Concise report

Alopecia induced by tumour necrosis factor-alpha antagonists: description of 52 cases and disproportionality analysis in a nationwide pharmacovigilance database

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Abstract

Objectives. The aim of this research was to describe the cases of TNF-α antagonist-related alopecia reported in the French Pharmacovigilance Database (FPVD) and to investigate the association between exposure to TNF-α antagonists and occurrence of alopecia.

Methods. All spontaneous reports of TNF-α antagonist-related alopecia recorded in the FPVD between January 2000 and April 2012 were colligated and described. We conducted disproportionality analyses (case/non-case method) to assess the link between the occurrence of alopecia and exposure to TNF-α antagonists. Cases were all reports of alopecia and non-cases were all other reports recorded during the study period. Exposure to TNF-α antagonists was sought in cases and in non-cases. Reporting odds ratios (RORs) were calculated to assess the association. Docetaxel was used as positive control and acetaminophen as negative control. We performed sensitivity analyses excluding cases of androgenic alopecia and those occurring in psoriatic patients.

Results. Among 282,590 spontaneous reports of adverse drug reactions (ADRs) collated in the FPVD, 1,068 cases (alopecia reports) were identified. Of these cases, 52 (4.9%) occurred during exposure to TNF-α antagonists (18 involved infliximab, 17 adalimumab, 15 etanercept and 2 certolizumab). Exposure to TNF-α antagonists was more frequent among alopecia reports than among other ADR reports for all TNF-α antagonists pooled (ROR 3.0, 95% CI 2.3, 4.0) as well as for each antagonist separately, with similar values. Sensitivity analyses yielded similar results. The RORs were 29.9 (95% CI 25.3, 35.5) with docetaxel and 0.3 (95% CI 0.2, 0.4) with acetaminophen.

Conclusion. The present study confirms a strong link between TNF-α antagonist exposure (class effect) and the occurrence of alopecia.

Key words: alopecia, TNF-α antagonist, infliximab, adalimumab, etanercept, adverse drug reaction, disproportionality analysis.

Introduction

TNF-α antagonists have dramatically improved the management of some inflammatory and immune-mediated diseases, including RA, AS, chronic juvenile arthritis, Crohn’s disease, ulcerative colitis and psoriasis [1]. Five TNF-α antagonists are currently marketed in France: three monoclonal antibodies (the chimeric antibody infliximab and the fully humanized antibodies adalimumab and golimumab), a soluble TNF-α receptor (etanercept) and an antibody Fab’ fragment (certolizumab pegol).
The most common adverse drug reactions (ADRs) to these agents are acute infusion reactions, infections and gastrointestinal symptoms. Alopecia in patients exposed to these drugs was described in clinical trials before marketing. As a result, this ADR is mentioned in the French and international product monographs. Nevertheless, only a few case reports and small case series of TNF-\(\alpha\) antagonist-related alopecia have been described in the literature [2–14]. All types of alopecia have been described, such as androgenic alopecia, alopecia areata and patchy alopecia. In most cases, because of exposure to other drugs known to induce alopecia (such as MTX) and active underlying disease such as psoriasis, it was thought that this association could be fortuitous. No comparative study assessing the link between exposure to TNF-\(\alpha\) antagonist and alopecia had previously been conducted.

The present study aimed to describe the cases of TNF-\(\alpha\) antagonist-related alopecia reported in the French Pharmacovigilance Database (FPVD) and to assess the putative association between exposure to TNF-\(\alpha\) antagonists and occurrence of alopecia.

Materials and methods

The French Pharmacovigilance Database

The FPVD records all spontaneous reports of ADRs collected by the 31 French regional pharmacovigilance centres since 1985 [15, 16]. By law, every health care professional must report serious and/or unexpected ADRs to their regional pharmacovigilance centre. Serious ADRs are lethal, life threatening, lead to hospitalization (or prolongation of hospitalization), lead to persistent or significant disability or incapacity or are judged clinically relevant by the physician who reports the case. Unexpected ADRs are those not listed in the drug monograph. Every ADR report is analysed by a college of pharmacologists and physicians in the regional pharmacovigilance centre. Causality is assessed for every suspected drug according to the French imputability method [17]. ADRs are then registered in the FPVD. They are encoded according to Medical Dictionary for Regulatory Activities (MedDRA) classification.

