EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Real world effectiveness of anti-IL-5/5R therapies is independent of co-eligibility for anti-IgE therapy

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Please cite this article as: Hearn AP, Hug OD, Somani ZA, *et al*. Real world effectiveness of anti-IL-5/5R therapies is independent of co-eligibility for anti-IgE therapy. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00166-2021).

Real world effectiveness of anti-IL-5/5R therapies is independent of co-eligibility for anti-IgE therapy

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Conflicts of interest: DJ, BK, GdA, reports advisory board and speaker fees and congress travel support from GSK, Astrazeneca, Chiesi, Napp, and Teva pharmaceuticals. JK reports congress travel support from Teva. JD reports congress support from Sanofi. AN reports speaker fees from Astrazeneca and congress travel support from Napp.

Funding: none declared

Brief Summary. In a real-world setting, the clinical response to the anti-IL-5/5R mAbs mepolizumab and benralizumab in patients with severe eosinophilic asthma is independent of co-eligibility with the anti-IgE mAb omalizumab.

Word count: 1198

To the Editor:

Mepolizumab and benralizumab are monoclonal antibodies (mAbs) approved for the treatment of severe eosinophilic asthma (SEA), targeting IL-5 and IL-5R respectively.[1] In appropriately selected patients, their use leads to significant reductions in asthma exacerbations and maintenance oral corticosteroid (mOCS) dose.[2, 3]

Omalizumab is a humanised anti-IgE mAb, shown to reduce exacerbation rates in subjects with severe allergic asthma.[4] Post-hoc analyses of the randomised controlled study of omalizumab suggest that it lacks clinical effectiveness in the absence of elevated T2 biomarkers.[5] Consequently, omalizumab may be most effective in patients with an allergic eosinophilic phenotype, making these patients equally appropriate for treatment with anti-IL5/5R mAbs. Data from phase 3 trials of mepolizumab and benralizumab have highlighted that neither baseline IgE level nor atopic status predict response to therapy.[6, 7] It remains unknown if the real world clinical effectiveness of anti-IL5/5R mAbs differs between patients who additionally meet omalizumab eligibility criteria compared to those who do not.

We performed a retrospective analysis of all patients with SEA who commenced mepolizumab or benralizumab between April 2017 and April 2019 at our regional, tertiary asthma centre. We compared annualised exacerbation rate (AER), reduction in mOCS dose, FEV1, asthma control questionnaire-6 (ACQ6) and mini-Asthma Quality of Life Questionnaire (mAQLQ), following 1 year of anti-IL5/5R therapy; between patients who additionally fulfilled omalizumab eligibility criteria as per NICE guidance [8] and those who did not.

Statistical data was analysed using SPSS (version 24) (IBM SPSS, Chicago, IL). Data are given as mean (standard deviation) if normally distributed or median (interquartile range [IQR]) if non-normally distributed. Parametric variables were compared using T tests (paired / independent) and non-parametric variables using Mann-Whitney U test (unrelated) / Wilcoxon Signed Rank (related).

Categorical variables were analysed by Chi-Square test / Fisher's exact where appropriate. Comparison of survival curves was performed using Log-rank (Mantel-Cox) test. Differences between multiple groups were identified using ANOVA (normally distributed) or Kruskal-Wallis one-way analysis of variance (non-normally distributed). Differences were considered significant at $P<0.05$. All P values are two-sided. Ethical approval to report observational outcomes of routine clinical care was granted (15/LO/0886).

We identified 229 cases treated with either benralizumab (n=130) or mepolizumab (n=99). These included 37 patients first treated with mepolizumab, then switched to benralizumab due to suboptimal response.[9] These patients had each treatment episode analysed individually to allow sub-analysis of mepolizumab and benralizumab cohorts. Aeroallergen sensitisation data was missing for 1 patient who was excluded. Of the total cohort, 111/228 (48.5%) fulfilled omalizumab eligibility criteria at the time of commencing anti-IL-5/5R therapy. At baseline, patients who were co-eligible for omalizumab were younger (mean age 50.6±13.2 vs 55.2±13.2 years, p=0.01), less likely to have adult-onset disease (45.9% vs 70.9%, p <0.001), had lower total IgE (289±250 vs 581±1126KU/l, p=0.009), higher ACQ-6 scores (3.03±1.34 vs 2.59±1.34, p= 0.014) and lower mAQLQ scores (3.24±1.50 vs 3.80±1.60, p= 0.007). Gender (53.8% female vs 63.0%), BMI (30.5±6.5 vs 30.4±7.6), AER (4.3±3.4 vs 4.1±3.1), and FEV1 (61.2±23.5% predicted vs 63.4±22.8%) did not differ significantly between groups.

