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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Real-world evidence on the risk of cancer with anti-IL-5 and anti-IL-4Ra biologicals

To the Editor,

Biologicals indicated for the treatment of severe asthma and other allergic/eosinophilic conditions include monoclonal antibodies which target interleukin (IL)-5 or IL-5R (mepolizumab, reslizumab, and benralizumab), IL4-Rα (dupilumab), and IgE (omalizumab). Previously, we have shown that omalizumab may be associated with an increased risk of cancer.[1]

Recent studies have suggested a role for eosinophils in cancer pathogenesis. Although still controversial, most studies point out an antitumorigenic role of eosinophils mediated by α-defensins, TNF-α, granzyme A, and IL-18, while in a few others, they are innocent bystanders or their presence in the tumor microenvironment have been linked to poor prognosis.[2,3] Furthermore, eosinophils have been proposed to be potential end-stage effector cells in cancer immunotherapy.[3]

Biological agents which antagonize IL-5 or IL-5R may lead to a reduction in peripheral blood eosinophil counts. The inhibition of the IL-4/IL-13 pathway might result in an inhibition of eosinophils recruitment from peripheral blood to inflamed skin tissues. Moreover, studies evaluating the safety of these drugs have not demonstrated an increased risk for malignancies.[4,5] However, neither the clinical trials' design nor included participants are broadly representative of patients found in everyday practice. Thus, we aimed to assess cancer risk associated with the use of these drugs in a real-world life dataset.

A disproportionality analysis (case/non-case study) was performed within the World Health Organization global database of individual case safety reports (VigiBase) developed and maintained by Uppsala Monitoring Centre, to identify a signal of cancer, expressed as the reporting odds ratio (ROR) and its 95% confidence interval (CI) for each biological (i.e., mepolizumab, reslizumab, benralizumab, and dupilumab). Cases were defined as adverse drug reactions (ADR) coded as Neoplasms according to the Medical Dictionary for Regulatory Activities terminology reported between 2008 and 2020. Non-cases were defined as all other ADRs reported during the same period. No data about the age or gender of cases were provided.

A total of 19,983,350 ADR reports were included and most were reported between 2018 and 2020 (Figure 1). Among biologicals,

