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REVIEW

Effectiveness and Safety of Dupilumab and Tralokinumab for Treating Atopic Dermatitis and Pruritic Skin Disorders in Oncological Patients: A Narrative Review

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Introduction: Atopic dermatitis (AD) and pruritic skin disorders are increasingly recognized in cancer patients. The management of these conditions in patients with a history or with concomitant cancer presents unique challenges, as traditional systemic therapies may pose risks due to their immunosuppressive effects. In recent years, biologic agents such as dupilumab and tralokinumab have emerged as promising treatments for AD, offering targeted modulation of the immune response with potentially fewer systemic side effects. This article aims to review the current evidence on the safety and efficacy of dupilumab and tralokinumab in treating AD and pruritus among cancer survivors, addressing the potential benefits and considerations for this unique patient population.

Methods: A comprehensive analysis of the current medical literature was performed on the PubMed, Ovid, Scopus, Embase, and Cochrane Library databases until December 15, 2024. In conducting this narrative review, Medical Subject Headings (MeSH) terms and medical terminology related to clinical trials and real-life studies were employed, focusing on the pharmacological agents dupilumab, and tralokinumab.

Discussion: Patients with active or past cancer are typically excluded from clinical trials of new medications, complicating the evaluation of cancer progression or recurrence risks in these patients setting. The potential use of biologic drugs like dupilumab and tralokinumab in oncological patients marks a significant breakthrough for treating conditions such as eczema and pruritus, which are common in this patient group. Although there are no explicit contraindications for using dupilumab and tralokinumab in patients with active cancer or a history of malignancy, there is no definitive guidance on their use in such cases. Real-world data is emerging, facilitated by collaboration between dermatologists and oncologists, supporting the effectiveness and safety of dupilumab and tralokinumab for managing AD in cancer patients. Nonetheless, larger studies with longer follow-up periods and dedicated pharmacovigilance programs are needed to substantiate these findings.

Keywords: atopic dermatitis, dupilumab, tralokinumab, oncological patients

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by intense pruritus and eczematous lesions, significantly impacting patients' quality of life.[1] AD and pruritic skin disorders are increasingly recognized in cancer patients, with pruritus affecting up to 30–50% of individuals undergoing cancer treatment.[2] Eczematous rashes and itching may exacerbate as a consequence of antineoplastic therapy in patients with a positive medical history but may also occur as a side effect of treatment.[2] The management of these conditions in patients with a history or with concomitant cancer presents unique challenges, as traditional systemic therapies may pose risks due to their immunosuppressive effects. These conditions can significantly impact the quality of life for cancer patients, who are already

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burdened by the physical and emotional toll of their primary illness. Persistent itch and skin discomfort can lead to sleep disturbances, increased stress, and a decline in overall well-being.[3] In recent years, biologic agents such as dupilumab and tralokinumab have emerged as promising treatments for AD, offering targeted modulation of the immune response with potentially fewer systemic side effects.[4–7] Dupilumab, an IL-4 receptor alpha antagonist, and tralokinumab, an IL-13-neutralising monoclonal antibody, have demonstrated efficacy in reducing the severity of AD and associated pruritus in the general population.[8] However, their use in patients with a history of cancer remains underexplored. This article aims to review the current evidence on the safety and efficacy of dupilumab and tralokinumab in treating AD and pruritus among cancer survivors, addressing the potential benefits and considerations for this unique patient population. In addition to dupilumab and tralokinumab, lebrikizumab—a newer IL-13-targeting monoclonal antibody—has also garnered interest for its potential efficacy in AD treatment.

Materials and Methods

A comprehensive analysis of the current medical literature was performed on the PubMed, Ovid, Scopus, Embase, and Cochrane Library databases until December 15, 2024. In conducting this narrative review, Medical Subject Headings (MeSH) terms and medical terminology related to clinical trials and real-life studies were employed, focusing on the pharmacological agents dupilumab, tralokinumab and lebrikizumab. The search strategy incorporated specific research terms such as "dupilumab", "tralokinumab" and "lebrikizumab" in conjunction with "atopic dermatitis", "pruritus", "cancer", "real-life studies" and "clinical trial". All fields including title, abstract, keywords, and full text were involved in the search. Additionally, references were reviewed to include manuscripts that might have been missed. This narrative review encompassed clinical and epidemiological studies, as well as reviews and systematic reviews focusing on drugs. Non-English manuscripts were excluded. It is crucial to highlight that the information presented in this article is derived from previously conducted studies.

