

Does Anti-Tumour Necrosis Factor-Alpha Increase Oral Candida Colonization? A Case-control Study in Psoriatic Patients

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Infliximab, etanercept and adalimumab are biologic agents used in psoriasis treatment that suppress the activity of tumour necrosis factor (TNF)- α , and are associated with a potential increased risk of infection (1). Invasive fungal infections and, rarely, superficial mycoses have been reported (2–7).

Candida spp., a yeast commonly present at low concentration in the oral cavity, can cause disease in immunocompromised hosts (8).

The aim of this study was to determine whether anti-TNF- α drugs, used in psoriatic patients, can affect oral colonization by *Candida*.

MATERIALS AND METHODS

A total of 30 patients affected by psoriasis vulgaris, attending our Psoriasis Unit were consecutively included in the study, after obtaining informed consent.

Male and female patients were enrolled with the following inclusion criteria: >18 years, regardless of the severity of psoriasis, in treatment with anti-TNF- α drugs (group A), or in treatment with non-immunosuppressive drugs (group B). Patients in group B had to have interrupted prior immunosuppressive systemic therapies at least 6 months earlier. Exclusion criteria were: <18 years of age, pregnant or breastfeeding, in treatment with cyclosporine or methotrexate, immunosuppressed for other reasons, or have forms of psoriasis other than psoriasis vulgaris.

Lifelong history of psoriasis and eventual diagnosis of diabetes mellitus (DM) were collected from hospital clinical records.

All the patients completed a questionnaire concerning oral hygiene habits (time devoted to daily oral hygiene, use of mouthwashes and dental floss) and smoking status (how long they had been smoking and number of cigarettes/day). They underwent clinical examination of the oral cavity to assess oral hygiene and denture wearing. Oral hygiene was globally assessed as good or poor by the same physicians (MC, AV) based on the presence of gingivitis (swelling, bleeding, redness), caries, dental plaque and epulis. All patients underwent oral swab cultured in Sabouraud dextrose broth (BioMérieux). *Candida* was researched through observation with phase-contrast microscope. If blastospores were present, identification of *Candida* species was performed.

Statistical analysis was carried out for all study data using the Fisher's exact test and Student's *t*-test.

RESULTS

Demographic and clinical features and data regarding psoriasis treatments, oral cavity hygiene and habits of the patients enrolled in both the study groups are summarized in Table I.

The results of oral swab for *Candida* in group A revealed viable strains in 8 patients (61.5%): 2 had poor oral

Table I. Demographic and clinical features and oral swab culture results of study patients

	Group A (n=13)	Group B (n=17)
Gender	4 F (30.8%) 9 M (69.2%)	10 F (58.8%) 7 M (41.2%)
Age, years, mean (SD)	58.2 (45–73)	63.9 (47–89)
Duration of psoriasis, years, mean (SD)	18.4 (6–30)	28.4 (1–50)
Treatment, n	8 etanercept 4 adalimumab 1 infliximab	11 acitretin 6 topicals only
Duration of treatment, months, mean (SD)	9.9 (1–36)	12.5 (1–27)
Diabetes mellitus, n (%)	6 (46.2)	5 (29.4)
Time devoted to daily oral hygiene, min, mean (SD)	8.5 (3–15)	8.9 (1–15)
Use of mouthwash, n (%)	7 (53.9)	10 (58.8)
Use of floss, n (%)	1 (7.7)	4 (23.5)
Oral hygiene, n (%)	10 good (76.9) 3 poor (23.1)	13 good (76.5) 4 poor (23.5)
Use of dentures, n (%)	7 (53.9)	8 (47.1)
Smokers, n (%)	13 (23.1)	6 (35.3)
Number of cigarettes/day	21.7 (15–30)	12 (15–30)
How long they had been smoking, years, median (range)	30 (15–40)	40 (6–60)
Positive <i>Candida</i> oral swab, n (%)	8 (61.5)	7 (41.2)

SD: standard deviation.

hygiene, 3 were affected by DM, and 3 were smokers. *C. albicans* was detected in 7 patients (87.5%), *C. glabrata* was found in one patient, while *C. parapsilosis* was present in one case, concomitant with *C. albicans*.

