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Incidence of adverse events prompting switching between biologics among adults with asthma: A retrospective cohort study

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To the Editor,

Six monoclonal antibodies (“biologics”) are currently approved for the treatment of asthma in the US.¹ While these biologics demonstrated favorable safety profiles in pre-approval

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in relation to this work. Dr. Alexander is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, for whom he has served as a paid expert witness; and is a past member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict-of-interest policies.

trials, these trials had relatively short follow up periods. We sought to evaluate the patterns of switching between biologics as a measure of safety. Additionally, we identified patient characteristics predicting an AE-related switch.

We used electronic health record data from a large health system in the US. We included individuals with asthma aged ≥ 18 years who initiated omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab between November 2005 and August 2021. Tezepelumab was not included as this was approved in December 2021. We identified patients who switched to another biologic and conducted chart reviews to identify the reason for each switch (Section E1.1). Switches were classified as adverse event (AE)-related, for switches due to any unwanted medical event, effectiveness-related, payment-related, and other. For switches due to multiple reasons, we sought to identify the main reason for discontinuation such as using the reason cited on the specific date of the switch.

We evaluated: (1) the odds of switching vs not switching, (2) the cumulative incidence of switches and AE-related switches; and (3) the predictors of AE-related switches. Covariates included age, sex, race, body mass index, allergic comorbidities (allergic rhinitis, atopic dermatitis, chronic rhinosinusitis with nasal polyposis), Charlson Comorbidity Index, smoking status, serum IgE level, peripheral eosinophil count, pre-index exacerbation rate, days of follow up, and the initial biologic. In sensitivity analyses, we evaluated the patterns of switching in individuals who were eligible for two or more biologics.

We included 1,032 individuals who accounted for a total of 1052 initiations of a biologic: 638 patients initiated omalizumab (61.8%), 235 (22.8%) dupilumab, 159 (15.4%) mepolizumab, 17 (1%) benralizumab, and 3 (0.3%) reslizumab. (Table E1). Eleven percent (116/1032) switched therapy during a median follow-up of 42.5 months (interquartile range, 18.7-58.8). These 116 individuals accounted for 143 switches over 28661 person-months (5.0 switches per 1000 person-months). This was 73 (11.3%) of omalizumab-initiators, 45 (28.3%) of mepolizumab-initiators, and 12 (5.1%) of dupilumab-initiators. Ten of the 17 who initiated benralizumab and all 3 who initiated reslizumab switched therapy. Eighty-three percent of these individuals switched once; no one switched more than twice.

Sixteen percent (23) of these switches were for AE-related events, 54.5% (78) for effectiveness-related reasons, 16.1% (23) due to comorbidity to be treated by alternate biologic therapy, 4.9% (7) for convenience, 3.5% (5) for insurance-related reasons, and 4.9% (7) for other reasons (Figure 1). None of the AEs led to hospitalization or death. These patterns were similar in patients who met eligibility for ≥ 2 biologics (Section E1.2; Figure E1). The median time to discontinuation for safety-related events was 8.3 months [95% confidence interval [CI] 2.1-26.7] and 17.8 months [6.7-38.2] for all other reasons (Figure 2). Females accounted for 92% of AE-related switches. In adjusted analyses, female sex (aOR, 3.7, 1.3-7.7) and younger age (1.06, 1.02-1.12) were associated with a higher odds of switching due to adverse events (Table E2). Compared to dupilumab, patients with omalizumab had a lower cumulative incidence of switching for safety reasons (aHR 0.04, 0.01-0.18).

These results should be interpreted with caution. Our sample size was low and despite our best efforts to mitigate confounding, there may be residual bias. Furthermore, although all these biologics are approved for the type-2 phenotype, patients still differed on key baseline characteristics which might affect switching patterns. This single health system study suggests that few individuals with asthma switched biologics due to adverse events. One in 9 individuals switched therapy and 1 in 6 switches were due to adverse events. Our findings are consistent with the reported proportion of switches (10.8%) from the International Severe Asthma Registry,² and the proportion of AE-related switches is consistent with the proportion of participants, 0.5-5%, who discontinued therapy due to adverse events in the randomized trials for these products.^{3,4} Safety-related switches tended to occur sooner than switches for other reasons. Females were more likely to switch for safety reasons. This may be due to multiple factors including physiologic and behavioral reasons.^{5,6} Given that women are more likely to have uncontrolled asthma, additional research into the possible mechanisms for heterogeneity of treatment effect by sex is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AA, GCA, and SS conceptualized the study. All authors were involved in the development of the appropriate methods for this research. AA and GZ conducted the data analyses. AA drafted the initial draft of this article. All authors were involved in the editing of the initial and subsequent drafts and approve this version.

