

# Synovitis Persists in RA Patients in 'Remission'

BY DENISE NAPOLI

FROM ANNALS OF THE RHEUMATIC DISEASES

Applying more stringent remission thresholds among rheumatoid arthritis patients lowered the percentage of those with lingering swollen and tender joints; however, the proportion of patients with synovitis on power Doppler ultrasound remained unchanged.

"Therefore, as clinical criteria cannot exclude the presence of active disease, the current re-

mission criteria are more appropriate for defining low disease activity states," concluded Dr. Benazir Saleem and colleagues.

According to the investigators, patients who are currently judged by American College of Rheumatology and European League Against Rheumatism criteria to be in remission – with a DAS28 (disease activity score based on a 28-joints count) less than 2.6 – may still have tender and swollen joints, and corresponding structural progression of disease.

VITALS

**Major Finding:** Among RA patients in remission, only 9% with DAS28 scores less than 1.17 were found to be free of synovitis on power Doppler imaging; among patients with correspondingly low SDAI scores, just 25% had similarly clear scans, with the remainder showing some degree of inflammation.

**Data Source:** A cohort of 128 outpatients seen at a clinic in Leeds, England.

**Disclosures:** The authors stated that they had no competing interests to declare in relation to this study.

**SIMPONI® (golimumab) Injection, solution for subcutaneous use**  
See package insert for full Prescribing Information.

**WARNINGS: SERIOUS INFECTIONS and MALIGNANCY**  
**SERIOUS INFECTIONS**

Patients treated with SIMPONI® are at increased risk for developing serious infections that may lead to hospitalization or death (see *Warnings and Precautions*). Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. SIMPONI® should be discontinued if a patient develops a serious infection.

Reported infections include:

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before SIMPONI® use and during therapy. Treatment for latent infection should be initiated prior to SIMPONI® use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with SIMPONI® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy (see *Warning and Precautions*).

**MALIGNANCY**

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI® is a member (see *Warning and Precautions*).

**INDICATIONS AND USAGE:** Rheumatoid Arthritis SIMPONI®, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis. Psoriatic Arthritis SIMPONI®, alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis. Ankylosing Spondylitis SIMPONI® is indicated for the treatment of adult patients with active ankylosing spondylitis. **CONTRAINDICATIONS:** None. **WARNINGS AND PRECAUTIONS (see Boxed WARNINGS):** Serious Infections Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers including SIMPONI®. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI® and these biologic products is not recommended (see *Warning and Precautions and Drug Interactions*). Treatment with SIMPONI® should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating SIMPONI® in patients: with chronic or recurrent infection; who have been exposed to tuberculosis; with a history of an opportunistic infection; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or with underlying conditions that may predispose them to infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI®. SIMPONI® should be discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with SIMPONI® should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI®-treated patients and 1.3% of control-treated patients. In the controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of serious infections per 100 patient-years of follow-up was 5.7 (95% CI: 3.8, 8.2) for the SIMPONI® group and 4.2 (95% CI: 1.8, 8.2) for the placebo group. Serious infections observed in SIMPONI®-treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal infections, and hepatitis B infection. **Tuberculosis** Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating SIMPONI® and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating SIMPONI®, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG). Anti-tuberculosis therapy should also be considered prior to initiation of SIMPONI® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tuberculosis should be strongly considered in patients who develop a new infection during SIMPONI® treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active

