipu (Shanghai CP Guojian Pharmaceutical Co. Ltd, Shanghai, People's Republic of China) (a recombinant TNF receptor Fc fusion protein available in the People's Republic of China that has the same structure as ETN) had better efficacy than MTX as measured by ACR 20/50/70 responses at 8 weeks. In line with the other monotherapy studies, this difference was ameliorated after 8 weeks, but the ACR70 response was still significantly greater for ETN from week 16 to study end (ACR70 at week 24, 20% vs 11%; P=0.0185).

Is the combination of ETN plus MTX better than MTX monotherapy?

The superior efficacy of ETN50 in combination with MTX (ETN50-MTX) versus MTX monotherapy was first demonstrated by Weinblatt et al.[19] ETN50 (25 mg biw) plus MTX demonstrated significantly better ACR20, ACR50, and ACR70 outcomes at week 24 compared with MTX monotherapy (ACR50, 39% vs 3%, respectively; P<0.001). This finding was confirmed in three subsequent large randomized controlled trials (RCTs) (Table 2).[15,19-20,22]

In TEMPO, patients with active RA were randomized to treatment with ETN50 (25 mg biw) plus MTX, MTX monotherapy, or ETN50 (25 mg biw) monotherapy. At week 52, ACR20/50/70 response rates were all significantly better for combination therapy than MTX monotherapy (ACR 50, 69% vs 43%; P<0.0001).[15] This difference was sustained at the 3-year point (ACR50 67% vs 44%; P<0.01). The proportion of patients in radiographic remission was also significantly better for combination therapy versus MTX monotherapy at 2 years (78% vs 60%; P<0.05)[16] and at 3 years (76% vs 61%; P<0.05).[17]

Superiority of ETN50-MTX over MTX monotherapy was confirmed by the Combination of Methotrexate and

Table 1 ETN monotherapy versus MTX monotherapy studies

Study	Study type	Key inclusion criteria	Number of subjects	Primary endpoint	Outcome	Additional information
Enbrel® ERA[9]	Placebo-controlled, double-blind 3-group RCT; 1-year duration	Disease duration less than 3 years; ETN- and MTX-naïve; high-risk for radiographic progression	Total: 632 patients ETN, 25 mg biw (207 patients): 74% women, 87% RhF-positive, average disease duration 12 months, average CRP 3.3 (mg/L); MTX (217 patients): 75% women; 89% Rhf-positive; average disease duration 12 months; average CRP 3.7 (mg/L)	ACR 20/50/70 response rate	All ACR responses better for ETN in up to 6 months, but only ACR70 better for ETN at 6 months; no difference after 6 months between ETN and MTX; at 2 years, ACR20, HAQ, and rate of radiographic nonprogression are better for ETN	Additional data from Genovese et al[14]
TEMPO, Klareskog et al[15]	Placebo-controlled, double-blind 3-group RCT; 3-year duration	Disease duration from more than 6 months to 20 years or less; failed ×1 DMARD ACR function class 1–3	Total: 682 patients ETN, 25 mg biw (228 patients): 77% women, 75% RhF-positive, average disease duration 76 months, average CRP 32 (mg/L); MTX (223 patients): 79% women, 71% RhF-positive, average disease duration 82 months, average CRP 25.8 (mg/L)	ACR 20/50/70 response rate	No significant differences between ACR 20/50/70 responses at 1, 2, or 3 years' follow-up	Additional data from van der Heijde et al[16,17]
Hu et al[18]	Placebo-controlled, double-blind RCT; 24-week duration	Active RA: ≥6 swollen joints and ≥6 tender joints plus one of: early-morning stiffness that lasts 45 minutes or longer, ESR of 28 mm/hour or higher, CRP of 20 μg/mL or higher	Total: 238 patients ETN, 50 mg ow (118 patients): 86% women, 89% RhF-positive, average disease duration 91 months, average CRP 26.4 (mg/L); MTX (120 patients): 84% women; 88% RhF-positive; average disease duration 94 months, average CRP 61.4 (mg/L)	ACR 20/50/70 response rate	All ACR responses better for ETN at week 8; only ACR70 response better for ETN at week 24	

Abbreviations: RCT, randomized controlled trial; ETN, etanercept; MTX, methotrexate; RhF, rheumatoid factor; CRP, C-reactive protein; ACR, American College of Rheumatology; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; ESR, erythrocyte sedimentation rate; biw, bi-weekly; ow, once weekly; ERA, early rheumatoid arthritis.

