

# Study: Altered Gait May Flag Early Knee OA

BY KERRI WACHTER

FROM ARTHRITIS & RHEUMATISM

Unilateral hip arthritis may cause alterations in the joint loading of the contralateral knee before the onset of symptomatic osteoarthritis in that knee, a small study has shown.

This finding could open up the possibility of interventions that could prevent or slow the progression of knee os-

teoarthritis (OA) in those with unilateral hip arthritis.

The results come from a study of 55 participants, who underwent gait analysis of dynamic joint loading and dual-energy x-ray absorptiometry (DXA) to determine bone mineral density (BMD) of the tibial plateau (Arthritis Rheum. 2011 30 Aug. [doi:10.1002/art.30626]).

"This study demonstrates that in unilateral hip OA, the contralateral knee is

subjected to significantly higher dynamic joint loading, as assessed by PAddM [peak external knee adduction moment] and by total medial compartment loads, relative to the ipsilateral knee. Importantly, this asymmetry of knee loading is observed even though the knees are asymptomatic and do not have clinical evidence of OA," wrote Dr. Najia Shakoor and her coinvestigators at Rush Medical College, Chicago.

Asked to comment on the findings,

Dr. Nancy E. Lane noted that "it is not a surprise that changes in gait are present before the disease becomes clinically symptomatic.

"The more we can study gait to provide early detection of OA, we might be able to provide an intervention that might slow the progression of the disease," noted Dr. Lane, professor of medicine and rheumatology at the University of California, Davis, and director of the

## Important Safety Information for SIMPONI® (golimumab) (continued)

### MALIGNANCIES

**Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers 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 usually associated with immunosuppression and malignancies not usually observed in children or adolescents. Malignancies occurred after a median of 30 months after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

In the controlled portions of clinical trials of all TNF-blocking agents including SIMPONI®, more cases of lymphoma have been observed among patients receiving TNF-blocking treatment compared with control patients. In clinical trials, 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 clinical trials, the incidence of malignancies other than lymphoma was not increased with exposure to SIMPONI® and was similar to what would be expected in the general population. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. The risks and benefits of TNF-blocker therapy should be considered prior to initiating therapy in patients with a known malignancy or who develop a malignancy.

### HEPATITIS B REACTIVATION

The use of TNF-blocking agents including SIMPONI® has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers. 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.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consult a physician with expertise in the treatment of hepatitis B before initiating TNF-blocker therapy. Exercise caution when prescribing SIMPONI® for patients identified as carriers of HBV and closely monitor for active HBV infection during and following termination of therapy with SIMPONI®. Discontinue SIMPONI® in patients who develop HBV reactivation, and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of SIMPONI®, and monitor patients closely.

### HEART FAILURE

Cases of worsening congestive heart failure (CHF) and new-onset CHF have been reported. Exercise caution and monitor patients with heart failure. Discontinue SIMPONI® if new or worsening symptoms of heart failure appear.

### DEMYELINATING DISORDERS

TNF-blocking agents, of which SIMPONI® is a member, have been associated with cases of new-onset or exacerbation of demyelinating disorders,

including multiple sclerosis (MS) and Guillain-Barré syndrome. In SIMPONI® clinical trials, cases of MS and peripheral demyelinating polyneuropathy were reported. Exercise caution in considering the use of SIMPONI® in patients with these disorders. Consider discontinuation if these disorders develop.

### HEMATOLOGIC CYTOPENIAS

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving SIMPONI® in clinical trials. Additionally, aplastic anemia has been reported in patients receiving TNF-blocking agents, of which SIMPONI® is a member. Exercise caution when using SIMPONI® in patients who have or had significant cytopenias.

### USE WITH OTHER DRUGS

The concomitant use of a TNF blocker and abatacept or anakinra was associated with a higher risk of serious infections, therefore the use of SIMPONI® in combination with these products is not recommended. Care should be taken when switching from one biologic to another since overlapping biological activity may further increase the risk of infection. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker.