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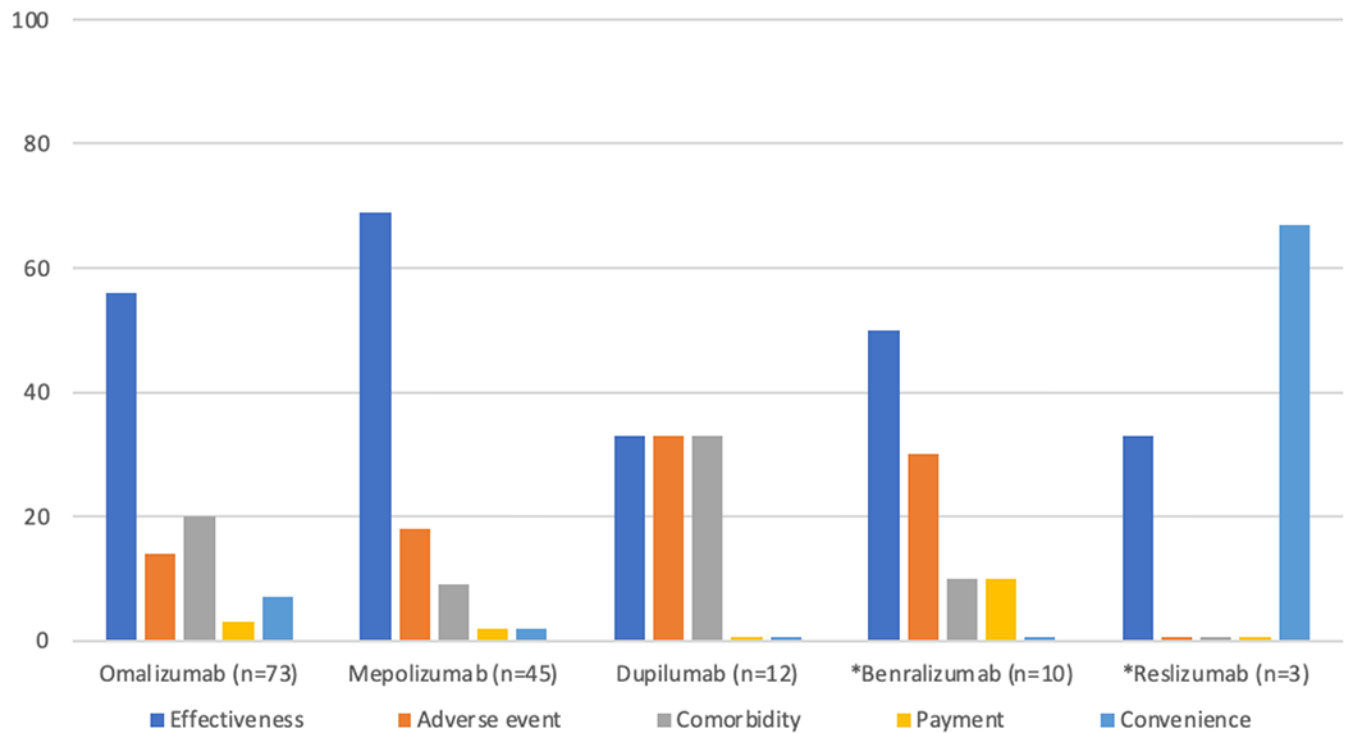


Figure 1:

Reasons for discontinuations with subsequent switch to another biologic.

*Data for benralizumab and reslizumab shown for completeness.

Adverse events documented: Omalizumab- Hives/pruritus (5), anaphylaxis (3), paresthesia (1), constellation of symptoms provider considered not directly related to omalizumab use (1); Mepolizumab- Headache (2), hives/pruritus (2), anaphylaxis-like reaction (1), fatigue (1), constellation of symptoms provider considered not directly related to mepolizumab use (1); Dupilumab- Arthralgia/myalgia (3), hives/pruritus (2), eosinophilia (1); Benralizumab- Headache (1), serum sickness like reaction (1), paresthesia (1); Reslizumab- None of the 3 switches were for safety events).