Table 2 ETN and MTX combination therapy versus MTX monotherapy studies

Study	Study type	Key inclusion criteria	Number of subjects	Primary endpoint	Outcome	Additional information
Weinblatt et al[19]	Placebo-controlled, double-blind 2-group RCT; 24-weeks duration	Active RA (≥6 swollen joints and ≥6 tender joints); ACR function class I–3; established on MTX for at least 6 months	Total: 89 patients ETN, 50 mg, and MTX (59 patients): 90% women, 84% RhF-positive, average disease duration 156 months, average CRP 2.2 (mg/L); MTX monotherapy (30 patients): 73% women, 90% Rhf-positive, average disease duration 156 months, average CRP 2.6 (mg/L)	ACR 20/50/70 response rate	ACR 20/50/70 responses all better for combination therapy	
TEMPO, Klareskog et al[15]	Placebo-controlled, double-blind, 3-group RCT; 3-year duration	Disease duration from longer than 6 months to 20 years or less; failed ×1 DMARD ACR function class I–3	Total: 682 patients ETN, 50 mg, and MTX (231 patients): 74% women, 76% RhF-positive, average disease duration 81.6 months, average CRP 29.7 (mg/L); MTX monotherapy (228 patients): 79% women, 71% RhF-positive, average disease duration 81.6 months, average CRP 25.8 (mg/L)	ACR 20/50/70 response rate	ACR 20/50/70 responses all better at 1, 2, and 3 years' follow-up for combination therapy; radiographic remission (change in TSS ≤0.5) more common with combination therapy at 1, 2, and 3 years' follow-up	Additional data from van der Heijde et al[16,17]
COMET, Emery et al[20]	Placebo-controlled, double-blind RC, 1-year duration	Disease duration 3–24 months; DAS ≥3.2 and ESR ≥28 mm/hour or CRP ≥20 mg/L	Total: 542 patients ETN, 50 mg, and MTX (274 patients): 74% women, 67% ACPA positive, average disease duration 8.8 months, average CRP 37 (mg/L) MTX monotherapy (268 patients): 73% women, 70% ACPA positive, average disease duration 9.3 months, average CRP 36.5 (mg/L)	DAS remission (DAS28 <2.6); change in modified TSS	DAS remission more common with combination therapy from week 2 onward; radiographic remission (change in TSS ≤0.5) more common with combination therapy; ACR 20/50/70 responses better for combination therapy	Additional data from Emery et al, 2010[21]
TEAR, Moreland et al[22]	Placebo-controlled, double-blind RCT; 2 × 2 factorial design with step-up to combination therapy at week 24 if DAS >3.2; 2-year duration	Disease duration less than 3 years; Active RA (≥4 swollen joints and ≥4 tender joints); positive for RhF or ACPA (or if negative, ≥2 erosions on X-ray)	Total: 755 patients Initial ETN, 50 mg, and MTX (IE) (244 patients): 74.2% women, 88.5% RhF-positive, average disease duration 3.5 months; initial MTX monotherapy (SE and ST groups) (379 patients): 69.4% women, 89.7% RhF-positive, average disease duration 3.4 months	Observed-group analysis of DAS28 ESR	Patients in the immediate ETN-MTX (IE) combination therapy group had superior ACR 20/50/70 responses and higher rates of DAS28 LDA week 24 compared with MTX monotherapy (step-up) groups	

Abbreviations: RCT, randomized controlled trial; RA, rheumatoid arthritis; ACR, American College of Rheumatology; MTX, methotrexate; ETN, etanercept; RhF, rheumatoid factor; CRP, C-reactive protein; TSS, Total Sharp Score; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; ACPA, anti-citrullinated protein antibody; IE, initial combination therapy group treated with etanercept and methotrexate; SE, step-up group escalated to combination of etanercept and methotrexate from methotrexate monotherapy; ST, step-up group escalated to triple therapy from methotrexate monotherapy.