tuberculosis. In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active TB was 0.23 and 0 per 100 patient-years in 2347 SIMPONI®-treated patients and 674 placebo-treated patients, respectively. Cases of TB included pulmonary and extra pulmonary TB. The overwhelming majority of the TB cases occurred in countries with a high incidence rate of TB. **Invasive Fungal Infections** For SIMPONI®-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. **Hepatitis B Virus Reactivation** The use of TNF-blockers including SIMPONI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI®, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely. **Malignancies** Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which SIMPONI® is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports. The risks and benefits of TNF-blocker treatment including SIMPONI® should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy. In the controlled portions of clinical trials of TNF-blockers including SIMPONI®, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI® group compared with an incidence of 0 (95% CI: 0., 0.96) in the placebo group. In the controlled and uncontrolled portions of these clinical trials in 2347 SIMPONI®-treated patients with a median follow-up of 1.4 years, the incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).<sup>1</sup> Patients with RA and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia. During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was not elevated in the combined SIMPONI® group compared with the placebo group. In the controlled and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in SIMPONI®-treated patients was similar to that expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race).<sup>1</sup> In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory 1-year clinical trial evaluating the use of 50, 100 and 200 mg of SIMPONI® in 309 patients with severe persistent asthma, 6 patients developed malignancies other than NMSC in the SIMPONI® groups compared to none in the control group. Three of the 6 patients were in the 200 mg SIMPONI® group. **Congestive Heart Failure** Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers, including SIMPONI®. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalization or increased mortality. SIMPONI® has not been studied in patients with a history of CHF and SIMPONI® should be used with caution in patients with CHF. If a decision is made to administer SIMPONI® to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI® should be discontinued if new or worsening symptoms of CHF appear. **Demyelinating Disorders** Use of TNF-blockers, of which SIMPONI® is a member, has been associated with cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. In clinical trials, cases of central demyelination, MS, and peripheral demyelinating polyneuropathy have been reported in patients treated with SIMPONI® (see *Adverse Reactions*). Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI®, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI® should be considered if these



It may therefore be expected that more stringent criteria – that is, the use of lower cut-points for DAS28/SDAI (Simplified Disease Activity Index) to define remission – “would be associated with less ... imaging-detected synovitis,” postulated Dr. Saleem, a clinical research fellow at the University of Leeds (England) and colleagues (Ann. Rheum. Dis. 2011;70:792-8).

“This would, for example, permit fewer (ideally zero) tender and swollen joints to be present in patients in remission, and thus there would be a better correlation with the absence of structural

progression,” according to Dr. Saleem and coauthors.

To test this theory, the researchers looked at 128 outpatients from the Chapel Allerton Hospital in Leeds who had DAS28 scores less than 2.6. Patients' mean age was 54 years, and the median disease duration was 8 years.

All study participants had been in remission for a period of at least 6 months. Roughly half of them had achieved remission through the use of disease-modifying antirheumatic drugs; the remainder had been treated with a regimen consisting of combination tumor necro-

sis factor blocker and methotrexate (45% infliximab, 45% etanercept, and 10% adalimumab).

Overall, a total of 31% of these patients who were classified as being in remission still had swollen joints, and 18% reported tender joints. In addition, more than half of the patients (51%) had synovitis that was detectable on power Doppler ultrasound, which is considered the “gold standard” of imaging for synovitis.

Dr. Saleem then divided the patients into four subcategories: In all, 32 patients had a DAS28 less than 1.17; 31 had a

score of 1.17-1.70; 32 patients registered a DAS28 of 1.71-2.03; and the remaining 33 patients had a DAS score greater than 2.03.

“As was to be expected, both swollen joint count in 28 joints [P less than .001] and tender joint count in 28 joints [P less than 0.001] decreased with decreasing DAS28,” Dr. Saleem and coinvestigators wrote.

However, the proportions of patients in imaging remission did not have a corresponding consistent decrease; indeed, only 9% of those in the lowest category were in strict imaging remission (defined as no joints showing synovitis in the dominant hand's metacarpophalangeal joints 2-5, plus the wrist, according to gray scale and power Doppler ultrasound).

The stratification of the study partic-

**The rheumatologic equivalent of true remission would ‘not rely solely on clinical examination but would require imaging to confirm the absence of subclinical inflammation.’**

ipants into increasingly stringent SDAI categories resulted in a similar, predictable decrease in the number of swollen and tender joints as the score decreased.

However, only 25% of those in the lowest SDAI category (score less than 1.51) were in strictly defined imaging remission.

“The use of the term remission in other areas of medicine implies the absence of active disease,” wrote the researchers.

The rheumatologic equivalent of this true remission “would therefore not rely solely on clinical examination but would require imaging to confirm the absence of subclinical inflammation,” according to Dr. Saleem and coinvestigators.

And although the widely used, easy-to-calculate DAS28 is a good tool, it is “insufficiently sensitive to exclude [clinically important] levels of inflammation,” they concluded.

