Melanoma and non-Melanoma Skin Cancer in Inflammatory Bowel Disease Patients following Tumor Necrosis Factor-α Inhibitor Monotherapy and in Combination with Thiopurines: Analysis of the Food and Drug Administration Adverse Event Reporting System

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ABSTRACT

Background & Aims: Reports have shown an increased risk of melanoma skin cancer (MSC) with exposure to tumor necrosis factor alpha (TNF-α) inhibitors and non-melanoma skin cancer (NMSC) with thiopurine exposure in inflammatory bowel disease (IBD) patients. Using the Food and Drug Administration Adverse Event Reporting System (FAERS) we sought to evaluate the odds of developing MSC and NMSC for patients on TNF-α inhibitors as monotherapy and in combination therapy with thiopurines and/or steroids.

Methods: The FAERS was queried for reports between January 2003 and June 2012. A proportional reporting ratio (PRR) metric analyses was performed on the data to determine the odds of developing MSC and NMSC.

Results: The PRR analysis showed increased odds of developing MSC and NMSC for patients on a TNF-α inhibitor (p-value = 0.035 and p-value = 0.03, respectively) and those on a TNF-α inhibitor in combination with a thiopurine (p-value < 0.001 and p-value < 0.001).

Conclusion: TNF-α inhibitor monotherapy or use with concomitant thiopurines in patients with IBD is associated with higher odds of developing MSC and NMSC.

Key words: tumor necrosis factor-alpha/antagonists and inhibitors – skin neoplasms/chemically induced – inflammatory bowel diseases/complications – inflammatory bowel diseases/drug therapy.

INTRODUCTION

Non-melanoma skin cancer (NMSC) is the most common malignancy in the United States, with an estimated 2.1 million people diagnosed with some form of NMSC in 2006 [1]. Fortunately, mortality resulting from NMSC is low, with both basal and squamous cell carcinomas, the two most common types of NMSC, having cure rates close to 95 percent when detected early [2]. Melanoma skin cancer (MSC), on the other hand, is less common but more often fatal. In 2013, it was estimated that nearly 77,000 Americans will be diagnosed with MSC and that 7,910 deaths will result from the disease [3]. Studies have shown that individuals suffering from inflammatory bowel disease (IBD), including both those with ulcerative colitis (UC) and Crohn’s disease (CD), are at a higher risk for developing NMSC [4-8] and MSC [8, 9].

Certain treatments for IBD are thought to further augment the risk of NMSC and MSC. It has been suggested that thiopurine usage increases the risk of developing NMSC [8] particularly squamous cell carcinoma [4, 6] but a similar association with MSC has not been shown [8]. Studies have shown varying results with regards to the risk of NMSC and MSC with tumor necrosis factor α (TNF-α) inhibitors in the treatment of IBD. Askling et al [10] noted that TNF-α inhibitors increase the short-term risk of NMSC, while other studies have suggested a link between the use of TNF-α inhibitors and an increased risk of MSC [8]. Various other studies have proven to be inconclusive or did not suggest a link with MSC [11-13].

It is important to determine if TNF-α inhibitors increase the risk of MSC and NMSC, and if so, to what extent, so that
clinicians can properly weigh the risks and benefits of TNF-α inhibitor therapy. This study aims to evaluate the odds of MSC and NMSC developing in patients with IBD with TNF-α inhibitors monotherapy and when used in combination with thiopurines and/or steroids utilizing the Food and Drug Administration Adverse Event Reporting System (FAERS).

METHODS

Databases

A total of 3,171,655 cases dated between January 2003 and June 2012 were downloaded from the FAERS database and analyzed using SPSS 20. The FAERS is a public access voluntary reporting system utilized by the FDA to help evaluate potential safety concerns with marketed medications [14].

