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Melanoma Associated with TNF α Inhibitors: a Research on Adverse Drug events And Reports (RADAR) Project

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Abstract

Background—Tumor necrosis factor-alpha inhibitors (TNF α Is) are used for treatment of inflammatory disorders. There is evidence linking these agents with occurrence of malignancies. For four out of five TNF α Is the Food and Drug Administration (FDA) label states, “melanoma has been reported in patients treated with these agents.”

Objectives—Determine whether a statistically-significant association exists between administration of TNF α Is and development of malignant melanoma.

Methods—We searched the FDA Adverse Events Reporting System (FAERS) database for terms related to melanoma and TNF α Is for detection of safety signals. We also searched a large urban academic electronic medical record (EMR) database for which we calculated the relative risk (RR) of melanoma in subjects exposed to TNF α Is vs. non-exposed subjects.

Results—There were 972 reports of melanoma associated with a TNF α Is identified in the FAERS database, with 69 reports among individuals using more than one TNF α I. A safety signal was detected for infliximab (I) golimumab (G), etanercept (E), and adalimumab (A). Cetrolizumab pegol (CP) had no detectible safety signal. For TNF α Is as a class of drugs, a safety signal was detectable in the FAERS database, and RR was significant in the EMR database. For the EMR cohort, 6,045 patients were exposed to TNF α Is and 35 cases of melanoma were detected. Significance for RR was detected for A (RR = 1.8, p = 0.02) and E (RR 2.35, p = 0.0004).

Conclusions—We identified a significant association between exposure to TNF α Is and malignant melanoma in two different analyses. Our findings add to existing evidence linking these agents with the occurrence of malignant melanoma. Additional investigations are required to further explore this association and the risk of melanoma with TNF α I therapy.

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Introduction

Tumor Necrosis Factor- α inhibitors (TNFaIs) are widely-used monoclonal antibodies for the treatment of several dermatologic, rheumatologic, and gastrointestinal inflammatory disorders. TNFa is an important cytokine that regulates systemic inflammation, and its inhibition results in immunosuppression and therapeutic benefit in the above systemic inflammatory disorders. Despite the potential therapeutic benefit of TNFaIs, there is some evidence that links TNFaIs with the occurrence of malignancies. Recently-reported retrospective cohort and case-control data have indicated that patients with inflammatory bowel disease who were treated with biologics have an increased risk of melanoma.¹ Moreover, a prospective cohort study showed an increased risk of melanoma in rheumatoid arthritis patients treated with TNFaIs,² and there are at least 10 case reports of patients developing melanoma after TNFaI treatment. Currently, for four out of five TNFaIs, the FDA package insert states that “melanoma has been reported in patients treated with these agents.” We elected to determine whether a statistically-significant association or safety signal exists between administration of TNFaIs and development of melanoma, regardless of concurrent diagnosis. Our local institution’s electronic medical record (EMR) database (2.2 million individuals) was used for assessing statistical association and the FDA Adverse Event Reporting System (FAERS) database was used for assessing safety signals.

Materials and Methods

Using RADAR methodology,³ we searched a large urban academic center EMR database and calculated the relative risk (RR) of melanoma in subjects exposed to TNFaIs compared with non-exposed subjects. Again using RADAR methodology, we also searched the FAERS database for terms related to melanoma, including malignant melanoma, malignant melanocytic tumor, melanoma in situ, amelanotic melanoma, metastatic melanoma, lentigo maligna, Hutchinson’s melanocytic freckle, uveal melanoma, and others, combined with all five currently FDA-approved TNFaIs. The search was carried out from the date of each drug’s FDA approval through August 2012. We performed a disproportionality analysis by calculating empirical Bayes geometric means (EBGM) with accompanying 95% confidence intervals (CIs) for detection of safety signals, specifically to determine whether melanoma was reported at a significantly higher rate when compared to reporting for all other drugs in the entire FAERS database.⁴

Results

For the EMR cohort, 6,045 patients were exposed to TNFaIs and 35 cases of melanoma were detected (I, n = 3; G, n = 1; E, n = 17; A, n = 14; CP, n = 0). Significance for RR was detected for A (RR = 1.8, 95% CI 1.06–3.00, p = 0.02) and E (RR 2.35, 95% CI 1.46 to 3.77, p = 0.0004) for prevalence rate of 58 patients per 10,000 patients receiving TNFaIs.

There were 972 reports of melanoma associated with a TNFaI identified in the FAERS database, with 69 reports among individuals using more than one TNFaI. A safety signal was detected for infliximab (I), n = 434 (EBGM 7.90, 95% CI 7.13–8.60), golimumab (G), n = 10 (EBGM 5.34, 95% CI 2.41–9.88), etanercept (E), n = 347 (EBGM 2.49, 95% CI 2.24–

2.76), and adalimumab (A), $n = 237$ (EBGM 2.49, 95% CI 2.19–2.83). Cetrolizumab pegol (CP), $n = 13$ had no detectible safety signal. For TNFaIs as a class of drugs, a safety signal was detectable in the FAERS database (EBGM 3.30, 95% CI 3.10–3.52) and RR was significant in the EMR database (RR = 1.75, 95% CI 1.25–2.43, $p < 0.0009$).

Discussion

We identified a significant association between exposure to TNFaIs and development of melanoma for all drugs except CP in the FAERS database. Concordantly, unlike the other four approved TNFaIs, the current FDA labeling for CP does not include melanoma as an adverse effect. We also identified a similar association for drugs A and E in the academic EMR dataset and for the TNFaI class of drugs taken as a whole. Our findings add to existing evidence linking these agents with the occurrence of melanoma, and are the first to analyze the linkage between TNFaIs and melanoma across all concurrent diagnoses. We estimated a prevalence rate associated with TNFaI drugs. However, malignant melanoma and other malignancies are associated with chronic inflammatory conditions in general. Additionally, immunosuppression itself is known to be associated with particular cutaneous malignancies, notably, malignant melanoma. Moreover, limitations of this study include the lack of known melanoma risk factors data, especially phototherapy commonly used in psoriasis patients who represent one of the target population for these drugs. Thus, we did not ascertain TNF alpha inhibitors as an independent risk factor for development of melanoma. Our findings imply that additional investigations are essential to further explore this association and the risk of melanoma with TNFaI therapy. Additionally, from a regulatory standpoint, it may be suggested that the FDA strengthen its labeling for TNFaIs to indicate that they as a drug class have been statistically associated with the development of melanoma.

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What is already known about this topic?

- Tumor necrosis factor-alpha inhibitors (TNFαIs) have been linked with the occurrence of malignancies, including melanoma. Statistical association has not been clarified yet

What does this study add?

- A safety signal has been detected in the Food and Drug Administration Adverse Event Reporting System (FAERS) database.
- Enhanced monitoring for patients receiving TNFαIs is therefore warranted.