

Cardiovascular adverse effects of anti-IL5/IL5R α therapies: a real-world study

Jean-Baptiste Quinta¹ M.D.[†], François Montastruc M.D PhD^{2,3*}, Agnès Sommet MD Ph.D^{2,3}, Anthony Touafchia MD⁴, Michel Galinier MD PhD⁴, Laurent Reber PhD⁵, PhD, Vanessa Rousseau PhD², Laurent Guilleminault^{1,5} M.D., PhD

1. Department of respiratory medicine, Toulouse University Hospital, Faculty of Medicine, Toulouse, France

2. Department of Medical and Clinical Pharmacology, Toulouse University Hospital, Faculty of Medicine, Toulouse, France

3. INSERM, UMR 1027 Pharmacoepidemiology, Assessment of Drug Utilization and Drug Safety, CIC 1426 - University Paul Sabatier Toulouse, Toulouse, France

4. Department of Cardiology, Toulouse University Hospital, Faculty of Medicine, Toulouse, France

5. Centre for Pathophysiology of Toulouse Purpan, INSERM U1043, CNRS UMR 5282, Université Toulouse III, F-CRIN CRISALIS, Toulouse, France

[†] The authors have equally contributed to the manuscript and are the co-first authors of the publication

*Corresponding author:

Laurent Guilleminault

Hôpital Larrey, CHU de Toulouse

24 chemin de Pourville

31059 Toulouse

Phone: 0033567771850

Fax : 0033567771472

guilleminault.l@chu-toulouse.fr

28 Co-authors' e-mail

29 QUINTA Jean-Baptiste: jeanb.quinta@gmail.com, MONTASTRUC Francois:

30 montastruc.f2@chu-toulouse.fr, SOMMET Agnès: agnes.sommet@univ-tlse3.fr,

31 TOUAFCHIA Anthony: touafchia.a@chu-toulouse.fr, GALINIER Michel: [galinier.m@chu-](mailto:galinier.m@chu-toulouse.fr)

32 toulouse.fr, REBER Laurent: laurent.reber@inserm.fr, ROUSSEAU Vanessa:

33 rousseau.v@chu-toulouse.fr

34

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42 Clinical implications: Cardiovascular events are not likely to be more reported with IL-5/IL-

43 5R α blocking drugs compared to omalizumab. Hypertension, ventricular arrhythmia and

44 venous thromboembolism were significantly more reported with omalizumab

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Omalizumab, an antibody directed against the receptor-binding domain of IgE, was the first biological therapy marketed in severe allergic asthma. Several observational studies including long-term analyses concluded that omalizumab has showed an overall optimal safety profile¹⁻⁵. Although higher incidence rate of cerebrovascular and cardiovascular adverse events emerged in some studies^{3, 4}, confounding factors between omalizumab and non-omalizumab patients were likely to explain those results. Recently, mepolizumab, reslizumab (both anti-interleukin 5 (IL5)) and benralizumab (an anti-IL5 receptor- α (IL5R α)) have been associated with a reduction of the exacerbation rate and the dose of oral steroids in eosinophilic severe asthma. In long-term safety studies, rare cardiovascular events such as myocardial infarction, deep venous thrombosis and stroke have been described with benralizumab and mepolizumab. Nevertheless, an association between these events and these drugs is still unknown^{6, 7}. We performed a pharmacovigilance study in order to assess the effect of anti-IL5/IL5R α therapies on cardiovascular events.

Disproportionality analyses (case non-case method) were performed using Vigibase®, the World Health Organization global database of Individual Case Safety Reports (ICSRs), to assess whether anti-IL5/IL5R α therapies (mepolizumab, reslizumab and benralizumab) are associated with an increased risk of cardiovascular events compared to omalizumab. The study protocol was approved by the Institutional Review Board of the *Société de pneumologie de langue Française* (CEPRO 2019-041).

All reports registered between January 1, 2000 and December 1, 2019 were considered. The reports containing patients aged 12 years or older with adverse events suspected from being triggered by at least one Anti-IL5/IL5R α therapies or omalizumab were included herein. The outcomes of interest were cardiovascular adverse events according to the 10th revision of the

International Statistical Classification of Diseases. Cases were identified as having cardiovascular events defined by the Standardized MedDRA queries (SMQs) or by the MedDra dictionary using the SOC (system organ class) classification. Non-cases were patients with adverse events except cardiovascular ones for the same drugs. For all cases and non-cases, we identified patients exposed to anti-IL5/IL5R α therapies and those to omalizumab (reference category) according to the anatomical therapeutic chemical dictionary. ICSRs with both anti-IL5/IL5R α therapy and omalizumab were excluded. Using a case/non-case design, we compared anti-IL5/IL5R α therapies to omalizumab regarding cardiovascular events using a multivariate logistic regression. Reporting odds ratios (RORs) with 95% confidence interval (CI) were adjusted for the following covariates: age, sex, type of reporters, countries, other drugs prescribed. For the robustness of our study, several sensitivity analyses were performed. Given, oral steroids are involved in the development of cardiovascular events, we made a sensitivity analysis in patients with no oral steroids.

