Etanercept in Psoriatic Arthritis

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ABSTRACT. In this update on etanercept (ETN) in psoriatic arthritis (PsA) we analyze this drug’s mechanism of action, clinical efficacy/effectiveness, optimal dosage, disease-modifying antirheumatic drugs (DMARD) association, radiological progression, safety, switching aspects, and pharmacoeconomy. The efficacy/effectiveness of ETN in PsA has been demonstrated in randomized placebo-controlled trials as well as in observational studies representing routine clinical practice. At 1 and 2 years, ETN inhibited radiographic disease progression, assessed by the modified total Sharp score. ETN (generally at a dosage of 50 mg/weekly) can be used either in monotherapy or in combination with DMARD such as methotrexate. A systematic search of randomized, placebo-controlled trials of ETN to treat adults with plaque psoriasis or PsA suggests that the short-term risk/benefit ratio is favorable. Longterm studies, such as observational studies, confirmed this safety profile of ETN. A variable percentage of patients withdrew anti-tumor necrosis factor-α (TNF-α) inhibitor treatment owing to inefficacy or poor tolerability. Observational studies showed that in the case of treatment failure with 1 agent, switching to the other agent may also be useful in patients with PsA because of the different molecular structures and targets of available TNF-α blockers. The clinical effect of ETN is associated with favorable pharmacoeconomic considerations. (J Rheumatol 2012;39 Suppl 89:74–6; doi:10.3899/jrheum.120250)

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In this update on etanercept (ETN) in psoriatic arthritis (PsA) we analyze this drug’s mechanism of action, clinical efficacy/effectiveness, optimal dosage, disease-modifying antirheumatic drugs (DMARD) association, radiological progression, safety, switching aspects, and pharmacoeconomy.

MECHANISM OF ACTION
ETN, a recombinant soluble tumor necrosis factor (TNF) receptor, is a fusion protein composed of 2 extracellular domains of the human p75-tumor necrosis factor (TNF)-receptor (sTNFRII), linked to the Fc portion of human immunoglobulin G-1. The 2 sTNFRII arms of ETN bind 2 of the 3 receptor-binding sites on the TNF trimer in a 1:1 ratio. This feature and the fast association/dissociation rates of the p75-TNF-receptor with TNF-α suggest that ETN may only transiently neutralize the activity of an individual TNF molecule. The mechanisms of action of ETN include blockade of TNFR and transmembrane-TNF mediated process. ETN differs from other TNF-α blockers regarding the capacity to inhibit members of the lymphotoxin (LT) family such as soluble LTα3, involved in immune functioning and inflammation. ETN does not induce apoptosis in some tissues (e.g., gastrointestinal mucosa), while in synovia, both anti-TNF-α soluble receptor and monoclonal antibodies seem to cause apoptosis. In contrast with adalimumab (ADA) or infliximab (IFX), ETN does not activate complement-dependent cytolysis and antibody-dependent cell-mediated cytotoxicity. These features may explain, partly, some differences between ETN and other anti-TNF-α drugs regarding their efficacy and safety.

CLINICAL EFFICACY/EFFECTIVENESS
PsA is a chronic systemic inflammatory disorder, and may include prominent involvement in the peripheral and axial joints, the skin and nails, and in periarticular structures such as entheses. Thus it is important to consider the efficacy/effectiveness of ETN in the context of different patterns of psoriatic disease.

The efficacy of ETN in PsA has been demonstrated in a placebo-controlled, randomized controlled trial (RCT) in which 60 patients with active PsA (nonresponders to nonsteroidal antiinflammatory drugs) received either ETN (25 mg subcutaneously twice weekly) or placebo. In each group, 47% of patients were allowed to continue methotrexate (MTX; < 25 mg/week). At Week 12, 87% of ETN-treated patients reached the primary arthritis endpoint, Psoriatic Arthritis Response Criterion (PsARC), compared to 23% of those on placebo. In 77% of the patients the response to ETN was quite rapid (at 4 weeks). Similar positive responses were noted using the American College of Rheumatology (ACR)20 improvement criteria (secondary endpoint), and
ACR50 and ACR70 responses. Further, no statistically significant difference was observed between patients who were receiving MTX and those who were not. ETN was also effective on the skin lesions of psoriasis evaluated by improvement of the Psoriasis Area and Severity Index (PASI) and improvement in prospectively identified individual target lesions.