### VACCINATIONS

People receiving SIMPONI® can receive vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to SIMPONI® *in utero* is not recommended for 6 months following the mother's last SIMPONI® injection during pregnancy due to an increased risk of infection.

### HYPERSENSITIVITY REACTIONS

Serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported with SIMPONI®, some occurring after the first dose. If an anaphylactic or other serious allergic reaction occurs, discontinue SIMPONI® immediately and institute appropriate therapy.

### ADVERSE REACTIONS

The most serious adverse reactions were serious infections and malignancies.

Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions reported in the combined Phase 3 trials through Week 16, occurring in 7% and 6% of patients treated with SIMPONI® as compared with 6% and 5% of patients in the control group, respectively. The rate of injection-site reactions was 6% with patients treated with SIMPONI® compared with 2% of patients in the control group.

**Please see Brief Summary of Prescribing Information on following pages.**

**Reference: 1.** SIMPONI® (golimumab) Prescribing Information. Janssen Biotech, Inc.

[www.simponi.com](http://www.simponi.com)

© Janssen Biotech, Inc. 2011 09/11 255MRP1110

**Janssen**  
PHARMACEUTICAL COMPANIES  
OF **Johnson & Johnson**

255M11034

center for healthy aging at UC Davis.

While no interventions are approved yet, there are braces and special shoes that may support the knee. In addition, ongoing research is evaluating gait interventions. "They may be efficacious if the interventions are initiated earlier in the disease state," according to Dr. Lane.

Individuals were included if they had symptomatic OA of the hip, as defined by the American College of Rheumatology's Clinical Criteria for Classification. They also had to have at least 30 mm of pain (on a 100-mm scale) while walking – which corresponds to question

1 of the visual analog format of the hip-directed WOMAC (Western Ontario and McMaster Universities Arthritis) Index. OA was confirmed radiographically.

Exclusion criteria included symptomatic OA of the contralateral hip or either knee with the presence of pain defined as 30 mm (on a 100-mm scale) while walking. They were also excluded if they had radiographic evidence of OA of the contralateral hip or either of the knees, in excess of grade 3, according to the modified Kellgren-Lawrence (KL) scale.

A total of 62 individuals met the study criteria and completed the study. The

mean age was 62 years, and more women (60%) were included than men. A total of 55 individuals had both appropriate gait data and evaluation of bone density at bilateral knees.

All individuals had anterior-posterior radiographs of the pelvis, which were evaluated for KL grade at the hips. They also underwent anterior-posterior standing knee radiographs that were evaluated for KL grade at the knees. All participants completed the WOMAC visual analog scale for pain at both knees and both hips. The WOMAC scores were normalized to a 100-mm scale.

Participants also underwent gait analysis to collect three-dimensional kinematics and ground reaction forces using optoelectronic cameras with passive markers and a multicomponent force plate. Passive markers were placed at the lateral-most aspect of the superior iliac crest, the superior aspect of the greater trochanter, the lateral knee joint line, the lateral malleolus, the lateral calcaneus, and the head of the fifth metatarsal.

DXA was used to scan the bilateral proximal tibia and determine BMD. Software was used to determine the subpe-

*Continued on following page*

#### 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 with TNF-blockers, of which SIMPONI is a member, 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, candidiasis, aspergillosis, blastomycosis 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, including Legionella and Listeria.

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 *Warnings 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 *Warnings and Precautions*).

#### SIMPONI® (golimumab)

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-Guerin (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. All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended 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

**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. **Psoarthritis** 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** Patients treated with SIMPONI® are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. 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 *Warnings and Precautions and Drug Interactions*]. Treatment with SIMPONI® should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. 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. **Monitoring** 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. **Serious Infection in Clinical Trials** 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

Continued from previous page

riostial surface of the tibia. Cortical bone of the subchondral plate was excluded from the measurements, as sclerosis in this region can alter BMD. Therefore, the medial and lateral regions of interest include subchondral trabecular bone.