Comparing omalizumab co-eligible patients with those eligible for anti-IL-5/5R only, no difference in time to first exacerbation was observed. 33.9% of co-eligible patients and 37.6% of the anti-IL-5/5R only cohort remained exacerbation free at 1 year (p=0.7) (figure 1A). The ability to wean patients off mOCS did not differ between groups, with median reductions after 48 weeks of 100% in both cohorts p=0.94 (figure 1B). Similar improvements in ACQ-6 were also observed between groups: Omalizumab co-eligible cohort 0.62±1.34 vs 0.59±1.09 in the anti-IL-5/5R only cohort (p=0.9) (figure 1C). Finally, no statistically significant differences in changes in FEV1 were observed between groups. (figure 1D).

We additionally compared the cohorts by responder definitions identified by an International Delphi process.[10] We found no statistically significant differences between the proportions achieving a 50% or 100% reduction in AER, a 50% or 100% reduction in mOCS use (the latter allowed for low-dose prednisolone purely for adrenal insufficiency), change in ACQ6 of at least 1.0, or change in m-AQLQ of at least 1.0 (data not shown). Finally, there were no significant differences in any clinical outcome measure between omalizumab eligible and ineligible patients when mepolizumab and benralizumab cohorts were analysed individually.

This real-world analysis of patients treated with anti-IL-5/5R mAbs demonstrates that clinical response is independent of omalizumab eligibility status. Our results reaffirm the central role of the IL-5/eosinophil pathway in severe asthma and mechanistically infers that from a clinical perspective, an appreciation of whether it is the adaptive allergen-induced Th2 pathway, or innate ILC2 directed pathway that is the dominant driver of airway eosinophilia may be less pertinent than previously thought. What appears clinically relevant is targeting the eosinophil. These findings are consistent with post hoc-analyses of controlled trials of mepolizumab and benralizumab which both showed similar improvements in outcome measures across baseline IgE levels.[6, 7]

The ability to reduce exacerbations whilst weaning mOCS appears to be the clinical outcome that most clearly differentiates eosinophil-targeting biologics from omalizumab. In the SIRIUS and ZONDA studies, treatment with mepolizumab and benralizumab led to exacerbation reductions of 32% and 70% respectively, whilst simultaneously reducing mOCS requirements by a median of 50% compared to placebo.[11, 12] In real-world mepolizumab and benralizumab cohorts, we have previously reported a median mOCS dose reduction of 100% after 12 months of treatment[2, 3]. In contrast, whilst no placebo-controlled steroid-sparing studies have been performed for omalizumab, the large real-world APEX II study of omalizumab reported a very modest fall in mOCS dose of only 2.4mg/day prednisolone following a year of treatment.[13] In the only placebo-controlled omalizumab trial that restricted

inclusion to severe asthmatics,[4] the OCS dependent subgroup did not exhibit any reduction in exacerbation rate, a finding highlighted in the 2014 Cochrane review.[14]

Within our atopic cohort we are not able to robustly distinguish between what may be clinically significant and insignificant allergy, however, all the atopic patients were sensitised to a minimum of 1 perennial aeroallergen. Additionally, the mean age of our cohort is slightly higher than the 44-45 in the omalizumab EXTRA study[4] and it is recognised that younger patients have a more typical allergic phenotype. This alongside problems inherent when reporting real-world data (lack of control arm and randomisation) are the main limitations of this report. During the period of this analysis, our centre commenced three patients on omalizumab, two had prior treatment with anti-IL-5/5R but were switched due to suspected adverse reactions. This low number reflects our practice of using anti-IL-5/5R mAbs as first-line in patients with SEA based on the published data described above highlighting equivalent efficacy of anti-IL-5/5R mAbs across IgE levels in controlled studies[7], and the limited efficacy of omalizumab in T2 biomarker low patients[5], or omalizumab-eligible patients requiring maintence OCS[14]. As a consequence of this, a meaningful comparison of outcomes in patients treated with omalizumab has not been possible. However, it does mean that our analysis is largely free from selection bias.

In summary, the clinical effectiveness of treatment with the anti-IL5/5R mAbs mepolizumab and benralizumab in SEA is independent of co-eligibility for omalizumab therapy. Prospective head-to-head studies of anti-IgE vs anti-IL5/5R (and vs anti-IL4R) therapies are needed, as it remains unclear which patients if any may have a superior response to an anti-IgE vs an anti-IL5/5R approach.