In 2004, a multicenter placebo double-blind RCT evaluated safety and efficacy of ETN in 205 patients with PsA. The patients were randomized to receive placebo (n = 104) or ETN (25 mg) subcutaneously twice weekly (n = 101) for 24 weeks. Then the patients could receive ETN in a 48-week open-label extension. This study showed that clinical efficacy on arthritis was evident at the first visit (Week 4). At 12 weeks, ETN reduced all individual measures of arthritis activity, as well as composite measures (ACR20, 50, 70, and PsARC). Clinical response was not affected by concomitant treatment with MTX. The skin lesions improved significantly during the blinded phase (BP) of the study. During the open-label extension, all patients received ETN: their response was maintained (ETN group BP) or improved (placebo group BP).

These RCT also assessed patient-reported outcomes (PRO), which provide better discrimination of the treatment effect and are less likely to exhibit a placebo effect than traditional physician-reported outcomes. In the double-blind period, patients with PsA treated with ETN reported significant improvements in PRO measures, including Health Assessment Questionnaire Disability Index, the Medical Outcomes Study Short Form-36, the EQ-5D visual analog scale, and the ACR patient pain assessment. Improvement in physical function was almost 10 times the improvement seen with placebo and was maintained for up to 2 years.

Nevertheless, relevant data can be obtained by observational studies that represent the real world of routine clinical practice. The British Society of Rheumatology Biologics Register examined in an observational study 566 patients treated with ETN, 162 (28.6%) with IFX, and 88 (15.6%) with ADA. In UK clinical practice, the retention with MTX, as well as cyclosporine.

Thus, ETN can be used either in monotherapy or in combination with MTX, as there is in rheumatoid arthritis (RA), but it underlined that concomitant MTX treatment does not seem to be a positive predictor of anti-TNF-α drug survival for AE in the treatment of patients with PsA. Thus, ETN can be used either in monotherapy or in combination with MTX, as well as cyclosporine.

DMARD ASSOCIATION
In PsA studies of all 3 anti-TNF-α agents, the concomitant stable use of MTX was allowed, but it did not seem to affect any of the clinical or radiographic responses. The South Swedish Arthritis Treatment Group registry showed that the concomitant use of MTX with ETN, ADA, or IFX was associated with longterm retention of TNF-α agents in patients with PsA. The positive effect of MTX was primarily linked to fewer dropouts due to adverse events (AE), but this analysis did not consider each anti-TNF-α drug subgroup. A prospective study of 82 patients with PsA showed that the probability curve of taking ETN alone was not significantly different from that of ETN plus MTX. In particular, this study did not deny synergy between the 2 drugs in PsA, as there is in rheumatoid arthritis (RA), but it underlined that concomitant MTX treatment does not seem to be a positive predictor of anti-TNF-α drug survival for AE in the treatment of patients with PsA. Thus, ETN can be used either in monotherapy or in combination with MTX, as well as cyclosporine.

RADIOGRAPHIC DISEASE PROGRESSION
At 12 months, radiographic disease progression, assessed by the modified total Sharp score (joint erosion plus joint space narrowing scores), primary radiographic endpoint, was inhibited in the ETN group compared with worsening in the placebo group (~0.03 vs 1 unit rate of change/year). The rate of change/year in the erosion and joint space narrowing score also were significantly different between groups. After the blind phase, 141 out 169 patients who entered the open-label phase had radiographic data available for analysis at 2 years. Radiographic progression was inhibited (mean adjusted change in total Sharp score of ~0.38 from baseline Bath Ankylosing Spondylitis Metrology Index, and single anthropometric measures were significantly improved, showing that ETN is effective on axial manifestations of PsA.