Results

Current biologic therapies for AD, such as dupilumab, tralokinumab, and lebrikizumab, are not classified as immunosuppressive. This classification suggests that these systemic treatments may pose a lower risk when used in patients with a history of cancer.[9] Considering clinical trial data, in a 5-year open-label extension study evaluating the efficacy and safety of dupilumab in adults with moderate to severe AD, 14 cases of squamous cell carcinoma of the skin (SCC) and 3 cases of mycosis fungoides emerged during treatment.[10] Regarding tralokinumab, based on pooled analysis of five randomized, double-blind, placebo-controlled trials the frequency of malignancy was similar for tralokinumab and placebo, occurring in 0.9% (n = 17) and 0.7% (n = 5) patients, respectively and the majority were skin malignancies.[11] Finally, from an integrated analysis of eight clinical trials of lebrikizumab emerged 5 cases of non-melanoma skin cancer (NMSC) and 8 of malignancies other than NMSC (1 patient with pancreatic carcinoma with metastasis to the bone and liver; 2 patients with cutaneous T-cell lymphoma (CTCL); and 1 patient each reporting prostate cancer, endometrial adenocarcinoma, ovarian germ cell teratoma, invasive breast cancer, and neuroendocrine tumor). Notably, all events were assessed by investigators as not related to the study drug.[12] Beyond clinical trials, there are real-life experiences concerning the use of dupilumab and tralokinumab for the treatment of AD and pruritus in patients with a history of neoplasia or concomitant cancer.[13,14]

Dupilumab

Patients with a history of malignancy were generally excluded from dupilumab clinical trials,[15,16] however this drug is not contraindicated in patients with malignancies or history of previous cancer and no specific laboratory or imaging tests are required before or during therapy.[17] Despite the absence of evidence in clinical trials, the efficacy and safety of dupilumab in cancer patients has been highlighted by real-life experiences (Table 1). The most extensive case series documented by Macagno et al involved 24 patients undergoing dupilumab treatment who had a history of cancer.[18] In 22 of these cases, the cancer diagnosis preceded the initiation of dupilumab. Over a follow-up period (median: 29 months, range: 4–53 months), two patients received systemic cancer therapies.[18] There were two instances where dupilumab was discontinued: one due to achieving excellent disease control and the other because of conjunctivitis.[18] Additionally, two

Table 1 Clinical Cases of Cancer Patients Treated With Dupilumab Reported in Literature

Real-Life Studies	Number of Patients	Type of Cancer	Cancer Recurrence or Progression
Macagno et al[18]	24	Hodgkin's lymphoma 3 Breast cancer 3 Prostate cancer 2 Intestinal carcinoma 2 Melanoma 2 Non-Hodgkin's lymphoma 1 Testicular lymphoma 1 Bladder carcinoma 1 Cutaneous mastocytosis 1 Cancer of the parotid gland 1 Seminoma 1	No* * two patients passed away—one due to cancer-related causes, unrelated to dupilumab, and the other from non-cancer-related causes
Patruno et al[19]	9	Endometrial cancer 1 Meningioma 1 Monoclonal gammopathy 1 Colorectal cancer 1 Osteosarcoma 1 Melanoma 1 Renal cell carcinoma 1 Breast cancer 1 Thyroid cancer 1	No
Tanczosova et al[20]	3	Colorectal carcinoma 1 Colorectal carcinoma and kidney cancer 1 Penile carcinoma and prostate cancer 1	No
Talmon et al[24]	3	Prostate cancer 1 CTCL 1 Melanoma 1	No
Fowler et al[21]	2	Melanoma 1 Anal squamous cell carcinoma 1	No
Qiu et al[22]	1	Non-Hodgkin's lymphoma 1	No

