Monitoring Biological Therapies in Psoriatic Arthritis

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ABSTRACT. Longterm use of tumor necrosis factor–α (TNF–α) blocking agents requires ongoing monitoring to confirm efficacy and to avoid drug toxicity. Epidemiologic studies may offer important complementary information about risks and benefits of this class of drugs. The safety profile of biologic therapies includes a wide spectrum of adverse events, of which the most relevant are risk of infections, malignancy, and cardiovascular diseases. The lack of published recommendations on monitoring suggests that clinicians must evaluate the patient for the risk or presence of any adverse events by regular checkups, with careful assessments, for their early detection. The safety profile in regard to psoriatic arthritis is discussed. (J Rheumatol 2009;36 Suppl 83:69-70; doi:10.3899/jrheum.090230)

Key Indexing Terms: BIOLOGIC THERAPIES ADVERSE EVENTS PSORIATIC ARTHRITIS

Successful longterm use of tumor necrosis factor–α (TNF–α) blocking agents and other biological agents requires ongoing monitoring to confirm efficacy and to avoid drug toxicity. Recommendations for the use of TNF–α blocking agents in the treatment of psoriatic arthritis (PsA) have been developed in many countries, including Italy1.

Randomized controlled trials are the gold standard for defining the benefits of a particular drug in ideal circumstances, conducted in highly selected populations for short periods of time and in strictly controlled settings. This scenario could be substantially different in a routine care setting, and for this reason epidemiologic studies may offer important complementary information about the full spectrum of benefits and risks of a drug. Key methodological issues in pharmacoepidemiologic studies are the window of exposure to risk, drug initiator cohorts versus ongoing user cohorts, comparator drugs, combination therapy, controlling for potential confounding, definition of the endpoint, time varying confounding, and different data sources2.

It is not known if the safety profile from rheumatoid arthritis (RA) trials is completely comparable with PsA, because there was a higher prevalence of hepatotoxicity due to methotrexate (MTX) and leflunomide in PsA3. Nevertheless, safety and tolerability data with TNF–α blocking agents in PsA have not demonstrated any adverse events that were significantly different from RA trials4, and none of the anti TNF–α drugs was discontinued for hepatotoxicity in the CIASsification of Psoriatic Arthritis (CASPAR) study5. Since 2001, we admitted to our rheumatology unit 165 patients with PsA treated with TNF–α blockers, and we observed 1.89 severe adverse events (SAE) per 100 patient years, ranging from 8.87 (infliximab) to 0.4 (etanercept).

Results from the South Swedish Arthritis Treatment Group register showed that TNF–α blocking agents were generally well tolerated during the observational period, with a similar incidence of SAE of around 5% to 6% per year in patients with PsA6. This analysis showed that the concomitant use of MTX with TNF–α blocking agents was associated with longterm drug survival, primarily linked to fewer dropouts due to adverse events5. Nevertheless, the analysis did not consider each anti-TNF–α drug subgroup; however, our data suggest that etanercept can be used either in monotherapy or in combination with MTX. And this does not seem to be a positive predictor of anti-TNF–α drug survival in the treatment of patients with PsA5. The safety profile of biologic therapies must cover a wide spectrum of adverse events, of which the relevant issues are risk of infections, malignancy, and cardiovascular diseases.

Risk of infections must include bacterial (i.e., reactivation of tuberculosis), viral (i.e., hepatitis B virus), and, rarely, fungal agents. There have been several epidemiologic studies regarding the association of TNF–α antagonists with infections, but 3 studies found no increase in the risk of bacterial infection associated to use of TNF–α antagonists as compared to MTX, whereas 3 studies showed a statistically significant increase in infection risk in RA6. There is some evidence that non-serious infections are slightly increased when patients use TNF–α blockers; however, it is probable that there is no increase in serious infections compared with patients using disease modifying antirheumatic drugs7. Data on infections during anti-TNF–α therapy display an increased risk shortly after treatment starts8.

The risk of malignancy during anti TNF–α therapy is a matter of debate. Observational studies of RA patients treated with or without anti-TNF–α have so far not been...
able to replicate the observations of a short term increase in risk, nor have they suggested any increased overall risk of cancer within 1 to 2 years\textsuperscript{9}. Analysis of incident cases of cancer among 13,001 patients during 49,000 patient years of observation in the years 1998 to 2005 showed that biologic therapy is associated with an increased risk for skin cancers, but not for solid tumors or lymphoproliferative malignancies. These associations were consistent across different biologic therapies\textsuperscript{10}. The incidence of malignancy in the large PsA cohort (655 patients) did not differ from that in the general population. There was no evidence that the treatment used in this patient cohort increased the risk of malignancy, but biologic agents had only ever been used by 9.7\% of patients in the non-malignancy group and by 2.9\% of patients in the malignancy group, prior to occurrence of malignancy\textsuperscript{11}.

Cardiovascular diseases and their risk factors are more common in patients with PsA than in controls\textsuperscript{12}, and PsA may be associated with obesity, hypertension, dyslipidemia, and insulin resistance because of the shared inflammatory pathway\textsuperscript{13}. This suggests that suppression of inflammation may reduce cardiovascular risk. Nevertheless, it has been recommended to avoid anti-TNF–\(\alpha\) therapy in patients with New York Heart Association (NYHA) Class III or IV congestive heart failure (CHF) and to discontinue these drugs in patients who develop new onset heart failure while on anti-TNF–\(\alpha\) therapy\textsuperscript{8}. Indeed, 2 randomized controlled clinical trials (RENAISSANCE-RECOVER and ATTACH) failed to show that mortality rate and CHF hospitalizations decreased with anti-TNF–\(\alpha\) therapy, with trends towards a worse prognosis that was dose-dependent, even if other studies did not indicate increased risk of CHF from anti-TNF–\(\alpha\) use\textsuperscript{7}.

In conclusion, considerable uncertainty remains regarding how best to monitor the safety of anti-TNF–\(\alpha\) drugs, although surveys of rheumatologists have provided useful information\textsuperscript{14,15}. The lack of published recommendations on monitoring suggests that the clinicians must evaluate the patient for the risk or presence of any adverse events by regular checkups, with careful assessments, for their early detection.

**REFERENCES**