

The effect of dupilumab in an HBV-HIV coinfecting atopic patient: a case report

Tommaso Bianchelli¹✉*, Anna Campanati^{1*}, Claudia Sapigni¹, Andrea Costantini², Luca Butini², Giulia Radi¹, Annamaria Offidani¹

¹Dermatology Unit, Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy. ²Clinical Immunology Service, Department of Internal Medicine, Ancona University Medical School, Ancona, Italy.

Abstract

Atopic dermatitis (AD) is a chronic immune-mediated inflammatory disease typical of childhood that can also affect adults. AD is clinically characterized by intensely pruritic eczematous lesions. The burden of this disease and its impact on quality of life are often substantial. Dupilumab is a fully humanized monoclonal antibody against interleukin 4 (IL-4) receptor α , capable of blocking IL-4 and IL-13 signaling. This novel therapy represents the first biologic approved for the treatment of moderate to severe AD. Our report describes the case of a 39-year-old adult patient affected by severe chronic AD with associated allergic and viral comorbidities for whom conventional systemic therapies proved ineffective or contraindicated. The main source of interest in this case is hepatitis B virus (HBV) and human immunodeficiency virus (HIV) coinfection because, to our knowledge, this is the first case of an adult atopic patient treated with dupilumab in the simultaneous presence of these comorbidities. Regarding coinfections, the patient was on antiretroviral therapy for HBV and HIV before starting dupilumab. Efficacy and safety data after 24 weeks of therapy are reported in detail.

Keywords: general dermatology, medical dermatology, atopic dermatitis, dupilumab, HIV, HBV, coinfection

Received: 22 October 2020 | Returned for modification: 2 February 2021 | Accepted: 12 February 2021

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory disease of the skin. The current prevalence of AD in most high-income and some low-income countries is up to 20% in children and 2 to 5% in adults (1). The etiopathogenesis is multifactorial, underpinned by T helper 2 (Th2) lymphocyte-dominant response with overexpression of inflammatory interleukins IL-4 and IL-13 (2). AD is often associated with elevated immunoglobulin E (IgE) levels and a personal or family history of atopy (3). IgE level tends to correlate with disease severity, although some patients with severe AD have normal IgE values (4). Sensitization to environmental or food allergens clearly associated with the phenotype of AD appears to be a feature that demonstrates full clinical expression in the subgroup of patients with severe disease (5).

Optimal management of AD requires a multifaceted approach that simultaneously involves elimination of exacerbating factors, restoration of barrier function and skin hydration, and topical or systemic pharmacologic treatment of skin inflammation. Established therapeutic options include emollient therapy, topical corticosteroids, and calcineurin inhibitors, as well as use of systemic immunosuppressive drugs (6).

In addition, new therapeutic choices are now available. The reason AD has captured the attention of researchers is its striking impact on the clinical course, as well as the safety profile of new drugs, such as dupilumab (7). Dupilumab is a fully humanized monoclonal antibody that binds to the alpha subunit of the IL-4 receptor and inhibits downstream signaling of IL-4 and IL-13, Th2 cytokines that play a key role in atopic diseases, including asthma and AD (8). It has been approved for the treatment of moderate to severe chronic AD, severe asthma, and severe chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults, as well as moderate

to severe chronic AD in patients \geq 12 years (9).

Biologics such as dupilumab are a highly effective and relatively safe treatment option for patients with recalcitrant immune-mediated disease. However, because of their modulation of the immune system, biologics have been associated with serious infections, including latent hepatitis B virus (HBV) reactivation (10). A case report on two patients affected by severe AD and chronic HBV infection shows no clinically evident hepatitis or viral reactivation (11).

The effect of dupilumab in patients that are human immunodeficiency virus (HIV)-positive is unknown because these patients have been excluded from clinical trials, although case series report no HIV reactivation during treatment other than efficacy on skin disease. A CD4+ lymphocyte count variability of more than 30% at follow-ups may be considered an indication of viral reactivation (12).

Case report

We report the case of a 39-year-old woman suffering from AD from the age of 3. Her medical history included hypertension and allergic sensitization to food antigens contained in peaches and nuts, confirmed by a serum total IgE value of 347 IU/ml and prick tests performed in February 2018.

The patient stated that HIV-HBV coinfection occurred in 2000. She has been receiving triple therapy with emtricitabine, rilpivirine, and tenofovir for HIV since 2004, whereas HBV infection appears to be a chronic disease phenotype, defined as persistent seropositivity for hepatitis B surface antigen (HBsAg) for at least 6 months prior to enrollment. HBV is currently kept under control by tenofovir in order to prevent reactivation of the virus or long-term complications.

✉ Corresponding author: tommaso.bianchelli@gmail.com

*The two authors contributed equally to the manuscript.

At the time of the first observation, the patient had severe AD, localized to the head, neck, trunk, hands, and limbs (Fig. 1).



Figure 1 | Face and neck lesions at T0.

Therefore, considering the patient's comorbidities and the severity of clinical features with localization of AD in visible areas, the decision to initiate dupilumab therapy using a standard dosing regimen (600 mg s.c. at induction dose followed by 300 mg s.c. every 2 weeks) was shared with colleagues from the Clinical Immunology Unit.

The patient started therapy on July 2nd, 2019 (T0). Clinical improvement was measured by the Eczema Area and Severity Index (EASI), Body Surface Area (BS), and Investigator's Global Assessment (IGA); the patient-reported outcomes were measured by the Dermatology Life Quality Index (DLQI) and Numeric Rating Scale itch intensity (NRSi).