Etanercept in Active Early Rheumatoid Arthritis (COMET) trial, which randomized patients with moderate to severe early RA to receive ETN50 plus MTX (ETN50-MTX) or MTX monotherapy. Disease Activity Score (DAS) remission (DAS28 <2.6) was significantly more likely with combination therapy from week 2 onward and was almost twice as likely at week 52 compared with MTX monotherapy (50% vs 28%; $P<0.0001$), with significantly higher ACR responses (ACR50, 71% vs 49%; $P<0.0001$) and rates of radiographic remission (80% vs 59%; $P<0.0001$).[20] In post hoc analysis,[21] the subgroup of patients with very early RA (less than 4 months' disease duration) had even better rates of DAS remission at week 52 for both combination therapy and MTX monotherapy (70% and 35%, respectively).

More recently, the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial has compared initial treatment with ETN50-MTX to either MTX monotherapy or triple therapy (MTX, sulfasalazine [SSZ], and hydroxychloroquine [HCQ]) in patients with RA of less than 3 years' duration.[22] Findings at 24 weeks confirmed the superiority of initial combination therapy over MTX monotherapy with better ACR20/50/70 responses (ACR50, 36% vs 22%, respectively; $P<0.0001$) and higher rates of DAS28-ESR low disease activity (LDA: ≤3.2) (41% vs 28% $P<0.0001$).

Is the combination of ETN plus MTX better than ETN monotherapy?

The superiority of ETN50-MTX compared with ETN50 monotherapy was first reported by TEMPO, with significantly greater ACR/20/50/70 responses at both 1 year and 3 years (Table 3). This finding was subsequently confirmed in a Japanese patient cohort by the Japanese Etanercept Study on Methotrexate Resistance (JESMR). Patients with active RA despite MTX were randomized to receive either ETN50 (25 mg biw) plus MTX or ETN50 (25 mg biw) monotherapy. Combination therapy (adding ETN) resulted in better radiographic and clinical outcomes at both week 24 (ACR50 64% vs 48%; $P=0.063$)[23] and week 52 (ACR50 77% vs 44%; $P<0.0001$)[24] compared with ETN monotherapy.

The only study not to demonstrate additional benefit from ETN50-MTX combination therapy over ETN50 monotherapy for MTX nonresponders is the Add Enbrel Or Replace Methotrexate (ADORE) study. Patients with active RA despite MTX were randomized to either the addition of ETN50 (25 mg biw) or a switch to ETN50 monotherapy. After 16 weeks, response rates as measured by ACR 20/50/70 were similar between the two groups.[25]

Is the combination of ETN and MTX better than triple therapy?

The TEAR study (Table 4) took a pragmatic approach to the treatment of early aggressive RA to determine whether initial treatment with ETN50-MTX combination therapy was better than initial triple-therapy (MTX, SSZ, plus HCQ) or MTX monotherapy. At the end of phase I of this study (weeks 1 to 23), there was no significant difference in ACR20/50/70 responses or DAS28-ESR LDA between the initial ETN50-MTX and initial triple-therapy arms.

In phase II (from week 24 onwards), participants in the MTX monotherapy arm with a DAS28-ESR of 3.2 or higher were escalated to either ETN50-MTX (addition of ETN) or triple-therapy (addition of SSZ and HCQ). At week 102, there was no significant difference in mean DAS28-ESR between ETN50-MTX and triple-therapy, although the ACR70 response rate at week 102 was significantly better for ETN50-MTX (18% vs 11%; $P=0.01$). ETN50-MTX therapy was also associated with a significantly higher rate of radiographic remission compared with triple therapy (77% vs 66%; $P=0.02$) at the study end. O'Dell et al[26] have also assessed the efficacy of ETN50-MTX combination therapy versus triple therapy (MTX, SSZ, HCQ) in patients with active RA despite treatment with MTX. In the RA: Comparison of Active Therapies (RACAT) trial, triple therapy was shown to be noninferior to ETN50–MTX combination therapy, with equal failure rates (27% for both groups) and DAS28 improvements (−2.1 vs −2.3, respectively; $P=0.26$) after 48 weeks.[26]

Is ETN effective with DMARDs other than MTX?

