Dermatol Ther (Heidelb) (2023) 13:7–12
https://doi.org/10.1007/s13555-022-00851-6

COMMENTARY

The Combination of Dupilumab with Other Monoclonal Antibodies

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Received: October 4, 2022 / Accepted: October 31, 2022 / Published online: November 10, 2022

ABSTRACT

Introduction: Dupilumab is an interleukin-4 (IL-4) receptor alpha antagonist indicated for the treatment of moderate-to-severe atopic dermatitis (AD), which could be associated with atopic and non-atopic comorbidities for which concomitant administration of targeted pharmacotherapy including monoclonal antibodies could be required. However, the safety of combining dupilumab with other monoclonal antibodies for different therapeutic indication may be debated.

Methods: We conducted an extensive search in MEDLINE via PubMed for original articles published from January 1, 2017 to October 22, 2022, reporting clinical cases in which dupilumab has been associated with other monoclonal antibodies.

Results: Four small case series were identified reporting data on a total of 16 patients. To them, we have added other patients (n = 8) derived from our clinical practice, achieving a total of 24 cases followed for a period of 2–-22 months. Patients were receiving dupilumab mainly because of AD (except one patient for bullous pemphigoid and one for asthma) and other monoclonal antibodies for psoriasis treated with guselkumab (n = 7) and secukinumab (n = 1), asthma with omalizumab or benralizumab (n = 3), Crohn's disease with adalimumab (n = 3), chronic spontaneous urticaria with omalizumab (n = 3), primary familial hypercholesterolemia with evolocumab (n = 2), hidradenitis suppurativa with adalimumab (n = 1), psoriatic arthritis with secukinumab (n = 1), rheumatoid arthritis with abatacept (n = 1), ankylosing spondylitis with secukinumab (n = 1) and colorectal carcinoma with cetuximab (n = 1). No adverse events related to the combination of the two monoclonal antibodies were reported except for a mild injection site reaction (n = 1) and arthralgia, which resolved spontaneously within a few weeks (n = 1).

Conclusions: Because the evidence is modest, the question remains open as to whether dupilumab can be safely combined with other monoclonal antibodies. Dupilumab does not exert immunosuppressive effects and does not

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impair the activity of cytochrome P450 isozymes.

Keywords: Dupilumab; Atopic dermatitis; Targeted pharmacotherapies; Monoclonal antibodies; Safety

Key Summary Points

Dupilumab, an interleukin-4 (IL-4) receptor alpha antagonist, is a human monoclonal antibody of the immunoglobulin G4 subclass that inhibits IL-4 and IL-13 signaling. It is approved for the treatment of moderate-to-severe atopic dermatitis in children, adolescents, and adults, eosinophilic esophagitis, and severe chronic rhinosinusitis with nasal polyposis.

Atopic dermatitis has been associated with atopic (asthma, allergic rhinitis) and non-atopic comorbidities including cutaneous and extra-cutaneous infections, mental health disorders (depression, anxiety, sleep disturbance), and autoimmune diseases (alopecia areata, intestinal bowel diseases) that could require concomitant administration of targeted pharmacotherapy including monoclonal antibodies.

Answering whether dupilumab can be safely associated appears to be an important issue, considering the extensive current and future availability of monoclonal antibodies (or other targeted therapies) for many common disorders.

Dupilumab does not exert immunosuppressive effects and does not impair the activity of cytochrome P450 isozymes.

Dupilumab, an interleukin-4 (IL-4) receptor alpha antagonist, is a human monoclonal antibody of the immunoglobulin G4 subclass that inhibits IL-4 and IL-13 signaling. It is approved for the treatment of moderate-to-severe atopic dermatitis (AD) in children, adolescents, and adults, eosinophilic esophagitis, and severe chronic rhinosinusitis with nasal polyposis. AD is the first disease for which dupilumab has been approved and the most common reason for dupilumab prescription [1, 2].

