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CASE REPORT

Squamous-cell carcinoma of the tongue following therapy of rheumatoid arthritis with abatacept

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Key Clinical Message

A patient affected by rheumatoid arthritis developed a squamous-cell carcinoma probably due to abatacept, according to Naranjo algorithm. The case describes this adverse reaction for the first time and highlights the need for additional studies to establish the long-term risk profile of abatacept.

Keywords

Abatacept, adverse drug reaction, carcinoma, rheumatoid arthritis.

Introduction

Abatacept is a fusion protein composed of the extracellular domain of Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and the Fc region of the human immunoglobulin G1 (IgG1) that acts as a selective T-cell costimulation modulator [1]. Therapeutic indications of abatacept include rheumatoid arthritis (RA) not responding to traditional disease-modifying antirheumatic drugs (DMARDs) and refractory active polyarticular juvenile idiopathic arthritis (JIA) [2].

Summary of product characteristics (SPC) [2] for abatacept reports the possibility of basal-cell carcinoma and skin papilloma as uncommon events, lymphoma and malignant lung neoplasm as rare events. We describe the case of a patient who developed a squamous-cell carcinoma (SCC) of the tongue after 1 year of treatment with abatacept for refractory RA. The case was reported by the University Hospital of Sassari (AOUSS) to the "Sardinian Regional Center of Pharmacovigilance", Unit of Clinical Pharmacology, University Hospital of Cagliari (AOUCA), as provided by the project entitled "Development of a

Pharmacovigilance Network in Sardinia". As biologics are newer drugs, there is a lack of long-term safety data. This case report adds to the little information available about them.

Case Report

A 50-year-old woman with a long history of RA presented a tongue ulcer after 1 year of therapy with abatacept 750 mg every 4 weeks intravenously and leflunomide 20 mg/day. The tongue ulcer was subjected to biopsy and histopathology revealed "moderately differentiated SCC of the lateral left border of the tongue." In view of the possible role of abatacept in the development of the adverse reaction, therapy with this drug was discontinued.

The patient was diagnosed with RA at the age of 33 years. Symptoms included stiffness and arthritis of metacarpophalangeals, proximal interphalangeal joints of the hand, metatarsal interphalangeals, ankle and left knee joints. The patients had no comorbidities, apart from a history of allergy to penicillin, wool, dermatophagoides farinae and pteronyssinus, crustaceans, and peas. The patient was treated up to 2005 with low doses of methylprednisolone and sulfasalazine (500 mg thrice daily, orally). Therapy with methotrexate IM was started and discontinued after 2 months for urticarial rush. In December 2005, the patient started therapy with adalimumab (40 mg twice weekly), leflunomide (20 mg, orally, one tablet every 2 days), and celecoxib (up to 200 mg twice daily, as needed). From May 2008, the patient switched to once-weekly treatment with adalimumab and daily treatment with leflunomide. In October 2009, therapy with adalimumab was suspended due to respiratory difficulty and urticarial rush following drug injection. The patient started receiving etanercept (50 mg weekly) but therapy was suspended 3 months later due to insurgence of urticarial reactions and respiratory difficulty. From April 2010 to August 2011, the patient was treated with abatacept 750 mg monthly in association with leflunomide 20 mg daily (reduced to 20 mg every 2 days from March 2011), achieving clinical remission. In September 2011, after histopathology confirmation of SCC of the tongue, therapy with abatacept was discontinued. From September 2011 to June 2012, the patient was treated with leflunomide 20 mg/day and methylprednisolone as needed. From June 2012, therapy included methotrexate (10 mg/week, subcutaneously, augmented to 15 mg/week from December 2012), calcium folinate 10 mg/week, leflunomide 20 mg/day, risedronate sodium (75 mg every 2 weeks), calcium carbonate and cholecalciferol (vitamin D3) 500 mg + 440 UI (2 tablets daily from December 2011), methylprednisolone, and non-steroidal anti-inflammatory drugs as needed.

The patient had no personal history of risk factors for SCC of the tongue: she was not a smoker at the moment of observation (albeit being an occasional smoker in her youth, smoking a cigarette every few days) and her alcohol intake was restricted to one glass of wine during meals in rare occasions. The patient had a familial history of RA (cousin of the mother) and lung cancer (first-grade cousin, 68 years old).