The efficacy of ETN in combination with non-MTX DMARDs, including SSZ,[28,29] intramuscular gold, HCQ,[27] and leflunomide (LEF),[30,31] has been examined in a number of small studies. SSZ has been demonstrated to be safe in combination with ETN. Although combination therapy was not demonstrated to be significantly better than ETN monotherapy during the 24-week trial by Combe et al[28] at 2 years, it was associated with a lower withdrawal rate than SSZ monotherapy, suggesting additional benefit (24% vs 37%; $P<0.05$).[29]

Can ETN be reduced or withdrawn for patients with low levels of disease activity?

The advent of biologics therapy has made clinical remission a realistic target for patients with RA. As a consequence,

Table 3 ETN and MTX combination therapy versus ETN monotherapy studies

Study	Study type	Key inclusion criteria	Number of subjects	Primary endpoint	Outcome	Additional information
TEMPO, Klareskog et al[15]	Placebo-controlled, double blind 3-group RCT; 3-year duration	Disease duration longer than 6 months to 20 or fewer years; failed ×1 DMARD ACR function class 1–3	Total: 682 patients ETN, 50 mg, and MTX (231 patients): 74% women, 76% RhF-positive, average disease duration 81.6 months; average CRP 29.7 (mg/L); ETN, 50 mg, monotherapy (223 patients): 79% women, 71% RhF-positive, average disease duration 75.6 months, average CRP 32.0 (mg/L)	ACR 20/50/70 response rate	ACR 20/50/70 responses all better at 1, 2, and 3 years' follow-up for combination therapy; radiographic remission (change in TSS ≤0.5) more common with combination therapy at 1, 2, and 3 years' follow-up	Additional data from van der Heijde et al[16,17]
JESMR, Kameda et al[23,24]	Open-label randomized trial, 24-week duration	MTX therapy ≥3 months; Active RA ≥6 swollen joints and ≥6 tender joints plus CRP ≥2 mg/dL or ESR ≥28 mm/hour; ACR function class 1–3	Total: 147 patients ETN, 50 mg, and MTX (76 patients): 80.3% women, 86.7% RhF-positive, average disease duration 96 months, average CRP 3.0 (mg/L); ETN, 50 mg, monotherapy (71 patients): 87.3% women, 91.5% RhF-positive, average disease duration 127.2 months, average CRP 2.5 (mg/L)	EULAR good response; ACR50 response rate	Significantly higher rate of EULAR good response from week 4 onward with combination therapy; ACR50 response better for combination therapy at week 24 and week 52; DAS remission and LDA at week 24 more likely with combination therapy	
ADORE, van Riel et al[25]	Open-label randomized trial; 16-week duration	ACR function class 1–3; MTX (≥12.5 mg/week) for 3 months or longer; DAS ≥3.2 or 5 or more swollen joints and 5 or more tender joints plus ESR ≥10 mm/hour	Total: 314 patients ETN, 50 mg, and MTX (155 patients): 76.8% women, 69.5% RhF-positive, average disease duration 117.6 months, mean ESR 36.7 mm/hour; ETN, 50 mg, monotherapy (159 patients): 79.2% women, 70.9% RhF-positive, average disease duration 120 months, mean ESR 33.2 mm/hour	Percentage of patients achieving DAS28 reduction greater than 1.2 units	No difference demonstrated between treatment groups for percentage achieving primary endpoint at week 16; no difference demonstrated between treatment groups for ACR 20/50/70 responses; mean ESR improvement greater for combination therapy (−14.6 mm/hour vs −7.8 mm/hour; P=0.001)	Patients in the ETN monotherapy group were initially receiving MTX, which was decreased and discontinued during the first 4 weeks of the study

Abbreviations: RCT, randomized controlled trial; DMARD, disease-modifying antirheumatic drug; ACR, American College of Rheumatology; ETN, etanercept; MTX, methotrexate; RhF, rheumatoid factor; CRP, C-reactive protein; TSS, Total Sharp Score; RA, rheumatoid arthritis; ESR, erythrocyte sedimentation rate; DAS, Disease Activity Score; LDA, low disease activity; EULAR, the European League Against Rheumatism; vs, versus.

