

Depressed Mood, RA Disease Activity Linked

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In patients with rheumatoid arthritis, higher disease activity scores were associated with more severe depression, both when measured at the same time and when measured 6 months apart, suggesting that the impact the two factors have on each other persists over time.

Similarly, depression predicted increased disease activity later.

The findings, while not necessarily causal, “support the notion that in patients with more severe depressed mood, disease activity is probably greater, not only at the same time but also several months later, and that in patients with more swollen and painful joints, psychological distress is probably greater at the same time and later on,” wrote Dr.

Cécile L. Overman of Utrecht (the Netherlands) University, and associates (Ann. Rheum. Dis. 2011 Sept. 14 [doi:10.1136/annrheumdis-2011-200338]).

Dr. Overman of the department of clinical and health psychology at Utrecht University looked at 545 patients with a recent diagnosis of rheumatoid arthritis (RA) recruited between 1990 and 2002 in the Utrecht region. The patients were enrolled

in a prospective drug trial at the time.

Patients with comorbid psychiatric disorders or drug use were excluded from the study.

Psychological distress was assessed at baseline, before randomization, and then annually for 5 years using the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) questionnaire.

The anxiety portion of IRGL consists of 10 items (scored from 10 to 40) derived from the Spielberger state-trait anxiety inventory; the depressed mood scale consists of six items (scored from 0 to 24).

Disease activity according to erythrocyte sedimentation rate (ESR) and the Thompson articular index was assessed at baseline, every 3 months for the first 2 years, and every 6 months for the next 3 years.

At baseline, the authors found that 45% of patients had a depressed mood according to the IRGL scale, while 36% had anxiety.

Also at baseline, the mean Thompson joint index was 146.0, while the mean ESR was 41.1 mm/hr.

Overall, these high levels of both disease activity and psychological distress decreased sharply in the first year, and continued to decrease over the course of the study, reported the authors, although 26% of patients still had depressed mood after 5 years and 23% reported anxiety.

However, looking prospectively, the authors found that that scores exceeding zero on the depressed mood scale were associated with a higher Thompson joint score ($P = .03$) and a higher ESR ($P = .04$) 6 months later.

Similarly, a higher Thompson joint score was associated with higher levels of depressed mood ($P = .03$) and anxiety ($P = .02$) at assessments occurring 6 months afterward.

On the other hand, elevated anxiety scores were not associated with higher disease activity later on.

“Our data do not support the notion that psychological stress may cause disease flares,” despite “weak” evidence that stress may exacerbate disease activity, they wrote. Nor did elevated ESR levels predict psychological distress down the line.

The authors did admit to several weaknesses in their study. For one, “we used existing data with relatively long intervals between assessments,” wrote Dr. Overman. “More frequent monitoring, for example, every 3 months during 5 years, will increase the chance of finding disease flares and substantial mood changes.”

Additionally, ESR levels and the Thompson joint index are not the only measurements of disease activity available. The authors pointed out that their findings “do not generalize to cytokine and hypothalamic-pituitary-adrenal axis functioning,” for example.

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SIMPONI® (golimumab)

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® and other biologic products approved to treat RA, PsA, or AS. **Live Vaccines** Live vaccines should not be given concurrently with SIMPONI®. Infants born to women treated with SIMPONI during their pregnancy may be at increased risk of infection for up to 6 months. 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 (see *Use in Specific Populations*). **Cytochrome P450 Substrates** The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF α) 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® 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® in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI® 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. IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of infants born to patients treated with these antibodies. Since SIMPONI is an IgG antibody, infants born to women treated with SIMPONI during their pregnancy may be at increased risk of infection for up to 6 months. 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 (see Warnings and Precautions). **Nursing Mothers** It is not known whether SIMPONI® 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®, 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® 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®-treated patients ages 65 or older (N=155) compared with younger SIMPONI®-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®. **OVERDOSAGE** In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of intravenous SIMPONI® 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®. There were no SIMPONI® overdoses in the clinical studies. **PATIENT COUNSELING INFORMATION Patient Counseling** Patients should be advised of the potential benefits and risks of SIMPONI®. Physicians should instruct their patients to read the Medication Guide before starting SIMPONI® therapy and to read it each time the prescription is renewed. **Infections** Inform patients that SIMPONI® 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®. **Allergic Reactions** Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled syringe in the prefilled SmartJect® 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>.

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