OPTIMAL DOSAGE
The optimal dosage of ETN was considered in the PRESTA trial, comparing the efficacy and safety of 2 ETN regimens (50 mg twice weekly vs 50 mg once weekly) on patients with psoriasis and PsA. PRESTA was a 12-week, randomized, double-blind, multicenter outpatient study followed by a 12-week open-label extension study. It showed that treatment with the higher weekly dose of ETN demonstrated significantly greater clearing of skin at Week 12. Both regimens achieved significant improvement of skin lesions at Week 24. Arthritis, enthesitis, and dactylitis improved at weeks 12 and 24, but there was little difference in their improvement with increased dose. Similar results were obtained by a posthoc analysis of PRESTA that quantified the proportion of patients with combined substantial improvement in skin symptoms, joint manifestations, and quality-of-life assessment.
to 2 years). After the blinded phase, in placebo patients who received ETN, disease progression was inhibited from 1 year to 2 (mean adjusted change of –0.22 years)\textsuperscript{10}.

SAFETY
The safety profile of anti-TNF-\(\alpha\) has been widely investigated in RA and spondyloarthropathies (SpA). A systematic study of randomized, placebo-controlled trials of TNF-\(\alpha\) antagonists [including 7 studies with ETN (1472 patients)] for adults with plaque psoriasis or PsA suggests that the short-term risk/benefit (12-24 weeks) profile of the TNF-\(\alpha\) inhibitors is favorable\textsuperscript{11}. The OR for overall infection associated with ETN was 1.14. The OR for malignancy associated with ETN was 1.61. However, the limit of this meta-analysis is the short duration of followup. In fact, longterm studies, such as observational studies, are necessary to fully assess the risk of cancer and serious infection associated with chronic use of TNF-\(\alpha\) inhibitors to treat psoriatic disease. British patient registry data suggest that about 3\% of patients with PsA discontinue ETN per year, citing AE\textsuperscript{5}.

SWITCHING
In controlled and observational studies, a variable percentage of patients withdrew anti-TNF-\(\alpha\) treatment owing to inefficacy or poor tolerability.

In the study by Delaunay, et al\textsuperscript{12}, all patients with PsA were responders after switching from IFX to ETN. In another study, 10 patients with PsA switched from IFX to ETN\textsuperscript{13}. After 3 months of ETN, PsARC responders increased from 10\% (baseline before ETN) to 70\%. In the same study, 7 patients with PsA switched from ETN to ADA. After 3 months of ADA, PsARC responders increased from 14.3\% (baseline before ADA) to 57.1\%\textsuperscript{13}.

A retrospective study showed that 47 patients with SpA (including 25 with PsA) who failed to respond to a first agent such as IFX or ETN responded to ADA as a second- or third-line drug regardless of the reason for switching\textsuperscript{14}.

These data showed that in the case of treatment failure with 1 agent, switching to the other agent may be useful in patients with PsA because of the different molecular structures and targets of available TNF-\(\alpha\) blockers.

PHARMACOECONOMY
Costs, benefits, and cost–effectiveness of anti-TNF-\(\alpha\) agents have been evaluated in 107 PsA patients with inadequate response to conventional treatment (87\% of them treated with ETN). There would be a 97\% likelihood that anti-TNF therapy would be considered cost-effective at the willingness-to-pay threshold of Euro 60,000 per quality-adjusted life-years gained\textsuperscript{15}.

ETN had a favorable benefit/risk ratio in the treatment of different clinical aspect of psoriatic disease in anti-TNF-\(\alpha\)-naive patients and after the failure of a previous anti-TNF-\(\alpha\) treatment. ETN can be used either in monotherapy or in combination with nonbiologic DMARD. Its clinical effect is associated with a slow radiological progression and favorable pharmacoeconomic considerations.

REFERENCES