Table 4 ETN and MTX combination therapy versus triple therapy (MTX, sulfasalazine and hydroxychloroquine) studies

Study	Study type	Key inclusion criteria	Number of subjects	Primary endpoint	Outcome	Additional information
TEAR (Phase I), Moreland et al[23]	Weeks 1–23 Placebo-controlled, double-blind RCT;2 x 2 factorial design with step-up to combination therapy at week 24 if DAS >3.2	Disease duration <3 years 'Active RA' (≥4 swollen joints and ≥4 tender joints) Positive for RhF or ACPA (or if negative ≥2 erosions on x-ray)	Total: 755 patients Initial ETN, 50 mg, and MTX (IE) (244 patients): 74.2% women, 88.5% RhF-positive, average disease duration 3.5 months; initial triple therapy (IT) (132 patients): 76.5% women, 91.7% RhF-positive, average disease duration 4.1 months	Observed-group analysis of DAS28 ESR	No difference in rate of DAS28ESR LDA or ACR20/50/70 response rates at week 24 between combination therapy groups	Additional data from O'Dell et al[50]
TEAR (Phase II), Moreland et al[23]	Weeks 24-102 Placebo-controlled,double-blind RCT;2 x 2 factorial design with step-up to combination therapy at week 24 if DAS >3.2					
	As above (week 24–102)	As above; patients initially treated with MTX monotherapy who did not achieve DAS28; LDA at week 24 stepped up to either ETN/MTX combination therapy or triple therapy (addition of sulfasalazine and hydroxychloroquine)	Total: 476 patients completed 102 weeks ETN, 50 mg, and MTX (IE, 159 patients; SE, 166 patients; total: 325 patients); triple therapy (IT, 76 patients; ST, 75 patients; total: 151 patients)	As above	At week 102 there was no difference in DAS28–ESR across the 4 treatment groups by medication received (ETN plus MTX vs triple therapy; *P*=0.48) or treatment regimen (immediate vs step-up; *P*=0.55); greater ACR70 responses with ETN-MTX compared with triple therapy (18.2% vs 11.3%; *P*=0.01) at week 102	
RACAT, O'Dell et al[26]	Double-blind, noninferiority trial; 48-week duration	Receiving MTX (15–25 mg weekly) for 12 weeks or longer; DAS28 ≥4.4	Total: 353 patients ETN, 50 mg, and MTX (175 patients): 48.6% women, 66.9% RhF-positive, average disease duration, 58.8 months; triple therapy (178 patients): 43.3% women, 65.7% RhF-positive, average disease duration 66 months	Change in DAS28	Mean difference between group change in DAS28 0.17±0.15; no significant difference in rate of radiographic progression between groups	Noninferiority defined as difference between the groups in the mean change in DAS28 from baseline to week 48 lower than 0.60

Abbreviations: RCT, randomized controlled trial; DAS, Disease Activity Score; RA, rheumatoid arthritis; RhF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; ETN, etanercept; MTX, methotrexate; IE, initial combination therapy group treated with etanercept and methotrexate; IT, initial triple therapy group treated with methotrexate, sulfasalazine, and hydroxychloroquine; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; LDA, low disease activity; ACR, American College of Rheumatology; vs, versus; TEAR, Treatment of Early Aggressive rheumatoid Arthritis; RACAT, Rheumatoid Arthritis: Comparison of Active Therapies in Patients with active disease despite methotrexate therapy.

there is growing interest in the possibility of reducing or even withdrawing biologics for those patients in remission, significantly reducing prescribing costs and the risk for medication-related adverse effects. Following observational data to support dose reduction for patients who achieve remission on biologics,[32] several RCTs (Table 5) are now investigating the feasibility of induction, maintenance, and withdrawal of biologics, including ETN, for patients with RA achieving disease remission or LDA.

In the PRESERVE (Prospective, Randomized Etanercept Study to Evaluate Reduced dose Etanercept combined with MTX versus full dose Etanercept combined with MTX versus MTX alone) trial, Smolen et al[33] investigated whether patients with moderately active RA (DAS >3.2 and ≤5.1) receiving MTX who achieved LDA or DAS remission with ETN50-MTX (open-label Phase I of the trial) would maintain a stable disease activity state after ETN withdrawal or ETN dose reduction to 25 mg/week. Patients were randomized to receive ETN50-MTX, ETN25 plus MTX (ETN25–MTX), or placebo plus MTX (PBO-MTX) and followed-up for 52 weeks. The primary endpoint of the study was the proportion of patients who maintained LDA at week 88.