patients passed away: one due to cancer-related causes, unrelated to dupilumab, and the other from non-cancer-related causes. Importantly, no cases of cancer recurrence or progression were reported during the study.[18] Another study reported by Patruno et al evaluated the efficacy and safety of dupilumab treatment for AD in 9 patients with a history of cancer.[19] Of these patients, three (33.33%) were undergoing concurrent treatments: one was taking tamoxifen at a dose of 20 mg daily for breast cancer, another was receiving pembrolizumab at 400 mg every six weeks for renal cell carcinoma, and the third was treated with nivolumab at 240 mg every two weeks for metastatic melanoma.[19] Treatment with dupilumab was effective and safe in all cases, with no statistically significant differences compared to the non-oncology patient groups.[19] Similarly, Tanczosova et al reported three cases with severe AD unresponsive to topical therapy and to narrowband phototherapy with a history of malignancy successfully treated with dupilumab.[20] Specifically, one patient had a history of colorectal carcinoma, another patient had a history of colorectal carcinoma and renal carcinoma and the last of penile spinocellular carcinoma and prostate cancer: dupilumab treatment was efficacious (all patients achieved a 75% reduction from baseline in the Eczema Area and Severity Index EASI-75) and no recurrence or progression of

Table 2 Clinical Cases of Cancer Patients Treated With Tralokinumab Reported in Literature

Real-Life Studies	Number of Patients	Type of Cancer	Cancer Recurrence or Progression
Potestio et al[25]	7	Prostate cancer 4 Lung cancer 1 Breast cancer 1 Colorectal cancer 1	No

malignant disease was observed.[20] Moreover, no adverse events (AEs) related to the dupilumab treatment were observed.[20] Additionally, Fowler et al and Qiu Y et al reported, respectively, two and one cases of patients with malignancy undergoing dupilumab treatment for AD showing remarkable efficacy in terms of reduction of eczematous manifestations and control of itching without evidence of tumour recurrence and/or progression.[21,22] Confirming this evidence, McClatchy et al recently reported the case of a 47-year-old patient with severe AD suffering from metastatic renal carcinoma successfully treated with dupilumab, further highlighting the safety of the drug in this patient setting.[23] In conclusion, Talmon et al presented a case study demonstrating the effectiveness and safety of dupilumab in treating severe pruritus associated with malignancies in three patients.[24]

Tralokinumab

Differently from dupilumab, data on cancer patients undergoing treatment with tralokinumab are scant. Potestio et al reported a real-life case series of 7 patients with history of cancer treated with tralokinumab for severe AD[25] (Table 2). Specifically, 4 out of 7 patients had a history of prostatic cancer, 1 of lung cancer, 1 of breast cancer and finally 1 of colorectal cancer.[25] Among the 7 patients, six received tralokinumab therapy concomitantly with antineoplastic therapy, while only the patient with a history of breast cancer received tralokinumab as monotherapy, having already completed antineoplastic therapy and being in a remission phase of the neoplasm.[25] In all 7 patients, treatment with tralokinumab proved effective with a statistically significant reduction in EASI and Pruritus Numeric Rating Scale (P-NRS) as early as week 4, maintaining a progressive improvement until week 24. Regarding safety, no evidence of AEs or recurrence or progression of the neoplasm up to 24 weeks of follow-up was observed.[25]

