

Circulating Cytokines May Retard Fetal Growth

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FROM THE JOURNAL OF
REPRODUCTIVE IMMUNOLOGY

Circulating cytokines appear to influence fetal growth in pregnant women who have rheumatoid arthritis, results of a Dutch study suggest.

High levels of interleukin-10, IL-6, and TNF-alpha might all play a role – at different stages of pregnancy – to increase

the risk of low birth weight among infants born to these mothers.

Dr. Radboud Dolhain of Erasmus University Medical Centre, Rotterdam, the Netherlands, and associates examined circulating cytokines in 134 pregnant patients with RA in their first trimester, 168 in their third trimester, and 33 healthy controls (J. Reprod. Immunol. [doi: 10.1016/j.jri.2010.08.010]).

Disease activity was based on the dis-

ease activity score for 28 joints (DAS28).

Among first trimester patients, 12 had detectable IL-10; all had a higher disease activity score than did those with no IL-10 (mean DAS28 4.4 vs. 3.6).

“In the first trimester, elevated IL-10 seems to protect against the negative influence of RA disease activity on birth weight, [while] IL-6 seems to amplify this negative influence,” they wrote. “In the third trimester, there is no influence,

suggesting an early critical window.”

TNF-alpha, however, did exert an influence in the third trimester. This association was not present in the first trimester. This finding implies that “TNF blockers, which are more and more prescribed during pregnancy to treat [RA], should be used with caution,” they said.

The study was funded by the Dutch Arthritis Association. Dr. Dolhain did not disclose any pertinent conflicts. ■

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

WARNING 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.

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 5.4 (95% CI: 4.0, 7.2) for the SIMPONI® group and 5.3 (95% CI: 3.1, 8.7) 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).¹ 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).¹ 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. 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