To assemble the dataset, the FAERS was queried through medication usage for cases of CD or UC using terms from the Medical Dictionary of Regulatory Activities (MedDRA). Cases reported as both UC and CD were grouped into the IBD category, and cases of ulcerative proctitis were included in the UC grouping. This database, limited by indication, was then searched for all instances of NMSC and MSC reported in patients with the IBD medications of interest: all three TNF-α inhibitors approved during the study's time span (infliximab, adalimumab, and certolizumab pegol), systemic corticosteroids, and thiopurines (6-mercaptopurine, 6-MP and azathioprine, AZA). Generics as well as trade names were included in the analysis. Control medications included mesalamine and sulfasalazine (generics as well as trade names) (5-aminosalicylate, 5-ASA), which were determined a priori to have no association with MSC or NMSC [15]. One of the study or control drugs had to be listed as the ‘primary suspect’ in the database for a report to be included in the dataset. Additionally, one of the study drugs had to be a TNF-α inhibitor to be included. Concomitant medications were analyzed, and any reports that contained a concomitant biologic medication not approved for the treatment of UC or CD or a non-TNF-α biologic medication were excluded from further analysis.

Predictor and outcome variables

The outcome variable of interest were the odds of NMSC and MSC for individuals on TNF-α inhibitor monotherapy or TNF-α inhibitor therapy with concomitant thiopurines and/or corticosteroids. To control for potential reporting biases, skin cancer reports were examined for control drug treatment. In this case, 5-ASA was used as a control drug since its use has not been previously linked with an increased risk of NMSC or MSC [15]. For a control drug report to be included in the control group, it had to be a primary suspect report without concomitant use of any corticosteroids, thiopurines, TNF-α inhibitors, or other biologic drugs. Control reactions for the study and control drugs, defined as events not known to have an association with either the study or control drugs, included "syncope," "hernia," "deafness," and "vertigo".

Statistical analysis

Since the FAERS depends on spontaneous reporting, this study utilized the proportional reporting ratio (PRR) metric. PRR has been discussed in prior studies as a way to help reduce potential reporting biases when examining the toxicity of medications using the FAERS [16, 17]. The number of reports of MSC or NMSC with a test drug was compared to the count of events of MSC or NMSC with the control drug and then to control reactions using 2x2 tables to perform Fisher’s exact test.

Ethical considerations

NorthShore University Health System’s Institutional Review Board deemed this research protocol exempt from review.

RESULTS

Patient characteristics
A total of 137 MSC, 169 NMSC, and 9 cases of both were identified in the FAERS system for a total of 315 cancer reports (Table I). Two hundred and forty-nine of those reports featured individuals with CD, which was greater than five times the number of UC reports. The largest number of skin cancer cases involved individuals utilizing TNF-α inhibitor monotherapy for the treatment of their IBD. However, the largest number of control reactions was also reported with TNF-α inhibitor monotherapy (Table II). The second largest number of skin cancer reports was associated with individuals managing their IBD through dual therapy of a TNF-α inhibitor and a thiopurine (Table II). As our group has previously described a potential bias in the FAERS related to lawyer reports, it is important to note that only one control reaction was reported by a lawyer and none of the MSC or NMSC cases were reported by lawyers [18].

Melanoma skin cancer in individuals with IBD

Individuals using TNF-α inhibitor monotherapy for their treatment of IBD were found to have higher odds of developing MSC in comparison to the control drug (p = 0.035) with the PRR analysis (Table II). Similar results were found in patients managing their IBD through dual therapy with a TNF-α inhibitor and a thiopurine (p < 0.001) and TNF-α inhibitor with concomitant thiopurine and corticosteroid treatment (p = 0.008) (Table II). However, use of TNF-α inhibitors with concomitant corticosteroids was not associated with increased odds of developing MSC (Table II).

Non-melanoma skin cancer in individuals with IBD

Using the PRR method, augmented odds of developing NMSC were seen in individuals exposed to TNF-α inhibitor monotherapy (p = 0.036), with concomitant thiopurine therapy (p < 0.001), or with concomitant corticosteroids and thiopurines (p < 0.005) (Table II). TNF-α inhibitor with concomitant corticosteroid treatment was not associated with increased odds of developing NMSC (p = 0.077).