The primary end point was the PAddM, which is a validated gait parameter that reflects the load at the medial compartment of the knee. This measure has been associated with pain, radiographic severity, and progression of knee OA. The PAddM was defined as

the external adduction moment of greatest magnitude during the stance phase of the gait cycle in this study. The copri-mary end points were total loading of the medial compartment and medial compartment BMD.

Both primary gait outcomes at the knees – the PAddM and the total medial knee load – were significantly greater for the contralateral knee relative to the ipsilateral knee. Lateral compartment load was also greater for the contralateral knee. In addition, the medial tibial plateau BMD was significantly greater at the contralateral knee relative to the ip-

silateral knee, though there were no significant differences at the lateral tibial plateau.

Interestingly, the ratio of the contralateral-to-ipsilateral medial compartment knee BMD was directly correlated with contralateral-to-ipsilateral knee PAddM and contralateral-to-ipsilateral knee medial compartment load, the investigators noted.

In addition, the significant asymmetries observed in the proximal tibial BMD of the contralateral vs. ipsilateral knees provide evidence of substantially altered load history in the knees as well.

“The current study demonstrates that loading asymmetries at the knees begin early in the disease course of hip OA to end-stage disease. These results may have implications for interventional strategies targeted in those with unilateral hip OA in order to prevent or minimize these asymmetries early in the disease course,” the researchers concluded.

The authors and Dr. Lane reported that they have no relevant financial disclosures. The study was sponsored by the National Institutes of Health and the Schweppe Foundation. ■

#### SIMPONI® (golimumab)

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 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® 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®, 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®-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI®, in patients who have or have had significant cytopenias. **Vaccinations** Patients treated with SIMPONI® 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®. In the Phase 3 PsA study, after pneumococcal vaccination, a similar proportion of SIMPONI®-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®-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® does not suppress the humoral immune response to the pneumococcal vaccine. **Hypersensitivity Reactions** In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following SIMPONI® administration. Some of these reactions occurred after the first administration of SIMPONI®. If an anaphylactic or other serious allergic reaction occurs, administration of SIMPONI® should be discontinued immediately and appropriate therapy instituted. **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®-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®-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI® in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine

#### SIMPONI® (golimumab)

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®-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®-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® 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®-treated patients, and ALT elevations  $\geq 3 \times$  ULN occurred in 2% of control-treated patients and 2% of SIMPONI®-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® and liver enzyme elevation is not clear. **Autoimmune Disorders and Autoantibodies** The use of TNF-blockers, including SIMPONI®, 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® 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®-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® developed anaphylactic reactions. **Immunogenicity** Antibodies to SIMPONI® were detected in 57 (4%) of SIMPONI®-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® with concomitant MTX had a lower proportion of antibodies to SIMPONI® than patients who received SIMPONI® without MTX (approximately 2% versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI® 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® 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® 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® 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® ± DMARD group and with a higher incidence than in the placebo ± 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® ± DMARDs-treated patients (n=1659) and Placebo ± 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%; Paresthesia 2%, 1%; **Gastrointestinal Disorders:** Constipation 1%, <1%. **Less common clinical trial adverse drug reactions** Adverse drug reactions that occurred <1% in SIMPONI®-treated patients during the SIMPONI® 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 *Neoplasms benign, malignant and unspecified:* leukemia and *subcutaneous tissue disorders:* psoriasis (new onset or worsening, palmar/plantar and pustular), vasculitis (cutaneous) **Vascular disorders:** Vasculitis (systemic) **Post-marketing Experience** The following adverse reactions have been identified during post-approval use of SIMPONI®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to SIMPONI® exposure. **Immune System Disorders:** Serious systemic hypersensitivity reactions (including anaphylactic reaction) (see *Warnings and Precautions*). **DRUG INTERACTIONS: Methotrexate.** For the treatment of RA, SIMPONI® should be used with MTX. Since the presence or absence of concomitant MTX did not appear to influence the efficacy or safety of SIMPONI® in the treatment of PsA or AS, SIMPONI® 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® with abatacept or anakinra is not recommended. A higher rate of serious infections has also been