After 88 weeks, the proportion achieving LDA was significantly greater in both the ETN50 and ETN25 treatment arms compared with placebo (83%, 79%, and 43%, respectively; $P<0.0001$). The proportion achieving DAS remission was significantly greater in the ETN50-MTX and ETN25-MTX arms compared with those in the PBO-MTX group (DAS remission, 66.7%, 60.2%, and 29.4%, respectively; $P<0.0001$ for all comparisons). Radiographic nonprogression (change in modified TSS ≤2.0) was more likely with ETN50 (97%) compared with placebo (89%; $P=0.0259$) but was not more likely compared with ETN25 (96%; $P=0.67$).

In a similar trial design, van Vollenhoven et al have randomized patients (treated with ETN50 and MTX) who achieved LDA (DAS <3.2) to receive ETN50-MTX, ETN25-MTX, or PBO-MTX for the DOSERA (Discontinuing Etanercept in Subjects With Rheumatoid Arthritis) study.[34] The primary outcome was nonfailure of treatment, which was defined as a DAS28 score higher than 3.2 and either an increase in DAS28 of 0.6 or more or disease progression (as defined by investigator or patient). Early data presented at EULAR 2013 shows that after 48 weeks, the proportion of patients still in LDA (DAS ≤3.2) was not significantly different between ETN50-MTX (52%) and ETN25-MTX (44%), although both were significantly greater than PBO-MTX (13%). Preliminary data (presented at EULAR 2013) is also available for the Productivity and Remission in a Randomized Controlled Trial of ETN vs Standard of Care in Early Rheumatoid Arthritis (PRIZE) study. This study is investigating whether treating patients with early RA (less than 6 months duration) who are initially treated with ETN and MTX can maintain remission after ETN dose reduction or withdrawal.[35] Patients who achieved LDA at 33 weeks and DAS28 remission at 52 weeks (Phase I) were then randomized to receive ETN25 and MTX, MTX monotherapy, or placebo (Phase II). Overall, 66% achieved DAS28 ESR remission at the end of Phase I, with significantly more patients with moderately active disease (DAS ≥3.2–5.1) at randomization likely to achieve this target as those with severe disease (DAS >5.1; 60.3% vs 44.0%, respectively; $P=0.02$).[36] After 48 weeks, patients receiving ETN25-MTX were significantly more likely to be in DAS28 LDA (88.9%) than those receiving MTX monotherapy (69.2%) or placebo-treated patients (46.2%). DAS28 remission was more likely in the ETN25-MTX group compared with MTX monotherapy or placebo (79.4%, 53.8%, and 38.5%, respectively), as was ACR/European League Against Rheumatism (EULAR) Boolean remission (67.7%, 46.0%, and 22.6%, respectively).[37]

Is ETN effective before clinical RA is present?

The "window of opportunity" model for RA has led to researchers using DMARDs[38] and biologic therapies,[39] including ETN, at the earliest stages of recognizable disease activity. Preliminary data from the Etanercept and Methotrexate to Induce Remission in Patients With Newly Diagnosed Inflammatory Arthritis (EMPIRE) trial[40] have compared remission rates with ETN50-MTX versus MTX monotherapy as the initial disease-modifying intervention in patients who are either RhF- or Anti-Citrullinated Protein Antibody-positive with synovitis in at least a single joint for less than 3 months. Preliminary data suggest that similar rates of DAS remission are achieved at 1 year (67% vs 64%; $P=0.688$), although patients receiving combination therapy achieve remission earlier.

Is intraarticular ETN an effective treatment strategy for chronic monoarthritis in RA?