DISCUSSION

Utilizing the FAERS, we examined the odds of developing NMSC and MSC in individuals with IBD using TNF-α inhibitor monotherapy or TNF-α inhibitor in combination with thiopurines and/or corticosteroids. The results of this study suggest an increased risk of both MSC and NMSC in
Development of MSC and NMSC in IBD patients

consistent with study findings, published literature has suggested increased odds of developing MSC and NMSC for IBD patients on TNF-α inhibitor monotherapy. In a retrospective study performed by Long et al [8], IBD patients were found to have higher incidence rates of MSC when on TNF-α inhibitor monotherapy. While Long’s study did not note an overall increased NMSC risk in the TNF-α inhibitor monotherapy cohort, further analysis identified an increased odds ratio for the subset of individuals on TNF-α inhibitor therapy for more than one year [8]. Askling et al [10] performed a meta-analysis of 74 randomized controlled trials and found that TNF-α inhibitor usage nearly doubled a person’s risk of NMSC. Several studies that did not establish the link between TNF-α inhibitors and augmented MSC risk were either limited in sample size or follow-up period [11-13].

On a physiological level, overexposure to insulin-like growth factor-1 (IGF-1) has been linked with augmented risks for several types of cancers [19, 20]. While the specific relationship between IGF-1 and MSC is still debated, previous research has noted that the presence of IGF-1 enhanced the proliferation of biologically early MSC [21]. TNF-α is a known inhibitor of the IGF-1 pathway due to cross-talk signaling, and has been shown to block IGF-1 mRNA production [22]. It has also been shown that introduction of binding proteins to TNF-α eliminates its ability to down regulate IGF-1 [22]. Since TNF-α inhibitors bind TNF-α, it is likely that IGF-1 levels rise in individuals using TNF-α inhibitor treatment, thus increasing the individual’s cancer risk.

Our results showed that while TNF-α inhibitor monotherapy increased the odds of MSC and NMSC, TNF-α inhibitor and corticosteroid dual therapy did not. This finding could be further indicative of the relationship between TNF-α inhibitors and IGF-1, as corticosteroids have been shown in prior studies to blunt IGF-1 release creating a protective effect [23]. Our results suggest that the limiting effect of corticosteroids offset the increased IGF-1 levels that could be associated with TNF-α inhibitor use as monotherapy.

Thiopurines have not been reported to augment an individual’s odds of developing MSC when used in monotherapy [8]. However, limited data exists regarding the MSC risk with combined TNF-α inhibitor and thiopurine dual therapy. Long’s study could not examine the relationship due to a limited sample size [8]. However, thiopurines do possess immunosuppressive properties [24], which suggest that combination therapy could be associated with increased odds of MSC as demonstrated in this study. Thiopurine use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Drug (N=22)</th>
<th>TNF-α inhibitors (N=607)</th>
<th>TNF-α inhibitors + Thiopurine (N=169)</th>
<th>TNF-α inhibitors + Steroid (N=123)</th>
<th>TNF-α inhibitors + Thiopurine + Steroid (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD</td>
<td>35.5±20.4</td>
<td>46.1±15.7</td>
<td>46.2±15.1</td>
<td>45.6±17.4</td>
<td>40.9±16.0</td>
</tr>
<tr>
<td>Female</td>
<td>15 (68.2)</td>
<td>356 (58.6)</td>
<td>91 (53.8)</td>
<td>70 (56.9)</td>
<td>37 (51.4)</td>
</tr>
<tr>
<td>Type of inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>10 (45.5)</td>
<td>69 (11.4)</td>
<td>19 (11.2)</td>
<td>16 (13.0)</td>
<td>10 (13.9)</td>
</tr>
<tr>
<td>CD</td>
<td>12 (54.5)</td>
<td>525 (86.5)</td>
<td>140 (82.8)</td>
<td>101 (82.1)</td>
<td>59 (81.9)</td>
</tr>
<tr>
<td>IBD</td>
<td>0 (0.0)</td>
<td>13 (2.1)</td>
<td>10 (5.9)</td>
<td>6 (4.9)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Type of skin cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSC</td>
<td>0 (0.0)</td>
<td>79 (13.0)</td>
<td>38 (22.5)</td>
<td>8 (6.5)</td>
<td>12 (16.7)</td>
</tr>
<tr>
<td>NMSC</td>
<td>0 (0.0)</td>
<td>89 (14.7)</td>
<td>51 (30.2)</td>
<td>15 (12.2)</td>
<td>14 (19.4)</td>
</tr>
<tr>
<td>MSC and NMSC</td>
<td>0 (0.0)</td>
<td>4 (0.7)</td>
<td>0 (0.0)</td>
<td>3 (2.4)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>7 (1.2)</td>
<td>6 (3.6)</td>
<td>5 (4.1)</td>
<td>4 (5.6)</td>
</tr>
</tbody>
</table>