Regarding ongoing therapies in patients with positive swabs, 5 patients were in treatment with etanercept, 2 with adalimumab and 1 with infliximab. The mean duration of treatment with anti-TNF- α drugs was 8.4 months (range 1–28) among patients with a positive swab and 12.4 months (range 3–36) among patients with negative results. No significant difference in treatment duration was found in patients with positive swabs with respect to patients with negative swabs ($p=0.54$). Only 2 patients (25%) with positive oral swabs showed clinical signs of oral candidiasis: pseudomembranous in one case and erythematous in the other. Both were in treatment with etanercept.

In group B *Candida*-positive swab was found in 7 patients (41.2%): one had poor oral hygiene, 2 were affected by DM, and 3 were smokers. *C. albicans* was found in 6 patients (85.7%), *C. dubliniensis* in one patient, while *C. krusei* was concomitant with *C. albicans* in only one case.

Only 2 patients (28.6%) with a positive oral swab showed clinical signs of erythematous oral candidiasis. Three patients were in treatment with acitretin (42.9%) and 4 with derivatives of vitamin D (57.1%).

No significant difference was found in the rate of positive swabs between the 2 groups ($p=0.23$). The detection of positive oral swab did not correlate with DM ($p=0.41$ in group A; $p=0.69$ in group B), with the use of dentures ($p=0.25$ in group A; $p=0.12$ in group B) or with smoking ($p=0.20$ in group A; $p=0.63$ in group B) in either group.

Considering all the enrolled patients, a significant correlation was found between positive oral swabs and the use of dentures ($p=0.03$), but not with DM ($p=0.50$) or smoking ($p=0.21$).

DISCUSSION

It could be hypothesized that patients receiving anti-TNF- α therapy are more susceptible to fungal infections, as their immune system may not be able to recognize fungal antigens through toll-like receptor signalling, and in particular through toll-like receptor 4 by host cells (e.g. dendritic cells and macrophages) (3). Moreover, blockage of TNF- α could inhibit the production of interferon- γ , leading to a defective activation of phagocytosis and killing of intracellular pathogens (3).

TNF- α inhibition could be associated with increased apoptosis of peripheral blood monocytes (3). TNF- α can also affect other mediators involved in *C. albicans* infection, such as E-selectin, vascular cell adhesion molecule 1, and IL-8, which act mainly by recruiting leukocytes at the site of fungal infection (3).

In the literature only 4 cases of oral candidiasis have been reported in patients in treatment with infliximab (5–7), which exert a pronounced effect in T-cell-mediated immunity and almost completely neutralize TNF- α activity (3).

In this study 30 patients, 13 in treatment with anti-TNF- α drugs (group A) and 17 in non-immunosuppressive treatment (group B), underwent oral swabs for testing for *Candida*.

In group A we found a more frequent colonization by *Candida* (61.5%) compared with the rate reported in healthy individuals (17.7–60%) (8, 9) and with the rate observed in group B (41.2%). But the difference between groups A and B was not significant ($p=0.23$). The restricted number of patients and the presence of only one patient in treatment with infliximab does not allow us to draw definitive conclusions. Further studies

on a larger number of patients would provide more data about the implication of anti-TNF- α drugs in the development of oral candidiasis and possible differences between etanercept, adalimumab and infliximab.

Considering other well-known predisposing factors for oral candidiasis in the enrolled population, such as DM, wearing dentures and smoking (9–11), a significant correlation was found only with the use of dentures.

In accordance with literature data, *C. albicans* was the species most represented in subjects with positive oral swab and a small proportion of patients with positive oral swab had clinical manifestations of oral candidiasis.

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