Two double-blind RCTs have investigated the potential of intraarticular (IA) ETN for resistant synovitis in the context of RA. Both studies compared IA ETN (25 mg) with IA corticosteroid, either triamcinolone 16 mg[41] or methylprednisolone 40 mg,[42] with joint pain improvement as the primary

Table 5 ETN dose-reduction studies

Study	Study type	Key inclusion criteria	Number of subjects	Primary endpoint	Outcome	Additional information
PRESERVE, Smolen et al[33]	36-week open-label induction with 50 mg ETN plus MTX weekly, followed by placebo-controlled, double-blind, 3-group RCT (Phase II); 88-week duration	DAS 3.2–5.1 at initiation; completed open-label induction and achieved sustained DAS LDA by week 36 (mean DAS28 ≤3.2 from weeks 12 to 36 and DAS28 ≤3.2 at week 36)	Total: 834 patients (Phase I) 604 (Phase II) ETN, 50 mg, and MTX (202 patients): 81% women, 73% RhF-positive, average disease duration 82.8 months; ETN, 25 mg, and MTX (202 patients): 78% women, 71% RhF-positive, average disease duration 76.8 months; placebo and MTX (202 patients): 84% women, 74% RhF-positive, average disease duration 87.6 months	DAS LDA maintenance	Similar rates of DAS LDA, DAS remission, ACR20/50/70 responses, and ACR/EULAR Boolean remission between ETN50 and ETN25 groups; both groups significantly more efficacious than the placebo group for these measures; no difference in the rate of radiographic nonprogression between ETN50 and ETN25 treatment groups	
DOSERA, van Vollenhoven et al.[34] Data published in abstract form only (EULAR 2013)	Placebo-controlled, double-blind 3-group RCT; 48-week duration	DAS ≤3.2; receiving 50 mg ETN (≥14 months) and MTX (≥4 months)	Total: 73 patients ETN, 50 mg, and MTX (23 patients): 74% women, average disease duration 138 months; ETN, 25 mg, and MTX (27 patients): 67% women, average disease duration 199.2 months; placebo and MTX (23 patients): 70% women, average disease duration 147.6 months	Nonfailure of dose reduction (failed defined as DAS28 ≥3.2 and an increase in DAS28 ≥0.6 or disease progression, as defined by investigator or patient)	Rate of nonfailure not significantly different between ETN50 and ETN25 groups; both groups significantly more efficacious than the placebo	
PRIZE, Emery et al.[35] Data published in abstract form only (EULAR 2013)	52-week open-label induction with 50-mg ETN plus MTX weekly, followed by placebo-controlled, double-blind 3-group RCT (Phase II); 91-week duration	Early RA (≤12 months); moderate to severe disease (3.2–5.1); completed open-label induction and achieved DAS ≤3.2 at week 39 and DAS ≤2.6 at week 52	Total: 306 patients (Phase I) 193 (Phase II) ETN, 25 mg, and MTX (63 patients): 74.6% women, average disease duration 6.5 months; placebo and MTX (65 patients): 55.4% women, average disease duration 6.9 months; placebo only (65 patients): 64.6% women, average disease duration 7.1 months	Sustained DAS28 and ACR/EULAR remission	Treatment with ETN25 and MTX associated with significantly better rates of sustained remission (both DAS and ACR/EULAR Boolean) compared with placebo and MTX group and placebo-only group; placebo-only group still achieved 23.1% sustained DAS28 remission and 22.6% ACR/EULAR remission at week 91	Additional abstract data from Emery et al[36,37]

Abbreviations: RCT, randomized controlled trial; DAS, Disease Activity Score; LDA, low disease activity; ETN, etanercept; MTX, methotrexate; RhF, rheumatoid factor; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; PRIZE, The Productivity and Remission in a Randomized Controlled Trial of ETN vs Standard of Care in Early Rheumatoid Arthritis; DOSERA, Discontinuing Etanercept in Subjects With Rheumatoid Arthritis; PRESERVE - Prospective, Randomized Etanercept Study to Evaluate Reduced dose Etanercept combined with MTX versus full dose Etanercept combined with MTX versus MTX alone.

outcome. Although ETN did provide short-term pain relief, neither study demonstrated a significant difference between treatment arms. This finding is in keeping with other RCTs of IA anti-TNF therapy[43] that have failed to demonstrate superiority over IA corticosteroid for recurrent monoarthritis.

