Need for longitudinal studies to assess the real-world effectiveness of allergy immunotherapy in patients with allergic rhinitis and asthma — Authors´ reply

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The real-world effectiveness of allergy immunotherapy (REACT)-study was an observational, retrospective database study that mirrored the scientific rigor of randomised controlled trials (RCTs) to provide robust and complementary long-term real-world evidence in AIT.[1] While most RCTs in AIT have demonstrated shorter-term efficacy on symptoms and use of symptom-relieving medication for allergic rhinitis (AR),[2] the REACT-study used routinely collected health care data to assess the long-term effectiveness in a large, unselected, patient population treated with AIT in clinical practice, i.e. without exclusion of patients with certain comorbidities or low adherence.[3]

It is an identified limitation of the REACT-study, that only prescription data were captured in the database since patients could also get symptom-reliving medications for AR as over-the-counter (OTC) drugs. As discussed in the REACT publication[3] and highlighted by Kamat et al.[4] it is possible that increased OTC use could, in part, explain the reductions in AR prescriptions over time. However, other factors like treatment fatigue and regression to the mean are also likely to have been important. Crucially, an increased use of OTC over time would impact all AR subjects and is therefore not likely to account for the consistently greater reductions in AR prescriptions over time seen in the AIT group compared to controls, and thus is not a source of bias in the principal objectives of the REACT study.[3]

Kamat et al. also speculate whether better access to specialist care could improve outcomes for AIT-treated subjects, since AIT is often administered by specialists.[4] The REACT-study did find that subjects treated with AIT were seen more frequently by specialists during the first 3–5 follow-up years.[3] While difference in access to care could lead to improved outcomes, it is also possible that the increased number of specialist visits would in fact disadvantage the AIT group. More frequent specialist visits may lead to more AIT subjects getting confirmed diagnosis codes or receiving more prescriptions to optimise the control of their allergic respiratory diseases. Despite OTC use of symptom-relieving medications for AR and difference in access to care during follow-up, the results from the REACT study were robust across multiple outcomes. While Kamat et al. focus mainly on AR prescriptions,[4] the REACT-study also reported greater reductions in both reliever and controller asthma prescriptions, which are not available as OTC medications, and concurrently, clinically important outcomes like asthma exacerbations, diagnosis of pneumonia and hospitalisations all favoured the AIT group.[3]

All analyses in the REACT-study were conducted in accordance with the pre-specified statistical analysis plan to support the objectives of the study, i.e. assess the long-term effectiveness of AIT. In accordance with the study objectives, all available types of AIT, except venom AIT, were included in the study.[3] Since the effectiveness is likely to vary between different AIT products within the AIT group, effect-size for the entire AIT class was not a pre-specified outcome.

While residual confounding is possible in retrospective database studies, the REACT-study took every possible step to mitigate the risk of bias.[1] The REACT-study provides results consistent with the major RCTs,[2] while also bridging from those trials to a broader unselected population with substantially longer follow-up.

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Declaration of interests

Dr. Fritzsching reports personal fees (pertaining travelling to study meeting) from ALK, during the conduct of the study; and personal fees from Novartis and from Merck Sharp & Dohme, outside the submitted work. Dr. Contoli reports personal fees from Alk-Abello, during the conduct of the study; grants, personal fees and non-financial support from Chiesi, personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, grants, personal fees and non-financial support from GlaxoSmithKline, personal fees and non-financial support from Novartis, personal fees and non-financial support from Zambon, grants from University of Ferrara - Italy, outside the submitted work. Dr. Porsbjerg reports grants from ALK, grants and personal fees from AstraZeneca, grants and personal fees from GSK, grants and personal fees from Novartis, grants and personal fees from Chiesi, grants and personal fees from Sanofi, grants and personal fees from TEVA, outside the submitted work. Sarah Buchs reports to be employed at ALK-Abello. Dr. Rask Larsen reports being an employee at ALK. Dr. Elliott has nothing to disclose. Ms. Romano Rodriguez reports she is an ALK employee. Dr. Freemantle reports personal fees from Astrazeneca, personal fees from Ipsen, personal fees from Sanofi Aventis, personal fees from Novartis, personal fees from Aimmune, personal fees from Vertex, personal fees from Gedeon Richter, personal fees from Galderma, personal fees from Novo Nordisk, outside the submitted work.

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