The case/non-case method

The case/non-case method measures the disproportionality between the combination of a given drug (here, a TNF-\(\alpha\) antagonist) and a particular ADR (here, alopecia) in a pharmacovigilance database. It is a validated method of safety signal detection [18–20]. In practice, cases are defined as all reports corresponding to the ADR of interest (here, alopecia) and non-cases are all reports of ADRs other than the ADR of interest during the same study period. Exposure is defined as exposure to the drug of interest (here, TNF-\(\alpha\) antagonists) at the time of the ADR occurrence, whether it is suspected of causing the ADR or not. The strength of the association between exposure to a given drug and occurrence of the ADR of interest is estimated by calculating the reporting odds ratio (ROR) and its 95% CI. The ROR is the odds of exposure to the drug among cases divided by the odds of exposure to the drug among non-cases. Drugs known to induce the ADR of interest can be used as positive controls to test the reliability of the method. Notably, the case/non-case method reveals an association but does not quantify the risk of occurrence for a given patient exposed to the drug.

Data collection

We included all cases of alopecia recorded in the FPVD from 1 January 2000 to 30 April 2012. The cases were selected using the MedDRA high-level term alopecia. All cases of TNF-\(\alpha\) antagonist-related alopecia were reviewed by pharmacologists (J.B., M.A. and S.G.) and an internist (G.M.).

Statistical analysis

We applied the case/non-case method to estimate the association between alopecia and TNF-\(\alpha\) antagonists in the FPVD by calculating RORs for TNF-\(\alpha\) antagonist exposure. Woolf’s method was used to calculate the 95% CI. The null hypothesis was that there was no association between exposure to TNF-\(\alpha\) antagonists and alopecia occurrence. If the 95% CI did not contain the value 1, the null hypothesis was rejected. We performed sensitivity analyses excluding cases of androgenic alopecia and those occurring in psoriatic patients (potential confounding factor). We used docetaxel (known to induce alopecia) as positive control and acetaminophen as negative control. The French Association of Regional Pharmacovigilance Centres, representing the French Pharmacovigilance Centres (which complements the FPVD), approved this study and use of the database.

Results

During the study period, 282 590 spontaneous reports of ADRs were collated in the FPVD, among which 1068 cases (alopecia reports) were identified. Of these cases, 52 (4.9%) involved TNF-\(\alpha\) antagonists (18 involved infliximab, 17 adalimumab, 15 etanercept and 2 certolizumab). Review of the cases did not detect misclassification.

Characteristics of the cases

The male:female sex ratio was 0.18 and the mean age was 39 years (see supplementary Tables S1–S4, available at Rheumatology Online). Seventeen patients were treated for RA, 13 for AS, 12 for Crohn’s disease and 7 for psoriasis. The mean time from TNF-\(\alpha\) antagonist introduction to alopecia onset was 11.3 months (range 4 days–8 years). The TNF-\(\alpha\) antagonist was withdrawn in 24 cases. Improvement was observed in 12 and worsening in 2, while in the remaining 10 cases the course was not described. TNF-\(\alpha\) antagonists were maintained in 20 cases. In seven patients alopecia improved despite continued exposure to the drug, while only two of
the seven received specific treatment for alopecia. In three cases a positive rechallenge was observed. Causality was rated as possible for 43 cases, probable for 4 cases, likely for 3 cases and unspecified for 2 cases. Another concomitant cause of alopecia was present in 17 cases. Two patients had a previous history of alopecia, one treated with adalimumab with a history of alopecia areata of the beard and scalp and one treated with etanercept. When the doses received were noted (n = 21), they were in accordance with the recommendations.

Exposure to TNF-α antagonists was more frequent among alopecia reports than among other ADR reports. This disproportionality was observed for all pooled TNF-α antagonists (ROR 3.0, 95% CI 2.3, 4.0) and for each drug separately (Table 1). RORs were similar for monoclonal antibodies (infliximab and adalimumab) and soluble receptor (etanercept). In parallel, the ROR was 29.9 (95% CI 25.3, 35.5) for etanercept. When the doses received were noted (n = 21), they were in accordance with the recommendations.