Discussion

ETN has proven efficacy in RA in both early and late disease. In a recent systematic review and meta-analysis, patients treated with ETN plus DMARD were 34% more likely to achieve an ACR50 response at 6–36 month points compared with DMARD monotherapy (95% confidence interval [CI], 26%–42%) and 20% more likely than ETN monotherapy (95% CI, 8%–32%). ETN monotherapy was associated with only a 7% additional likelihood of achieving the ACR50 at 3–36 month points compared with DMARD monotherapy (95% CI, 1%–13%).[44] It is perhaps surprising that increased doses of ETN have not demonstrated greater efficacy than the licensed 50 mg per week regime. In the context of psoriasis, ETN 100 mg weekly has been shown to be more effective than standard dose, whereas an increased incidence of adverse events was not reported.[45–47] Some studies have shown that nonresponders to ETN50 have lower serum levels of ETN,[48] but this finding was not borne out by trial data in which serum levels did not appear to predict response to higher doses of ETN.[11]

Early use of biologics is a highly effective strategy for suppressing inflammation and limiting damage in RA, although superiority over conventional therapy with DMARDs and corticosteroids has not been conclusively proven.[49] The EMPIRE study is investigating the role of the ETN-MTX combination in early (pre-RA) inflammatory arthritis and has reported high levels of DAS28 remission at 2 years (67%), but not levels significantly greater than MTX monotherapy (64%).[40] The TEAR study reported that 30% of patients achieved DAS28 LDA with MTX monotherapy alone and demonstrated that delaying escalation (addition of ETN) for 6 months had no clinical or radiographic adverse outcomes at 2 years.[22] The rates of remission with MTX monotherapy reported by these studies reinforce the point that not all patients with RA require escalation to biologic therapy. Therefore, where clinically appropriate, a "MTX-first" policy is suitable for patients, even when markers for poor prognosis are present. The noninferiority of triple therapy compared with ETN50-MTX combination therapy is also reassuring,[26] especially for clinicians operating with restricted access to biologic therapies.

Whether ETN can be used to induce long-term biologic-free remission remains to be determined. The PRESERVE study[33] has demonstrated that for patients with established RA (average, 83 months) who achieve DAS LDA, withdrawing ETN tends to lead to loss of DAS remission. Preliminary data from the PRIZE study suggests that significantly better clinical outcomes may be achievable if patients with early RA (average, 7 months) are selected for ETN discontinuation. Emery et al[35–37] have reported that 1 year after stopped ETN, 46% of patients receiving MTX monotherapy still achieved ACR/EULAR remission criteria (compared with 11% for patients receiving MTX monotherapy in PRESERVE), with almost a quarter of patients receiving no active treatment in PRIZE meeting the same goal. For patients reduced to ETN25-MTX, PRIZE demonstrated better DAS28 remission rates than PRESERVE (79% vs 60%), with more than double the proportion achieving ACR/EULAR remission (68% vs 33%). Therefore, disease duration appears to be a significant factor in predicting the future success of a dose-reduction strategy. Using DAS remission (PRIZE) as opposed to DAS LDA (PRESERVE) for the threshold at which to consider patients for dose reduction may be equally important in the higher rates of remission reported at 1 year.

Conclusion

ETN is a safe and well-tolerated treatment for RA. It has demonstrated efficacy as monotherapy, although combination therapy (usually with MTX) is significantly more clinically effective than either DMARD monotherapy or ETN monotherapy. A MTX-first approach is supported by the current literature,[50] with escalation to ETN50-MTX combination therapy for those patients not achieving an acceptable level of disease control. Although there are guidelines for biologic initiation in RA, there is currently an absence of published advice for clinicians considering dose reduction of biologic therapies. At this time, the optimum strategy for dose-reducing biologics is uncertain. Ongoing and recently published studies, including PRIZE,[51–53] should provide important data to aid clinical decision making when considering biologic dose reduction. It appears that for patients achieving LDA or remission, up to 80% may be maintained in DAS28 remission on reduced dose treatment (ETN25), with up to 40% able to stop ETN for at least 1 year. Personalized medicine to identify patients likely to require ETN, respond to treatment, and achieve good outcomes with a dose-reduction strategy is set to be a major area of research during the coming years. In some countries, the health economics associated

with better long-term functional outcomes and reduced prescribing costs are likely to support the lowering of clinical thresholds[54] at which ETN can be initiated.

Disclosure

The authors report no conflicts of interest in this work.

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