Discussion

The link between AD and cancer remains debated, with some theories proposing that enhanced immune surveillance may lower cancer risk, while others suggest that immune activation could elevate the risk.[26,27] However, some evidence suggests a slight increased risk for non-Hodgkin lymphoma in a severity-dependent manner.[28,29] This remains unconfirmed, as confounding factors, such as the overlap between CTCL and severe erythrodermic AD, complicate the analysis..[30] Traditional systemic treatments for AD are non-selective immunosuppressants, and their immunosuppressive effects might increase the risk of cancer.[31] Nevertheless, the specific carcinogenic potential of these immunosuppressive agents, whether used alone or in combination, is not well understood. Cyclosporine (CsA) is associated with an increased risk of SCC, and possibly more invasive cancers, particularly in solid organ transplant recipients.[32,33] Azathioprine (AZA) is linked to a higher risk of developing cSCC, and patients with inflammatory bowel disease treated with AZA might face an elevated risk of lymphoma.[34] While many studies do not indicate a risk, low-dose methotrexate (MTX) might be linked to a slight increase in non-basal cell skin cancers.[35] The research on mycophenolate mofetil (MMF) is limited and inconclusive, though one meta-analysis in solid organ transplant patients suggests that exposure to mycophenolic acid does not correlate with a heightened cancer risk and might even present a lower risk compared to AZA or no treatment.[36] Since Jak inhibitors (JAKis) act by blocking several immune signalling pathways, including those of interferons and natural killer (NK) cells that play a key role in anti-tumour surveillance, they are contraindicated in patients with active cancer and require adequate prior screening and monitoring for cancer risks.[37] Nevertheless, the few instances of cancer reported in clinical trials involving JAKis for atopic dermatitis do not provide enough evidence to confirm any causal links.[38] Additionally, no cases of malignancy were observed in a combined long-term extension study across eight clinical trials involving adult AD patients treated with baricitinib.[39] Ultimately, there is a lack of sufficient

clinical trial and post-marketing data to assess the long-term cancer risk associated with JAKis in the AD population.[40] Consequently, these medications cannot be regarded as a safe treatment option for cancer patients, as well as effective for AD management.[41] Anti-interleukin drugs approved for AD, including dupilumab, tralokinumab, and lebrikizumab are not classified as immunosuppressive representing a safer option for patients with active malignancy or history of cancer. These two drugs have an extremely selective mechanism of action, blocking IL-4 receptor alpha chain (IL4Rα) and IL-13 respectively, reducing Th2-mediated inflammation typical of atopic dermatitis without producing a broad-spectrum immunosuppressive effect.[8] Fortunately, data from real life confirm the efficacy and safety of dupilumab and tralokinumab also in this class of subjects and literature also suggests no association between dupilumab and immunosuppression in primary or recurrent malignancies.[42] Of note, their efficacy has been also confirmed for AD comorbidities and during COVID-19 era.[43–45] Finally, according to the consensus by Adam et al, biologics are preferred for AD treatment in cancer patients due to their mechanism of action and expert recommendations.[46] This aligns with the International Eczema Council's current guidelines, which advocate for dupilumab as the primary treatment choice for patients with a history of cancer.[47]

Conclusion

Patients with active or past cancer are typically excluded from clinical trials of new medications, complicating the evaluation of cancer progression or recurrence risks in these patients setting. The potential use of biologic drugs like dupilumab and tralokinumab in oncological patients marks a significant breakthrough for treating conditions such as eczema and pruritus, which are common in this patient group.[48] Eczematous rashes and pruritus are frequent side effects of oncological therapies, including cytotoxic chemotherapy, targeted therapy and immunotherapy.[49] Pruritus, in particular, can become intolerable for cancer patients and is often unresponsive to antihistamine treatment, sometimes necessitating the discontinuation of antineoplastic therapy. Additionally, dupilumab has been approved by the FDA for the treatment of prurigo nodularis in adult patients and there is growing evidence of its efficacy and safety in treating oncotherapy-induced pruritus.[50] In summary, although there are no explicit contraindications for using dupilumab and tralokinumab in patients with active cancer or a history of malignancy, there is no definitive guidance on their use in such cases. Emerging real-world data, driven by collaboration between dermatologists and oncologists, supports the effectiveness and safety of dupilumab and tralokinumab for managing AD in cancer patients. Nonetheless, larger studies with longer follow-up periods and dedicated pharmacovigilance programs are needed to substantiate these findings.

Data Sharing Statement

Data are reported in the current study.

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Disclosure

C. Patruno acted as investigator, speaker, consultant and advisory board member for AbbVie, Amgen, Almirall, Eli Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Pierre Fabre and Sanofi. M. Napolitano acted as speaker, consultant and advisory board member for Sanofi, AbbVie, LEO Pharma, Amgen, PFIZER, Bionike, Pierre Fabre and Eli Lilly. The remaining authors have no conflicts of interest to declare in this work.

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