An initial EASI of 27, BSA of 20, IGA of 4, DLQI of 10/30, and NRSi of 10/10 were reported. Pre-dupilumab viral loads of HIV-RNA and HBV-DNA were undetectable, and the absolute CD4+ lymphocytes count was 511/mmc.

At the 1-month follow-up (week 4) on July 31st, 2019, EASI of 9, BSA of 10%, IGA of 3, DLQI of 2/30, and NRSi of 1/10 were the clinical and patient-reported scores, whereas HIV-RNA and HBV-DNA viral loads were still undetectable, and the absolute CD4+ count was 526/mmc (Fig. 2).



Figure 2 | Face and neck lesions at week 4.

At the 3-month (week 12) follow-up in October 2019, the scores and values reported were EASI of 3, BSA of 5%, IGA of 2, DLQI of 1/30, and NRSi of 1/10; HIV-RNA and HBV-DNA viral loads were undetectable, and the absolute CD4+ count was 413/mmc.

At the 4-month follow-up (week 16) in January 2020, the scores and values were EASI = 3, BSA = 3%, IGA = 1, DLQI = 0/30, and NRSi = 0/10; HIV-RNA and HBV-DNA viral loads were still undetectable, and the absolute CD4+ count was 427/mmc. The patient was considered a responder because she reached a 75% reduction from baseline on the initial EASI (EASI75; Fig. 3).



Figure 3 | Face lesions at week 16.

At the 6-month follow-up (week 24) in late February 2020, the scores and values were EASI = 2, BSA = 3%, IGA = 1, DLQI = 1/30, and NRSi = 3/10; HIV-RNA and HBV-DNA viral loads were undetectable, and the absolute CD4+ count was 482/mmc (Fig. 4).



Figure 4 | Face lesions at week 24.

The overall therapy duration was 24 weeks from baseline (13 s.c. injections including the initial dose), and the patient is continuing the treatment.

Summarizing the results, from baseline (T0) to week 24 the EASI improved from 27 to 2 (over 90%), BSA from 20 to 3%, and IGA from 4 to 1, and in the patient-reported outcomes DLQI improved from 10 to 1 and NRSi from 10/10 to 3/10. The patient maintained undetectable HBV DNA and HIV RNA quantitative values in all observations and CD4+ lymphocyte counts with a variability of < 30% at follow-ups, with no need to modify the antiretroviral therapy already in place (Table 1).

Table 1 | Summary of results.

Time	EASI	BSA	IGA	DLQI	NRSi	CD4+ count	HIV-RNA/ HBV-DNA
T0	27	20%	4	10/30	10/10	511/mmc	Undetectable
W4	9	10%	3	2/30	1/10	526/mmc	Undetectable
W12	3	5%	2	1/30	1/10	413/mmc	Undetectable
W16	3	3%	1	0/30	0/10	427/mmc	Undetectable
W24	2	3%	1	1/30	3/10	482/mmc	Undetectable

EASI = Eczema Area and Severity Index, BSA = Body Surface Area, IGA = Investigator's Global Assessment, DLQI = Dermatology Life Quality Index, NRSi = Numeric Rating Scale itch intensity, HIV-RNA = human immunodeficiency virus RNA, HBV-DNA = hepatitis B DNA.

Discussion

There is a high prevalence of reported atopic diseases and elevated total IgE in patients with HIV (13). The safety profile of dupilumab, derived from clinical trials, does not include patients with a clinical profile similar to our case. However, cases of HIV patients on antiretroviral treatment treated with dupilumab have been reported in the literature, with satisfactory results in terms of both efficacy and safety (12, 13). Periodic monitoring of blood tests, focusing on viral load and CD4+ lymphocyte count, is necessary to avoid a reduction in the efficacy of antiretroviral therapy. In this regard, changes of at least 30% of the absolute value of the CD4+ count between evaluations are considered significant (12). An increased Th2 response has already been reported in HIV-

infected patients, also supported by the stimulatory action on IL-4 by glycoprotein-120 (gp120), the protein constituting the HIV viral envelope (14). It should be considered that genetic mutations related to IL-4, resulting in a reduction of its expression, have been demonstrated in individuals with resistance to HIV infection. In this regard, it is plausible to speculate that inhibition of IL-4 might play a favorable role in the state of HIV infection status (15).

IL-4 is also involved in progression to cirrhosis in HBV-positive patients. In patients with atopic dermatitis and HBV, monitoring the patient's hematochemical and functional status, with particular regard to liver functional indices, is strongly recommended (16).

The only two case reports in the literature concerning patients with chronic HBV and AD treated with dupilumab and specific antiviral therapy (entecavir) showed no laboratory changes inherent to functional liver status, HBV viral activity, and stiffness at fibroscan, whereas the clinical benefit in atopic dermatitis was significant and satisfactory (11).

Conclusions

Currently there are no documented cases of patients with HIV-

HBV coinfection being treated with antivirals and dupilumab; therefore, the case described confirms its efficacy in the management of skin pathology and adds real-life significance on its safety even in a complex setting such as the one described here. Given the small number of patients treated and the short observation time generally reported in literature worldwide, dupilumab seems to be a valid therapeutic option. Some aspects related to the drug interference between dupilumab and antiviral therapy are unknown, and the possible favorable/neutral role of dupilumab on the evolution of HBV and HIV infection is not clear, given the role played by the drug on IL-4 (16). Therefore, the use of dupilumab in these patients appears justified if associated with periodic clinical and laboratory monitoring of the patient. Our suggestion is to follow up HBV and HIV reactivation every 4 months during treatment with specific blood tests such as liver function and HBV-DNA and with CD4+ count and HIV-RNA. Changes of at least 30% of the absolute value of CD4+ count between assessments are considered significant.

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