The relevance of this finding is not clear, because “the threshold level of ultrasound-determined inflammation that is of importance for subsequent clinical and radiographic progression has not yet been established,” according to the investigators.

disorders develop. **Use with Abatacept** In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI<sup>®</sup> and abatacept is not recommended (see *Drug Interactions*). **Use with Anakinra** Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI<sup>®</sup>, is not recommended (see *Drug Interactions*). **Switching Between Biological Disease Modifying Antirheumatic Drugs (DMARDs)** Care should be taken when switching from one biologic to another since overlapping biological activity may further increase the risk of infection. **Hematologic Cytopenias** There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. In clinical studies, cases of pancytopenia, leukopenia, neutropenia, and thrombocytopenia have also occurred in SIMPONI<sup>®</sup>-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI<sup>®</sup>, in patients who have or have had significant cytopenias. **Vaccinations** Patients treated with SIMPONI<sup>®</sup> may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection after the administration of live vaccines to patients receiving SIMPONI<sup>®</sup>. In the Phase 3 PsA study, after pneumococcal vaccination, a similar proportion of SIMPONI<sup>®</sup>-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI<sup>®</sup>-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving methotrexate (MTX) compared with patients not receiving MTX. The data suggest that SIMPONI<sup>®</sup> does not suppress the humoral immune response to the pneumococcal vaccine. **ADVERSE REACTIONS** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. **Clinical Studies Experience** The safety data described below are based on 5 pooled, randomized, double-blind, controlled Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA and AS) (see *Clinical Studies*). These 5 trials included 639 control-treated patients and 1659 SIMPONI<sup>®</sup>-treated patients including 1089 with RA, 292 with PsA, and 278 with AS. The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI<sup>®</sup>-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI<sup>®</sup> in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%). The most serious adverse reactions were: Serious Infections; Malignancies. Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and 6% of SIMPONI<sup>®</sup>-treated patients as compared with 6% and 5% of control-treated patients, respectively. **Infections** In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28% of SIMPONI<sup>®</sup>-treated patients compared to 25% of control-treated patients. **Liver Enzyme Elevations** There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI<sup>®</sup> in patients with RA, PsA, and AS through Week 16, ALT elevations  $\geq 5 \times$  ULN occurred in 0.2% of control-treated patients and 0.7% of SIMPONI<sup>®</sup>-treated patients, and ALT elevations  $\geq 3 \times$  ULN occurred in 2% of control-treated patients and 2% of SIMPONI<sup>®</sup>-treated patients. Since many of the patients in the Phase 3 trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDs, MTX), the relationship between SIMPONI<sup>®</sup> and liver enzyme elevation is not clear. **Autoimmune Disorders and Autoantibodies** The use of TNF-blockers, including SIMPONI<sup>®</sup>, has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI<sup>®</sup> treatment and the development of newly positive anti-dsDNA antibodies. **Injection Site Reactions** In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI<sup>®</sup> treated patients had injection site reactions compared with 2% of control-treated patients. The majority of the injection site reactions were mild and the most frequent manifestation was injection site erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with SIMPONI<sup>®</sup> developed anaphylactic reactions. **Immunogenicity** Antibodies to SIMPONI<sup>®</sup> were detected in 57 (4%) of SIMPONI<sup>®</sup>-treated patients across the Phase 3 RA, PsA, and AS trials through Week 24. Similar rates were observed in each of the 3 indications. Patients who received SIMPONI<sup>®</sup> with concomitant MTX had a lower proportion of antibodies to SIMPONI<sup>®</sup> than patients who received SIMPONI<sup>®</sup> without MTX (approximately 2% versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI<sup>®</sup> in the Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as measured by a cell-based functional assay. The small number of patients positive for antibodies to SIMPONI<sup>®</sup> limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures. The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI<sup>®</sup> in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI<sup>®</sup> with the incidence of antibodies to other products may be misleading. **Other Adverse Reactions** The adverse drug reactions that occurred at a rate of at least 1% in the SIMPONI<sup>®</sup>  $\pm$  DMARD group and with a higher incidence than in the placebo  $\pm$  DMARD group during the controlled period of the 5 pooled Phase 3 trials through Week 16 in patients with RA, PsA, and AS are summarized below. Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids ( $\leq 10$  mg of prednisone/day or equivalent), and/or NSAIDs during the trials. The numbers (percentages) of adverse drug reactions for SIMPONI<sup>®</sup>  $\pm$  DMARDs-treated patients (n=1659) and Placebo  $\pm$  DMARDs-treated patients (n=639), respectively, were: **Infections and Infestations:** Upper

respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinitis) 16%, 13%; Viral infections (such as influenza and herpes) 5%, 3%; Bronchitis 2%, 1%; Superficial fungal infections 2%, 1%; Sinusitis 2%, 1%; **General disorders and administration site conditions:** Injection site reaction (injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation, paresthesia) 6%, 2%; **Investigations:** Alanine aminotransferase increased 4%, 3%; Aspartate aminotransferase increased 3%, 2%; **Vascular disorders:** Hypertension 3%, 2%; **Nervous system disorders:** Dizziness 2%, 1%; Paraesthesia 2%, 1%; **Gastrointestinal Disorders:** Constipation 1%, <1%. **Less common clinical trial adverse drug reactions** Adverse drug reactions that occurred <1% in SIMPONI<sup>®</sup>-treated patients during the SIMPONI<sup>®</sup> clinical trials that do not appear in the Warnings and Precautions section included the following events listed by system organ class: **Infections and infestations:** Septic shock, atypical mycobacterial infection, pyelonephritis, arthritis bacterial, bursitis infective **Skin and subcutaneous tissue disorders:** psoriasis (new onset or worsening, palmar/plantar and pustular), vasculitis (cutaneous) **Vascular disorders:** Vasculitis (systemic) **DRUG INTERACTIONS: Methotrexate.** For the treatment of RA, SIMPONI<sup>®</sup> should be used with MTX. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI<sup>®</sup> in the treatment of PsA or AS, SIMPONI<sup>®</sup> can be used with or without MTX in the treatment of PsA and AS. **Biologic Products for RA, PsA, and/or AS** An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI<sup>®</sup> with abatacept or anakinra is not recommended. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. There is insufficient information to provide recommendations regarding the concomitant use of SIMPONI<sup>®</sup> and other biologic products approved to treat RA, PsA, or AS. **Live Vaccines** Live vaccines should not be given concurrently with SIMPONI<sup>®</sup>. **Cytochrome P450 Substrates** The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF $\alpha$ ) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI<sup>®</sup> in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **USE IN SPECIFIC POPULATIONS: Pregnancy** Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI<sup>®</sup> in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI<sup>®</sup> can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI<sup>®</sup> should be used during pregnancy only if clearly needed. An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MHRD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus. A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants. **Nursing Mothers** It is not known whether SIMPONI<sup>®</sup> is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from SIMPONI<sup>®</sup>, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations. **Pediatric Use** Safety and effectiveness of SIMPONI<sup>®</sup> in patients less than 18 years of age have not been established. **Geriatric Use** In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious infections, and AEs in SIMPONI<sup>®</sup>-treated patients ages 65 or older (N=155) compared with younger SIMPONI<sup>®</sup>-treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI<sup>®</sup>. **OVERDOSAGE** In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMPONI<sup>®</sup> without serious adverse reactions or other significant reactions. The highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000 mg of SIMPONI<sup>®</sup>. There were no SIMPONI<sup>®</sup> overdoses in the clinical studies. **PATIENT COUNSELING INFORMATION Patient Counseling** Patients should be advised of the potential benefits and risks of SIMPONI<sup>®</sup>. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI<sup>®</sup> therapy and to read it each time the prescription is renewed. **Infections** Inform patients that SIMPONI<sup>®</sup> may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation. **Malignancies** Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI<sup>®</sup>. **Allergic Reactions** Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect<sup>®</sup> autoinjector contains dry natural rubber (a derivative of latex). **Other Medical Conditions** Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

**REFERENCES:** 1. SEER [database online]. U.S. Population Data—1969-2004. Bethesda, MD; National Cancer Institute. Release date: January 3, 2007. Available at: <http://www.seer.cancer.gov/popdata>.

© Centocor Ortho Biotech Inc. 2011  
Horsham, PA 19044 1-800-457-6399

US License No. 1821  
Revised: 3/2011 25SM11008

**Get Greener**

To access the Digital Edition, and to Renew your Free Subscription to RHEUMATOLOGY NEWS, go to [www.med-pub.com/rhu](http://www.med-pub.com/rhu)