Figure 1. Co-eligibility to omalizumab and clinical outcome with anti-IL-5/5R mAbs

Kaplan-Meier curve of patients remaining exacerbation-free at 48 weeks (A); reduction in maintenance oral corticosteroid dose (mOCS) (B); absolute change in asthma control questionnaire-6 (ACQ-6) from baseline at 48 weeks (C); absolute change in forced expiratory volume in 1 second (FEV1) from baseline at 48 weeks (D). Error bars represent standard error of mean for parametric variables and IQR for non-parametric variables. All differences between groups are non-significant. Dotted line represents the minimal clinically important difference (MCID).

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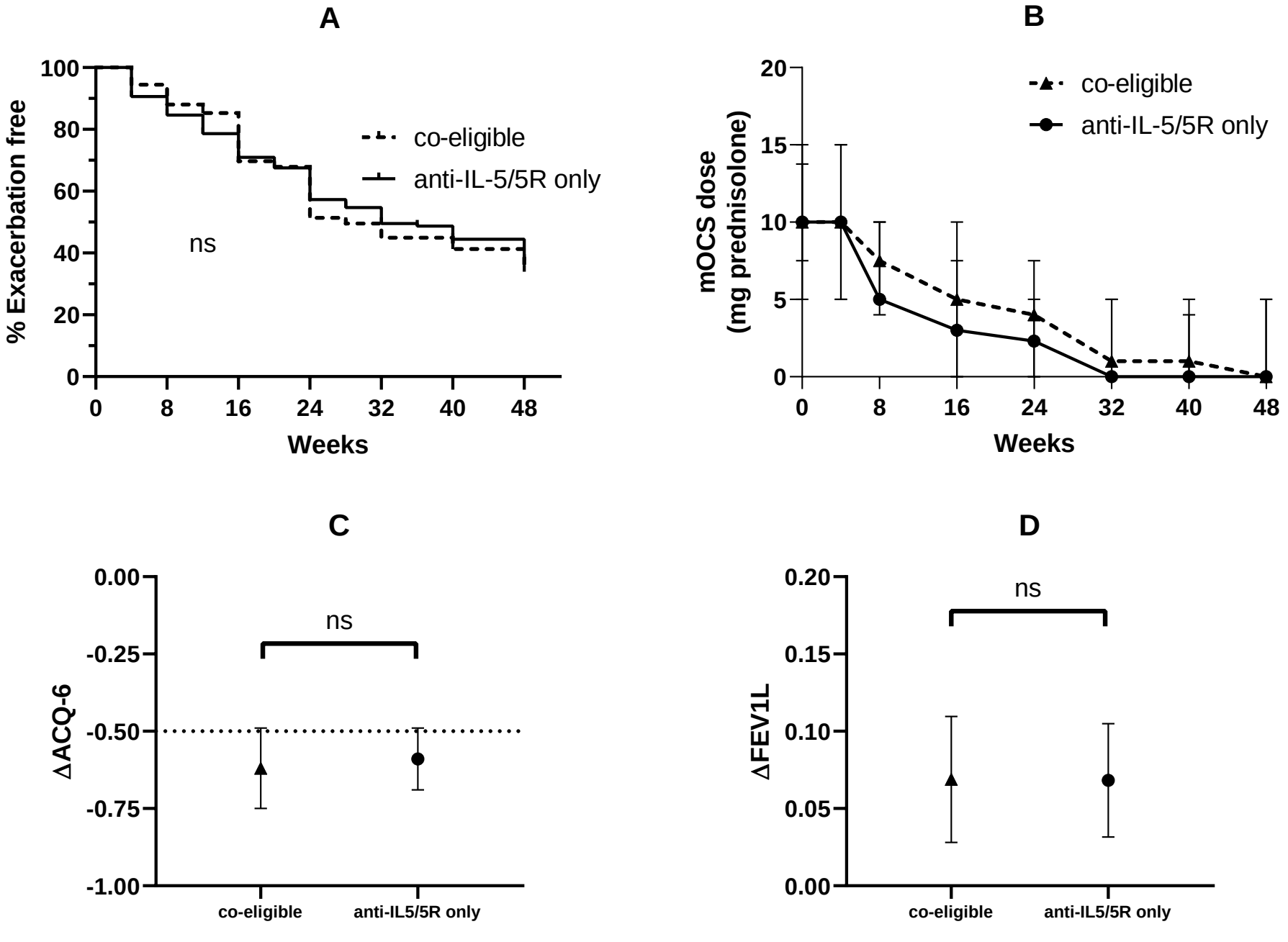
Figure 1.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