We identified 22,236 adverse events associated with omalizumab, reslizumab, mepolizumab or benralizumab in Vigibase®. After using all inclusion and exclusion criteria, 21,052 reports were selected for the final analysis. Among these 21,052 adverse events, 2,955 cardiovascular events were presented including 435 reports for anti-IL5/IL5R α therapies (378 for mepolizumab, 48 for benralizumab and 9 for reslizumab) and 2,520 for omalizumab. In the patients treated with anti-IL5/IL5R α therapies and omalizumab, mean age was 56.0 ± 15.1 and 47.9 ± 17.1 and females were 67.0% and 69.6%, respectively. Most of the reports come from America (74.3%) and Europe (18.8%). Overall cardiovascular events were significantly less reported with anti-IL5/IL5R α therapies compared to omalizumab (adjusted RORs 0.41 [95%CI 0.36-0.46]) (Figure 1). Ischemic stroke was more reported with anti-IL5/IL5R α

therapies compared to omalizumab (adjusted RORs 1.69; 95%CI 1.02-2.74). Hypertension, ventricular arrhythmia and venous thromboembolism (VTE) were significantly lower with anti-IL5/IL5R α therapies compared to omalizumab (adjusted RORs 0.26 [95%CI 0.22-0.30], 0.55 [95%CI 0.32-0.90] and 0.68 [95%CI 0.45-0.99], respectively). A sensitivity analysis was performed on the reports restricted to the declarations made by healthcare workers or regarding patients receiving no oral steroids. Thus, these results remained the same, except ischemic stroke for which no difference was observed. If we only considered the adverse events reported during the first 4 years with omalizumab and anti-IL5/IL5R α therapies, cardiovascular adverse events were similar between both of them.

Although the safety profile of anti-IL5/IL5R α therapies appears to be acceptable in phase III trials, the number of patients exposed to these drugs is limited. Moreover, these patients are highly selected in clinical trials and do not fully correspond to patients treated in real life. According to the recent EAACI guidelines, anti-IL5/IL5R α therapies have shown an increased likelihood of drug-related adverse events (AE) compared to placebo⁸. Serious AE were inconclusive due to the low number of events. In phase III extension studies conducted with mepolizumab, 2% and 4% of cardiovascular events have been observed in both COSMOS and COSMEX studies, respectively^{6, 7}. Hence, the cardiovascular safety of anti-IL5/IL5R α therapies remains a concern.

Vigibase® gathers drug-related AE all around the world and constitutes a powerful and unique tool for rare events. In our study, omalizumab was chosen as the control because of being a treatment for severe asthma like anti-IL5/IL5R α therapies. Indeed, the acceptable safety profile of omalizumab has been well established. Although cardiovascular adverse

events have been suggested by EXCELS study⁴, after adjustment for confounding factors, no association between omalizumab and cardiovascular events has been shown.

Herein, cardiovascular events were not more likely to be reported with anti-IL5/IL5R α therapies compared to omalizumab except ischemic stroke. However, an increased risk of ischemic stroke reports was no longer observed in sensitivity analyses. This means that it is highly likely that there is no association between ischemic stroke and anti-IL5/IL5R α therapies. Hypertension, VTE and ventricular arrhythmia had a significant higher adjusted ROR with omalizumab compared to anti-IL5/IL5R α therapies. However, omalizumab was commercialized 10 years before anti-IL5/IL5R α therapies. This duration of the administration may be associated with an increased risk of incidental events. Nevertheless, an association between a very long-term exposure to omalizumab and hypertension, VTE or ventricular arrhythmia cannot be ruled out from our study. Immune cells including mast cells seem to play a role in the pathophysiology of arteriosclerosis, cardiac disorders or venous thrombosis⁹.

Given the interaction between IgE and the immune system, particularly mast cells, an impact of a long term use of omalizumab on these diseases cannot be excluded.

In conclusion, cardiovascular events were not likely to be more reported with anti-IL-5/IL5Ra therapies compared to omalizumab in the first 4 years after they became available. However, overall, hypertension, VTE or ventricular arrhythmia were more likely to be reported with omalizumab, suggesting that long-term studies are warranted for all biological therapies in severe asthma