In September 2011, following the histopathology report, the patient was admitted to hospital and subjected to left glossectomy, left cervical lymphadenectomy, and reconstruction of the intraoral defect using a myomucosal flap from the buccinator muscle. Surgical pathology report showed resection margins were free of involvement and reactive lymph nodes were metastasis-free. Thus, cancer was staged as T1N0Mx. At the last infusion of abatacept, physical examination revealed normal findings and clinical remission. Laboratory test results showed normal except for mild neutropenia and relative lymphocytosis: neutrophils 1.49×10^3/mL (1.8–8), 23.3% (35–80), and lymphocytes 3.59×10^3/mL (1.5–4). Six and 10 months after surgery, no clinical, echography, or computed tomography (CT) signs of relapse were observed.

The case was reported to the Italian regulatory authority (report number of Italian spontaneous-reporting database: 157854) and to the manufacturer of the drug.

Discussion

Case report information was collected according to "Guidelines for submitting adverse event reports for publication" [3] in order to offer a clearer differential diagnosis for the event. Applying Naranjo algorithm [4] and World Health Organization (WHO) algorithm of Uppsala Monitoring Centre [5], the score generated suggested that the adverse reaction was probable due to abatacept and to leflunomide. Other causes of SCC of the tongue were considered rather unlikely, as suggested by personal and familial history of the patient. The adverse reaction had a reasonable time relationship to abatacept intake and could be speculated as an adverse reaction arising from long-term use (type C according to Edwards and Aronson, 2000)[6].

On the basis of available evidence, the adverse reaction described seems to be more probably due to abatacept than leflunomide, as therapy with leflunomide does not seem to be associated to insurgence of malignancies, according to data from large European registers [7]. In fact, even if an increase in the risk of pancreatic cancer was hypothesized on the basis of seven cases detected in the German biologics register (RABBIT), this risk was not confirmed by a subsequent replication analysis conducted

on the national biologics registers in the UK and Sweden [7]. However, interaction between the two drugs cannot be completely excluded.

To the best of our knowledge, this adverse reaction during therapy with abatacept has not been previously reported: although SPC for abatacept [1] does report incidence of malignancies (in particular, basal-cell carcinoma and skin papilloma as uncommon events; lymphoma and malignant lung neoplasm as rare events), specific cases of SCC of the tongue associated to use of this drug have not been described until now. SPC for abatacept [1] states that "the potential role of abatacept in the development of malignancies, including lymphoma, in humans is unknown."

A Cochrane review on efficacy and safety of abatacept in patients with RA [8] outlined the necessity of long-term studies and postmarketing surveillance to assess harms and sustained efficacy of abatacept. This necessity was also confirmed by the overview of Cochrane reviews on biologics for RA [9]: even though the review did not show statistically significant difference between patients receiving abatacept and placebo with regard to safety, the authors outlined the lack of precise information about rare side effects, including certain types of cancer. The recent network meta-analysis and Cochrane overview [10] showed that abatacept seemed to be associated with significantly fewer serious infections and serious adverse events compared to other biologics. However, a limitation of this review is the choice of limiting inclusion to RCTs and their open label extensions, whereas long-term observational studies, including population-based registries, could provide better estimates of the long-term safety of biologics. The authors outlined the urgent need for more research addressing the issue of rare or long-term adverse effects of biologics. A recent systematic review and meta-analysis [11] showed no statistically significant increased risk of malignancy among RA patients treated with biologic response modifiers (BRMs) compared with other DMARDs or with placebo in RCTs with a duration of at least 6 months. However, additional observational studies are warranted to establish risk in the longer term.

Conclusions

Based on the case presented, our opinion is that a relation between therapy with abatacept and onset of the SCC of the tongue is plausible. Active postmarketing surveillance is essential to a better understanding of the safety profile of this drug. Even if the limitation of being a single case report must be taken into account, given the urgent necessity of collecting more information on the possible relation between malignancies and abatacept, we believe this work could be a valid contribution to the existing literature.

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Conflict of Interest

None declared.

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