Discussion

We found a significant association between exposure to TNF-α antagonists and alopecia. Analysis of each TNF-α antagonist separately also showed a significant and stable association for infliximab, adalimumab and etanercept, suggesting a class effect independent of the TNF antagonist’s structure. The high ROR found with certolizumab deserves careful interpretation because of the small number of reports of alopecia with this drug, which was marketed in France at the end of 2010. Further studies may conclude whether there is a higher risk of alopecia with this drug. In our study, the alopecia induced by TNF-α antagonists appeared at various doses, but never during overdosage.

In a few cases, another potential cause of alopecia was identified, i.e. concomitant use of immunosuppressant drugs (MTX, LEF, AZA or ciclosporin) [21–23]. Nevertheless, some of these drugs have been successfully used for treating alopecia areata, underlining the complexity of the immune pathogenesis of this disease [24]. Sensitivity analyses confirmed the potential link between alopecia and TNF-α antagonists after exclusion of well-known causes of alopecia.

Complete or partial remission in 12 patients after discontinuation of a TNF-α antagonist, as well as positive rechallenge in three cases, are additional arguments in favour of the causality.

Use of the FPVD presents some advantages for such analyses. Unlike other national or international databases, notifications in the FPVD are reported by health care professionals and validated by a college of pharmacologists and clinicians before they are recorded. This ensures the reliability and quality of the reports. In our study, review of the 52 cases of alopecia occurring during exposure to TNF-α antagonists and recorded in the database did not reveal misclassification. Moreover, the method was validated by a positive control, docetaxel, an anti-mitotic chemotherapy medication well known to induce alopecia, and by a negative control, acetaminophen, which is not known to induce alopecia.

However, working with a pharmacovigilance database carries a few limitations. The FPVD is composed of spontaneous reports of ADRs. In some reports, despite meticulous care in data recovery, missing data such as previous history of alopecia, concomitant treatments or other triggers of alopecia (iron or zinc deficiency) artificially decreased the causality assessment. In addition, ADRs are generally underreported (only 5% of ADRs are reported to the French regional pharmacovigilance centres) [25]. Nevertheless, bias in disproportionality measures only occurs when there is differential reporting between cases and non-cases exposed to the drug of interest. Alopecia induced by TNF-α antagonists is a rare and unrecognized ADR compared with the other ADRs induced by these drugs. As a result, we may hypothesize that TNF-α antagonist-induced alopecia is underreported compared with other TNF-α antagonist-induced ADRs. Under this assumption, the RORs of this study may be underestimated.

The mechanism by which TNF-α antagonists induce alopecia is not well understood. The immune system is very likely an integral part of normal hair growth and of the hair growth cycle since epidermal keratinocytes, including those of the hair follicle, synthesize numerous cytokines, including TNF-α. These cytokines have been particularly incriminated in alopecia areata. However,

### Table 1: Association between TNF-α antagonists and alopecia measured with reporting odds ratio (ROR)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cases (n = 1068) % (n)</th>
<th>Non-cases (n = 282,590) % (n)</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TNF-α antagonists</td>
<td>4.9 (62)</td>
<td>1.7 (4742)</td>
<td>3.0 (2.3, 4.0)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.7 (18)</td>
<td>0.9 (2517)</td>
<td>1.9 (1.2, 3.1)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.6 (17)</td>
<td>0.3 (960)</td>
<td>4.8 (2.9, 7.7)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.4 (15)</td>
<td>0.4 (1229)</td>
<td>3.3 (2.0, 5.4)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>0.2 (2)</td>
<td>0.01 (36)</td>
<td>14.7 (3.5, 61.3)</td>
</tr>
<tr>
<td>Acetaminophen (negative control)</td>
<td>2.1 (22)</td>
<td>7.0 (19,823)</td>
<td>0.3 (0.2, 0.4)</td>
</tr>
<tr>
<td>Docetaxel (positive control)</td>
<td>16.2 (173)</td>
<td>0.6 (1817)</td>
<td>29.9 (25.3, 35.5)</td>
</tr>
</tbody>
</table>

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Online. Conflicts of interest.
Consequently alopecia induced by TNF-α antagonists seems paradoxical. Nevertheless, these drugs are not effective for alopecia areata treatment. A suggested explanation is that TNF-α is just one of numerous cytokines involved in the complex and poorly understood pathogenesis of the disease.

**Rheumatology key messages**

- The suspected link between TNF-α antagonist exposure and the occurrence of alopecia is confirmed.
- This concerns alopecia areata as reported in the literature but also other types of alopecia.
- This adverse drug reaction appears to be a class effect.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**

