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Accepted Date : 13-Jan-2011

Article Type : Correspondence

TITLE PAGE

Re: Incidence of cancer in the general population and in patients with and without atopic dermatitis in the UK

A. Arana^a, C.E. Wentworth^b, C. Fernández-Vidaurre^c, R.G. Schlienger^d, E. Conde^{e,f}, F.M. Arellano^{a, b}

^a Risk MR Pharmacovigilance Services, SL, Zaragoza, Spain

^b Risk MR, LLC, Bridgewater, NJ, USA

^c Novartis Pharmaceuticals Corp., Global Clinical Epidemiology, East Hanover, NJ, U.S.A.

^d Novartis Pharma AG, Global Clinical Epidemiology, Basel, Switzerland.

^e Universidad de Cantabria, Santander, Spain

^f Hematology Deptment, Hospital Marqués de Valdecilla, Santander, Spain

Corresponding Author:

Alejandro Arana
Risk MR Pharmacovigilance Services,SL
Zurita 14, 1-D
50001 ZARAGOZA
Spain
+34 661 200 307

Email: arana.riskmr@gmail.com

Declaration of funding: The study was funded by an unrestricted grant from Novartis. Risk MR had contractually the final decision on content and destination of the manuscript, as well as where to submit it. Carlos Fenández-Vidaurre and Raymond Schlienger are Novartis employees.

Madam,

We read with great interest the comments by Wedgeworth et al. However, it is important to emphasize that there is not much information on the incidence of cancer or subtypes of cancer in atopic dermatitis (AD) patients, and that the primary objective of the study was to describe the incidence rates of cancer in patients with and without AD in the UK, using information from a primary care electronic medical record database [i.e. The Health Improvement Network (THIN)]. For that purpose we reported the incidence rate of the first occurrence of cancer overall [excluding non melanoma skin cancer (NMSC)], and of lymphoma, melanoma or NMSC individually. We reported incidence rates in patients without AD, patients with AD and in all patients, stratified by sex and eleven age categories. We additionally calculated age- and sex-adjusted incidence rate ratios (IRR) to compare the risk of cancer in AD patients versus subjects without AD. We also reported the non-adjusted, crude IRR for patients with AD vs. patients without AD.

Since we did not control for confounding factors other than age and sex, it is neither possible to establish a causality of AD with the occurrence of cancer, nor did we aim to do so in our paper. That is why we always refer in our report to age-sex adjusted IRR. Referring to IRR, without mentioning the restriction to age-sex adjustment – as Wedgeworth et al. do in their letter – could lead to a misinterpretation of the results, as the reader may assume the results come from a model adjusted for all relevant risk and/or confounding factors (some of which are discussed by Wedgeworth et al.).

The THIN database uses Read codes and we agree that Read codes have previously been shown to have limitations in allergic conditions. We used Read

codes or the record of a specialist's diagnosis, and did our best to classify the condition, achieving a good specificity, although our identification process is still far from perfect as we described in the discussion section. We believe however, that the method of AD validation proposed by Wedgeworth et al – i.e. a direct comparison of the Read code system with the diagnosis made by an independent physician using validated diagnostic criteria – would have been impracticable in our sub-cohort of over 66,000 AD patients.

We also used Read codes for the identification of the outcomes. In an attempt to assess the risk of lymphoma associated with AD and use of topical immunomodulators we validated the electronic records of patients with a recorded diagnosis of lymphoma using medical information, which yielded good specificity and sensitivity (1). It is unclear whether these results could be extrapolated to other types of cancer.

Like all epidemiologic research, our study has limitations but is in line with a body of evidence suggesting an increased risk of cancer in patients with AD. However, as discussed in our paper, confirmation is needed from other studies that are able to control for all confounding factors and can address some of the limitations described by Wedgeworth et al.

1. Arellano F, Arana A, Wentworth CW, Fernandez-Vidaurre C, Schlienger RG, Conde E. Lymphoma among patients with atopic dermatitis and/or treated with topical immunosuppressants in the United Kingdom. *J Allergy Clin Immunol* 2009; 123:1111-1116.