Comorbidities prompting switch: Omalizumab- atopic dermatitis (10), chronic rhinosinusitis with nasal polyposis (CRSwNP) (4), eosinophilic esophagitis (1); Mepolizumab- CRSwNP (3), atopic dermatitis (1); Dupilumab- chronic spontaneous urticaria (2), idiopathic anaphylaxis/mast cell activation syndrome (1), CRSwNP (1); Benralizumab- CRSwNP (2).

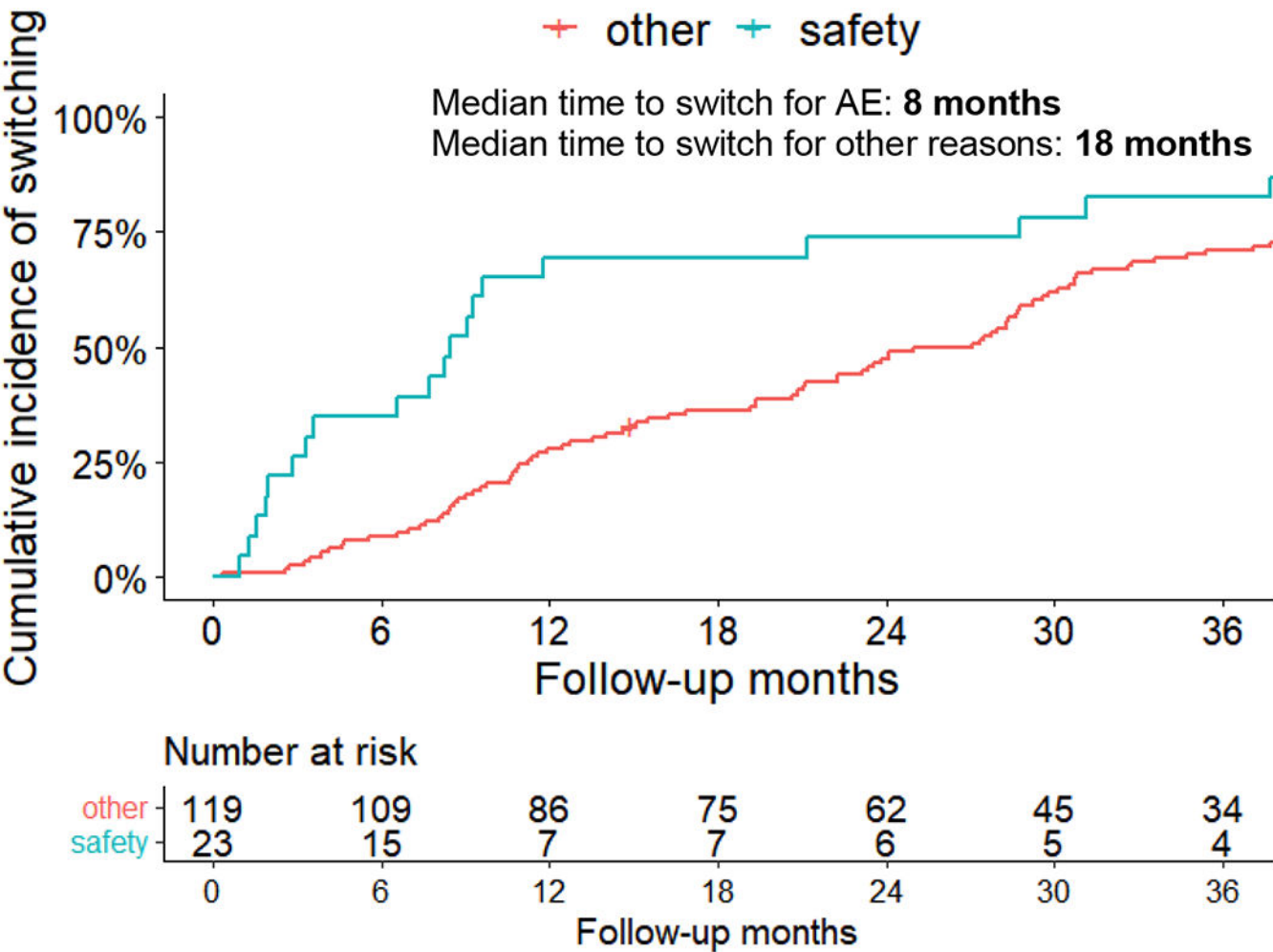


Figure 2:
Time to discontinuation and switch to another biologic for safety reasons compared to time to switch for other reasons.