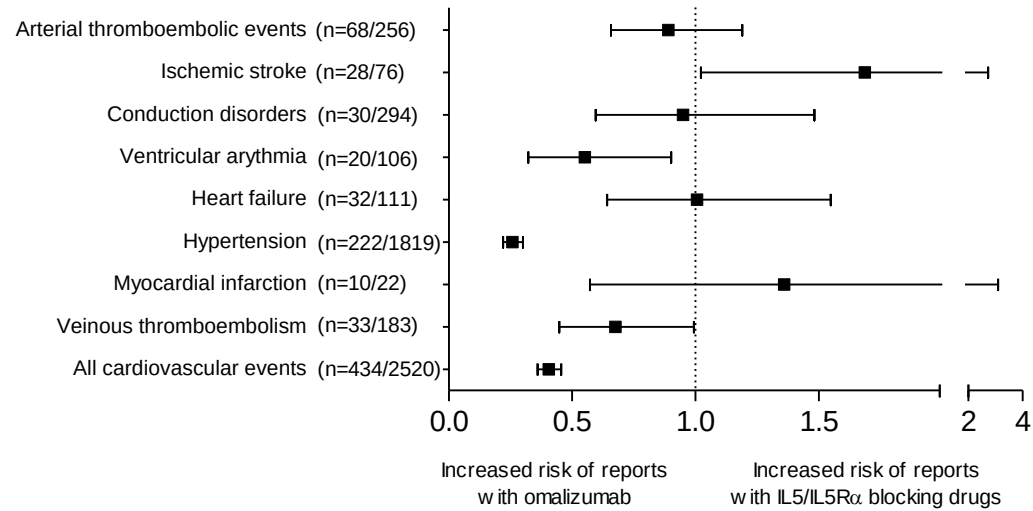
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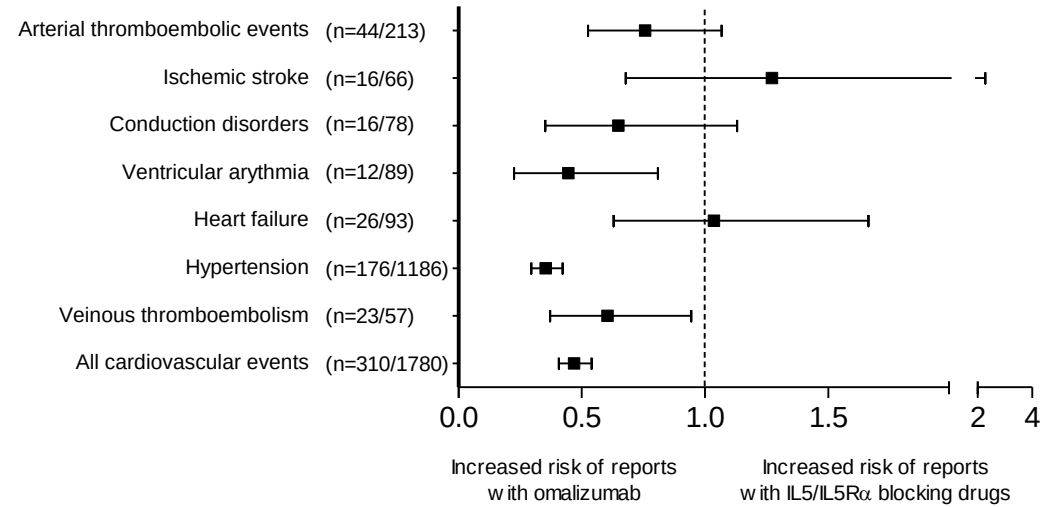
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Figure 1: forest plot of adjusted reporting odd ratio (ROR) regarding cardiovascular events of anti-IL5/IL5R α therapies (benralizumab, mepolizumab and reslizumab) compared to omalizumab in the overall reports, in the reports restricted to the healthcare workers, in the reports restricted to patients with no oral steroids, in the reports restricted to the first 4 years of declaration. n=number of events with anti-IL5/IL5R α therapies/number of events with omalizumab

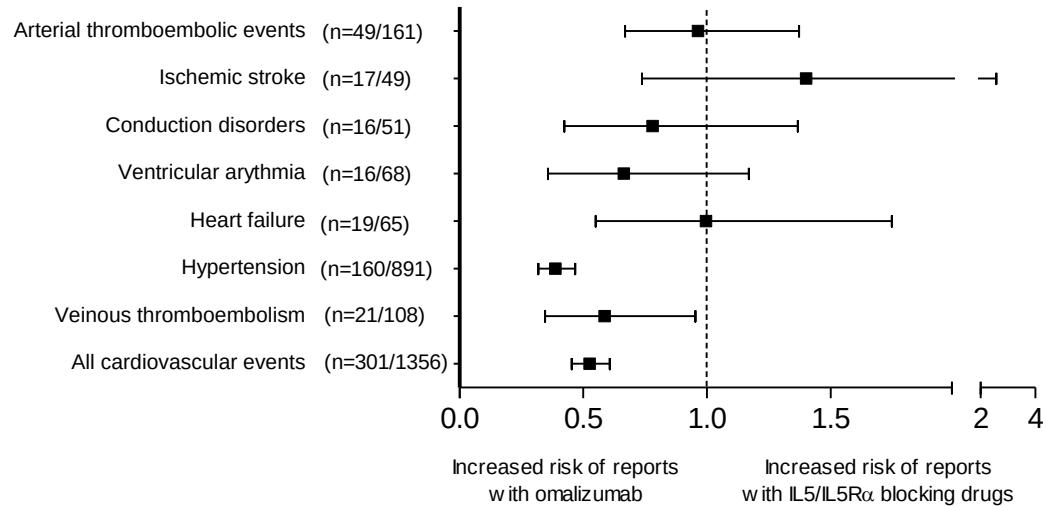
Overall



Healthcare professionals



No oral steroids



First 4 years of reporting