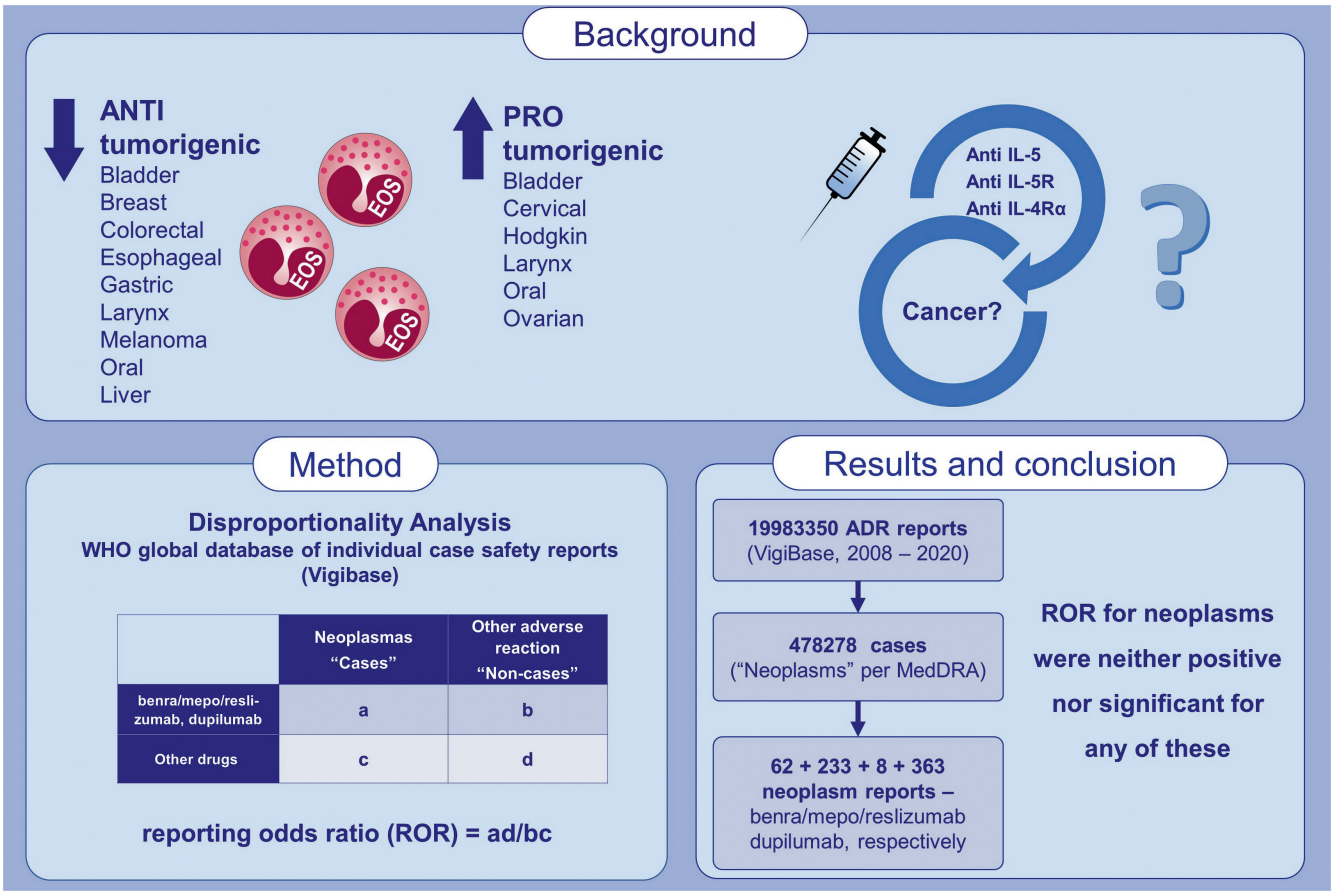

FIGURE 1 Overview of study rationale, methodology, and main findings

Biological	Cases associated with biological, *n*	Total of reports of ADR, *n*	ROR	95% CI
Benralizumab	62	4026	0.64	0.50–0.82
Breast Cancer	4		0.69	0.26–1.84
Lung Cancer	3		0.94	0.30–2.92
Malignant Melanoma	3		1.92	0.62–5.97
Pancreatic Carcinoma	3		1.60	0.52–4.96
Mepolizumab	233	9920	0.98	0.86–1.12
Breast Cancer	19		1.33	0.85–2.09
Lung Cancer	18		2.29	1.44–3.64
Prostate Cancer	15		2.26	1.36–3.75
Colon Cancer	7		2.04	0.97–4.28
Reslizumab	8	382	0.87	0.43–1.76
Dupilumab	363	37,602	0.40	0.36–0.44
Breast Cancer	22		0.41	0.27–0.62
Cutaneous T-cell lymphoma	16		11.11	6.77–18.23
Lymphoma	15		1.07	0.64–1.77
Lung Cancer	13		0.44	0.25–0.75
Omalizumab[1]	1380	36,164	1.65	1.56–2.74

Abbreviations: ADR, adverse drug reactions; CI, confidence interval; ROR, reporting odds ratio.

TABLE 1 Disproportionality analysis (reporting odds ratio and its 95% confidence interval) of total neoplasms (cases) and more frequent cancers for each specific biological in VigiBase for the period between 2008 and 2020

dupilumab had the most reported cases with a total of 363, followed by mepolizumab with 233 and benralizumab with 62. Only 8 cases were linked to reslizumab. The most frequently reported malignancies for each biologic drug included breast cancer and lung cancer. ROR for neoplasms was neither positive nor significant for any biological (Table 1).

Overall, no signal of cancer was detected for any biological drug, as ROR was <1 for the total number of neoplasms (i.e., when compared to other drugs, there were no more reports of cancer related to these biologicals). Considering specific cancers, there may be some associations, but the number of cases is too small to be considered as a strong signal. Cutaneous T-cell lymphoma cases associated with dupilumab showed the most significant positive signal (ROR = 11.11), and this connection has been reported before and is under investigation.[6]

The strength of our study results from the analysis of real-world life data, in which no exclusion criteria were applied. However, our observations are limited as the information present in VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. Some important data such as the demographic profile of patients or the duration of therapy with these biologicals were not available, which would have allowed the analysis of other factors that could impact the risk of cancer. Another limitation of our study may be related to competition biases, since some of these biologicals have been strongly associated with other adverse drug reactions (i.e., dupilumab and ocular disorders), and this may have led to an underestimation of ROR.

In conclusion, real-world life data do not support any association between anti-IL-5 and anti-IL-4Ra biologicals and cancer. Since these biologicals have only been available for a short period, the effect may be underestimated, and a larger period may be needed to better assess cancer incidence.

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DM drafted the manuscript. AM conceived and coordinated subsequent edits and revisions. TAR participated in drafting the manuscript and its finalization. All authors have read and approved the final manuscript. The information does not represent the opinion of the Uppsala Monitoring Centre (UMC) or the World Health Organization.

CONFLICT OF INTEREST

All authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence their work.

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