AD has been associated with atopic (asthma, allergic rhinitis) and non-atopic comorbidities including cutaneous and extra-cutaneous infections, mental health disorders (depression, anxiety, sleep disturbance), and autoimmune diseases (alopecia areata, intestinal bowel diseases) that could require concomitant administration of targeted pharmacotherapy including monoclonal antibodies [3, 4]. However, the safety of combining dupilumab with other monoclonal antibodies for different therapeutic indication may be debated.

The objective of this review was to investigate whether dupilumab could be safely combined with other monoclonal antibodies for different therapeutic indications.

We conducted an extensive search in MEDLINE via PubMed for original articles published from January 1, 2017 to October 22, 2022. The following research string was applied: (“dupilumab”[All Fields] AND (“biologic”[All Fields] AND “drugs”[All Fields])) AND (“drug”[All Fields] AND “interaction”[All Fields]); ((“dupilumab”[Supplementary Concept] OR “dupilumab”[All Fields]) AND ((((“biological products”[MeSH Terms] OR (“biological”[All Fields] AND “products”[All Fields])) OR “biological products”[All Fields]) OR (“biologic”[All Fields] AND “drugs”[All Fields])) OR “biologic drugs”[All Fields])) AND ((“concomitance”[All Fields] OR “concomitant”[All Fields]) OR “concomitants”[All Fields]). An additional literature review to include articles that have both dupilumab and psoriasis in the abstract was performed. All the references that resulted from the research were included without restrictions of sex, race, or geographic area. The following data were retrieved from the studies including the number of patients, age, gender, type of concomitant disorders and its treatment with the monoclonal antibody, length of the observation period, and eventual adverse drug reactions.

Table 1 Atopic dermatitis patients treated with dupilumab combined with other monoclonal antibodies for concomitant disorders

Cases from the literature						
First author	**Number of patients**	**Age, gender**	**Concomitant disorders**	**Concomitant monoclonal antibody**	**Period of observation (months)**	**Adverse drug reactions**
Barry K	7	31, M	Psoriasis	Guselkumab	2	None
		56, M	Psoriasis	Guselkumab	12	None
		62, F	Psoriasis	Guselkumab	13	None
		78, M	Psoriasis	Guselkumab	6	None
		67, M	Psoriasis	Guselkumab	8	None
		65, F	Psoriasis	Guselkumab	12	Mild injection site reaction
		70, F[a]	Psoriasis	Guselkumab	6	None
Lima H	3	n.a.	Asthma	Omalizumab (n = 2)/ Benralizumab	> 6	None
	2	n.a.	Crohn's disease	Adalimumab	> 6	None
	1	n.a.	Chronic spontaneous urticaria	Omalizumab	> 6	None
	1	n.a.	Hidradenitis suppurativa	Adalimumab	> 6	None
Balestri R	1	68, M	Psoriatic arthritis	Secukinumab	15	None
Mahar PD	1	40, F[b]	Psoriasis	Secukinumab	7	None
Original cases						
	2	68, F	Hypercholesterolemia	Evolocumab	3	None
		62, M	Hypercholesterolemia	Evolocumab	12	None
	2	22, F	Chronic spontaneous urticaria	Omalizumab	12	None
		40, F	Chronic spontaneous urticaria	Omalizumab	14	None
	1	46, M	Ankylosing spondylitis	Secukinumab	18	None
	1	60, M	Colorectal cancer	Cetuximab	15	None
	1	82, M	Rheumatoid arthritis	Abatacept	15	None

Table 1 continued

Cases from the literature						
First author	**Number of patients**	**Age, gender**	**Concomitant disorders**	**Concomitant monoclonal antibody**	**Period of observation (months)**	**Adverse drug reactions**
	1	47, M	Crohn's disease	Adalimumab	22	Arthralgia

