TNF Inhibitors and the Risk of Melanoma

New research offers a deeper look into the potential elevated risk for malignant melanoma from TNF treatment.

BY JONATHAN WOLFE, MD

Commonly prescribed for conditions such as rheumatoid arthritis and Crohn’s disease, TNF inhibitors have also gained considerable momentum within dermatology for the treatment of moderate to severe psoriatic disease. While TNF inhibitors are powerful, effective agents in managing psoriasis and other conditions, their complex adverse event profiles require physicians to screen patients for potential risks. Among the conditions with which TNF inhibitors have been associated are skin cancers, such as basal cell and squamous cell carcinoma. Other malignancies, on the other hand, are much less common. However, new research looking into the potential link between TNF inhibitors and melanoma has revitalized interest in the topic and may carry certain implications for dermatologists.

TNF and Melanoma
A study published this year in the British Medical Journal represents one of the few major studies to examine the potential association between TNF inhibitors treatment and malignant melanomas in rheumatoid arthritis patients. The researchers examined prospectively recorded data from national clinical, health, and demographic registers, with the primary outcome being the first invasive melanoma in people without any history of invasive cancer of any type. They found that 113 first invasive melanomas occurred in rheumatoid arthritis patients not treated with biological drugs, and 393 occurred in the general population comparator cohort. Rheumatoid arthritis patients not treated with biological drugs were not at significantly increased risk of melanoma compared with the general population. Interestingly, 38 first invasive melanomas occurred in rheumatoid arthritis patients treated with TNF inhibitors. These patients had an increased risk of melanoma compared with rheumatoid arthritis patients not treated with biological drugs. The authors concluded that rheumatoid arthritis patients selected for TNF inhibitor treatment are not at increased overall risk for cancer but have a 50 percent increased relative risk of invasive melanoma.

These findings were published shortly after the publication of a case report in which a patient treated with adalimumab (Humira, AbbVie) for severe Crohn’s disease for three years before the occurrence of malignant melanoma. The researchers suggested that the long duration of the adalimumab therapy coupled with the patient’s lack of a predisposition to skin cancer suggests an association between anti-TNF drugs and melanocytic proliferation. Another case report from 2011 offered similar findings: a psoriatic arthritis patient treated with adalimumab for three years developed melanoma with metastatic involvement of regional lymph nodes. In both cases, the investigators went on to recommend further long-term controlled clinical trials and registries to investigate the risk of malignancy with biological therapy.2,3

Other case reports detailing the occurrence of malignant melanomas in patients treated with TNF inhibitors go back as far as 2009; a patient with recalcitrant moderate to severe psoriasis was treated for a 30-month treatment period with TNF-alpha-antagonists, incorporating infliximab (Remicade, Janssen), adalimumab, and etanercept (Enbrel, Amgen/Pfizer) and then developed a malignant melanoma.4 Then, again, in 2010 a patient with rheumatoid arthritis was treated with adalimumab for roughly 12 months and was diagnosed with a malignant melanoma on his right leg.5

NMSC and Other Cancer Risks
While recent research into TNF inhibitors and skin cancer risks has emphasized the link between TNF agents and melanoma, biological treatments have also been associated with slightly elevated risk of certain carcinomas, though data in recent years have been somewhat murky as to the exact level of risk. For example, a recent meta-analysis of clinical trials leading to the approval of TNF inhibitors for the treatment of RA found no evidence for an excess cancer risk on TNF antagonists in adult rheumatoid arthritis patients.6 The researchers did not rule out an excess cancer risk after several years of exposure, however.

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Other studies have reached similar conclusions.\(^7\,8\) However, the incidence of non-melanoma skin cancer has been fairly consistent, with elevated risk having been documented in numerous cases.\(^7\,10\) In a large, national cohort study, for example, researchers found an unadjusted incidence rate for reported NMSC among patients with RA and osteoarthritis were 18.1 and 20.4 per 100 patient years, respectively.\(^9\) After adjustment for co-variates, while RA was independently associated with an increased risk of NMSC, the development of NMSC was also associated with use of TNF inhibitors.\(^9\)

**CONCLUSION**

The studies I’ve highlighted here support the notion that the immunosuppressive properties of TNF agents may lead to reduced immune surveillance and tumor formation, thus possibly increasing the risk of malignancies or the reactivation of latent malignancies. For dermatologists, it is imperative to realize that these studies are in patient populations with different disease states than the classic psoriasis indication we face. Further, these patients often have received other immunomodulatory agents predisposing them to malignancies. However, these studies reveal that compounding immunosuppressive agents may alter immune surveillance systems, leading to long-term toxicity. These findings might not be substantive enough to shift the safety profiles of these agents or their use in practice, however, they represent important clinical development about which all clinicians prescribing these agents should be informed. As more studies examine the link between these drugs and malignant melanoma and NMSCs, we hope to learn more about this potentially significant relationship.

Jonathan Wolfe, MD is a Clinical Associate Professor of Dermatology at the University of Pennsylvania in Philadelphia, PA, where he is on the staff of the Pigmented Lesion Clinic. He is also in private practice in Plymouth Meeting, PA.