Rheumatoid Arthritis Drugs

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Rheumatoid arthritis patients suffering from interstitial lung disease may eventually have more targeted therapies, thanks to new evidence on the pathophysiology of the pulmonary condition.

Using computer-assisted image analysis, a team of investigators from the Mayo Clinic in Rochester, Minn., demonstrated an increased number of certain subtypes of T cells in the lung tissue of rheumatoid arthritis (RA) patients with interstitial pneumonitis (IP) compared with patients with the same pulmonary diagnosis who did not have RA.

The results support the long-held hypothesis that lung disease associated with RA might be a T-cell driven, said Eric Matteson, M.D., one of the principal investigators.

“The fact that rheumatoid arthritis is thought to be a largely T-cell-driven disease has led to suspicions that T cells also play a major role in lung disease in RA patients.”

This study is the first to demonstrate the association through laboratory testing, he noted. “Up to this point, the possibility that extraarticular organ disease in RA is T-cell [mediated] has not been shown, other than studies of salivary glands in patients with Sjogren’s disease,” he said.

The results also support the contention that rheumatoid interstitial lung disease is fundamentally different from other forms of the chronic, progressive pulmonary disorder, despite similarities in radiographic and histopathologic appearance. As such, the treatment approach “should likely be different as well,” Matteson said.

In their investigation, the Mayo Clinic researchers compared the prevalence of T-cell subtypes in lung biopsy specimens from 15 patients with rheumatoid IP with that observed in the specimens from 16 non-RA patients with idiopathic IP. Using immunohistochemical staining to enhance the T cells for microscopy and a high-resolution digital camera, the investigators acquired a total of 11,412 digital images of the stained specimens magnified 100 times (Arthritis Rheum. 2005;52:73-9).

They found that T cells also play a major role in lung disease in RA patients. “Steroids would be expected to be effective in rheumatoid lung disease, which is estimated to affect 500,000 patients in the United States. The image analysis technique employed by the investigators could be used to identify patients with RA-related lung disease early in the disease process. Rheumatoid arthritis that is complicated by interstitial lung disease is more likely to be fatal if not treated aggressively in its early stages, Matteson said. These findings also may help guide the use and/or development of more drugs that specifically target the involved immune system,” he noted.

There is a certain nihilism about treating putatively immune mediated interstitial lung disease in idiopathic cases as well as in inflammatory rheumatic diseases, because so many patients seem to respond poorly to therapy, which is relatively nonspecific,” said Dr. Matteson.

The conventional treatment approaches include high-dose glucocorticosteroids, cyclophosphamide, and cyclosporine, although there are no data demonstrating the efficacy of these agents on lung function or survival.

“T-cell directed therapies such as the anti-CD4 therapies under development may be more appropriate for managing rheumatoid lung disease,” Matteson said.

“T cells also govern, and are governed by, the cytokine milieu in rheumatoid arthritis, including tumor necrosis factor. These therapies could also be helpful, although emerging reports of TNF-related pulmonary toxicity indicate there is still much to be learned before these approaches are considered safe.”

In addition to T-cell involvement, the B cell may be of central importance to lung disease, and may also provide a potential target. The Mayo team is actively investigating the possibility of B-cell involvement, as well as antigen development and processing in the rheumatic lung.

The autoimmune disorder rheumatoid arthritis occurs in about 1% to 2% of the population. The disease is more prevalent in women than men by about a 3:1 ratio, but in the reproductive years, the ratio may be as high as 7:1. During pregnancy, the incidence is about 1:1,000.

RA is characterized by the production of cytokines, including tumor necrosis factor (TNF) - and interleukin-1 in the synovial cavity, and irreversible damage to soft tissues and bones. Drug therapy of RA involves the use of disease-modifying antirheumatic drugs (DMARDs) to prevent or lessen this damage. The therapy can be categorized as biologic DMARDs, synthetic DMARDs, and anti-inflammatory agents.

Biologic DMARDs include three agents that inhibit TNF — adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade) — and one interleukin-1 receptor antagonist, anakinra (Kineret). Although the human pregnancy data for these four drugs are very limited or completely absent, animal studies suggest they pose a low risk for developmental toxicity (growth retardation, structural defects, functional/behavioral defects, or death).

The safest course is to avoid these agents in the first trimester, but with their long elimination half-lives, inadvertent exposures during organogenesis of unplanned pregnancies is likely.

The synthetic DMARDs include azathioprine (Imuran), cyclosporine (Sandimmune, Neoral), gold compounds, hydroxychloroquine (Plaque-Nil), methotrexate, penicillamine, and sulfasalazine (Azulfidine).

The two immunosuppressants, azathioprine and cyclosporine, do not appear to cause congenital defects, but may be associated with growth retardation. There is limited human pregnancy experience with the gold compounds — auranofin (Ridaura), aurothioglucone (Solganol), and gold sodium thiocelate (Aurosole) — but animal data suggest the risk for developmental toxicity is low.

Hydroxychloroquine is probably compatible in pregnancy. But there is limited pregnancy experience with the high doses used in RA. The drug has a long elimination half-life from maternal tissues (weeks to months) so stopping the drug when pregnancy is confirmed will not prevent embryo/fetal exposure.

Leflunomide, a pyrimidine synthesis inhibitor, causes a related teratogenicity and toxicity in animals at doses much lower than those used in humans. Human pregnancy experience is too limited to draw conclusions about the drug for the embryo or fetus, and the drug is contraindicated in pregnancy.

Exposure of unplanned pregnancies will probably occur because the drug and its active metabolite may take up to 2 years to reach nondetectable plasma levels.

The folic acid antagonist methotrexate is contraindicated during pregnancy.

The drug is associated with spontaneous abortions and a spectrum of congenital defects collectively termed methotrexate embryopathy. The critical exposure period for structural defects is 8-10 weeks after the first day of the last menstrual period. Exposure after this period is associated with fetal toxicity and mortality. The critical dose is thought to be 10 mg or more per week.

Another folate antagonist, sulfasalazine, does not appear to cause developmental toxicity, but supplemental folic acid (1 mg/day) should be used if there is a risk of unplanned pregnancy or if pregnancy occurs.

The drug has caused bloody diarrhea in a nursing infant, so breast-feeding should be undertaken cautiously. Penicillamine, a chelating agent, is associated with a risk of fetal connective tissue defects (cutis laxa) and should be avoided during pregnancy.

The anti-inflammatory agents include prednisone and the NSAI ds, which include aspirin. There is considerable potential for embryo/fetal toxicity from NSAI ds: spontaneous abortions when used around the time of conception, fetal renal toxicity, and premature closure of the ductus arteriosus in the third trimester. Aspirin use near term may increase the risk of bleeding in the mother and the infant. The use of prednisone during organogenesis carries a low risk for oral clefts and prolonged use in pregnancy has been associated with growth retardation.

The biologic DMARDs, gold compounds, hydroxychloroquine, NSAI ds (except high-dose aspirin), and prednisone are probably compatible with breastfeeding. The other agents are either contraindicated (methotrexate) or should be avoided because of potential toxicity. High-dose aspirin and sulfasalazine have been associated with toxicity in nursing infants.

The organization of histology Information Services is conducting a study of pregnancy exposure to RA drugs. Call the toll-free number (877-311-8972) for information on enrolling patients in the study.

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