n.a. not available, *M* male, *F* female

[a]This patient was receiving dupilumab for bullous pemphigoid

[b]This patient was receiving dupilumab for asthma

Four small case series were identified reporting data on a total of 16 patients whose details are reported in Table 1 [5–8]. One additional manuscript reported a case of a dupilumab-treated patient who developed new-onset psoriasis, but the type of biologic prescribed for psoriasis, the duration of the treatment, the age and gender of the patient were missing in the full text of the manuscript [9], so that we could not include this case in our analysis. To these patients, we have added other original patients ($n = 8$) derived from our clinical practice, achieving a total of 24 cases followed for a period of 2–22 months. Patients were receiving dupilumab mainly because of AD (except one patient for bullous pemphigoid and one for asthma) and other monoclonal antibodies for psoriasis treated with guselkumab ($n = 7$) and secukinumab ($n = 1$), asthma with omalizumab or benralizumab ($n = 3$), Crohn's disease with adalimumab ($n = 3$), chronic spontaneous urticaria with omalizumab ($n = 3$), primary familial hypercholesterolemia with evolocumab ($n = 2$), hidradenitis suppurativa with adalimumab ($n = 1$), psoriatic arthritis with secukinumab ($n = 1$), rheumatoid arthritis with abatacept ($n = 1$), ankylosing spondylitis with secukinumab ($n = 1$) and colorectal carcinoma with cetuximab ($n = 1$). No adverse events related to the combination of the two monoclonal antibodies were reported except for a mild injection site reaction ($n = 1$) and arthralgia, which resolved spontaneously within a few weeks ($n = 1$). The limitations of our study are represented by the small sample size and the short follow-up. The novelty of the study is that it comprehensively collects all the cases in the literature and adds original ones.

Because the evidence is modest, the question remains open as to whether dupilumab can be safely combined with another monoclonal antibodies. However, there are no clinically relevant effects of dupilumab on the activity of cytochrome P450 isozymes which are predominantly responsible for the metabolism of most small-molecule drugs [10]. Moreover, there is no evidence that dupilumab exerts immunosuppressive effects. On the contrary, by decreasing *Staphylococcus* colonization and partially normalizing the skin microbiome, dupilumab appears to improve immunologic protection against infections. No study has reported reactivation of latent infections (HBV, tuberculosis, fungal, or opportunistic infections) or progression of malignancy in association with dupilumab [11]. Consequently, if dupilumab is combined with other immunosuppressive drugs, it is not expected to potentiate these effects. Considering the extensive current and future availability of monoclonal antibodies (or other targeted therapies) for other diseases [12], answering whether dupilumab can be safely associated appears to be an important issue.

ACKNOWLEDGEMENTS

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed

by any of the authors.This manuscript has not been previously presented/published.

Funding. No funding or sponsorship was received for this study or publication of this article.

Medical Writing and/or Editorial Assistance. Not applicable.

Author Contributions. Gisondi P: concept, design, and drafting the manuscript; Maurelli M: design and drafting the manuscript; Costanzo A: collected the data; Esposito M: collected the data; Girolomoni G: design and drafting the manuscript.

Prior Presentation. Not applicable.

Disclosures. Gisondi Paolo has been consultant and/or speaker for AbbVie, Almirall, Amgen, Janssen, Leo-pharma, Eli Lilly, Novartis, Pierre Fabre, Sandoz, Sanofi and UCB. Maurelli Martina has no conflict of interest to disclose. Costanzo Antonio has been a consultant and/or speaker for AbbVie, Galderma, Almirall, Janssen, UCB, Sanofi, Novartis, Lilly, Sandoz, Biogen, Pfizer. Esposito Maria has served as speaker and/or consultant for AbbVie, Almirall, Biogen, Celgene, Eli-Lilly, Janssen, Leo Pharma, Novartis, Sanofi Genzyme and UCB. Girolomoni Giampiero served as consultant and/or speaker for AbbVie, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Novartis, Pfizer, Regeneron, Samsung Bioepis, Sanofi and UCB.

Compliance with Ethics Guidelines. The study is compliant with standards of research involving humans as subjects. The ethics committee exempted such kind of research from the formal study protocol approval, because we only accessed retrospectively a de-identified database for the purpose of data analysis. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The research data associated with a paper is available on request to the authors.

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