CD – Crohn’s disease; IBD – Inflammatory Bowel Disease; MSC – Melanoma Skin Cancer; NMSC – Non-melanoma skin cancer; UC – Ulcerative Colitis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MSC</th>
<th>P Value</th>
<th>NMSC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α inhibitors</td>
<td>83</td>
<td>0.035</td>
<td>93</td>
<td>0.036</td>
</tr>
<tr>
<td>TNF-α inhibitors and thiopurines</td>
<td>38</td>
<td>&lt;0.001</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF-α inhibitors and steroids</td>
<td>11</td>
<td>0.209</td>
<td>18</td>
<td>0.077</td>
</tr>
<tr>
<td>TNF-α inhibitors, steroids, and thiopurines</td>
<td>14</td>
<td>0.008</td>
<td>16</td>
<td>0.005</td>
</tr>
<tr>
<td>5-ASA / Sulfasalazine</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

MSC – Melanoma Skin Cancer; NMSC – Non-melanoma skin cancer; UC – Ulcerative Colitis; 5-ASA - 5 aminosalicylate.
has also been shown to increase an individual’s risk of NMSC [4, 6, 8, 25, 26]. The mechanism for this reaction is thought to be a result of incorporation of 6-thioguanine into the DNA of skin cells [24, 27]. This increases the cell’s photosensitivity to UVA light which can augment DNA damage.

Limitations of this study include those associated with biases from spontaneous reporting. Limitations of the FAERS database, including overreporting and underreporting, have been previously described [28, 29]. To circumvent these shortcomings in our PRR calculations, we utilized control reactions to ensure that if test drugs or events were reported at an overall increased rate, the OR would remain unaffected. However, with these control reactions, the assumption was made that control reactions are not causally related with the study or control drugs [30].

As previously noted, 78.6 percent of cases in this study were reported with CD. This skewed sampling, which is not characteristic of cancer rates in the general IBD population [31], is probably a result of the search criteria which necessitated that TNF-α inhibitor use be included as part of the treatment for the report to be included in the assembled data set. Only one TNF-α inhibitor, infliximab, was FDA approved for treatment of UC during the time period we examined, and that approval was not until 2006 [32]. Lastly, further exploration of the association between treatment duration and cancer risk is required. However, the spontaneous nature of reporting did not allow us to examine this relationship.

CONCLUSIONS

This study demonstrates increased odds of developing both MSC and NMSC in individuals whose IBD treatment involved TNF-α inhibitors monotherapy, TNF-α inhibitor with concomitant thiopurine or with concomitant thiopurine and steroid therapy. It should be noted that this study has only demonstrated a correlation between IBD treatment medication and increased cancer risk; causation cannot be established. However, it is our recommendation that providers should advise the use of preventive steps for at-risk populations. Daily sun-screen application in organ transplant patients has been shown to help reduce the risk of NMSC [33]. Consultation with a dermatologist for annual comprehensive skin examination for all patients undergoing treatment with a TNF-α inhibitor either in monotherapy or in combination with a thiopurine should be considered as well, similar to protocols in organ transplant patients [34].

Conflicts of interest: No conflicts to declare.

REFERENCES


