

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

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To the editor:

Biologics 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-R α (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 anti-tumorigenic 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}. Therefore, biological agents which antagonize IL-5/IL-5R may lead to a reduction in peripheral eosinophil counts. Concerning the inhibition of the IL-4/IL-13 pathways no evidence of potential safety signals related to malignancy exists. 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 19983350 ADR reports were included, from which 478278 cases referred to these biologics (Figure 1). Most data were reported between 2018 and 2020. Among biologics, 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 less than 1 for the total number of neoplasms (i.e., when compared to other drugs, there were no more reports of cancer related to these biologics). 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 investigation⁶.

The strengths of our study result from the analysis of real-world life data, from an uncontrolled population of patients. 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 biologics 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 biologics 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 does not support any association between anti-IL-5 and anti-IL-4Ra biologics and cancer. Since these biologics 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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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. ADR, adverse drug reactions; CI, confidence interval; ROR, reporting odds ratio.

Biological	Cases associated with biological, n	Total
Benralizumab	62	4026
Breast Cancer Lung Cancer Malignant Melanoma Pancreatic Carcinoma	4 3 3 3	
Mepolizumab	233	9920
Breast Cancer Lung Cancer Prostate Cancer Colon Cancer	19 18 15 7	
Reslizumab	8	382
Dupilumab	363	37602
Breast Cancer Cutaneous T-cell lymphoma Lymphoma Lung Cancer	22 16 15 13	
Omalizumab¹	1380	36164

Figure 1 Flow chart of the study. ADR, adverse drug reaction; MedDRA – Medical Dictionary for Regulatory Activities