Journal of Asthma and Allergy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

SHORT REPORT

Reduced Effectiveness of Anti-IgE Treatment Among Adults with Severe Asthma with Older Age of Asthma Onset: Results from the CHRONICLE Study

Dennis K Ledford[1], Warner W Carr[2], Wendy C Moore[3], Njira L Lugogo[4], Arjun Mohan[4], Bradley Chipps[5], Alexander R Mackie[6], Andrew W Lindsley[7], Joseph Spahn[6], Christopher S Ambrose[8]

[1]Division of Allergy and Immunology, University of South Florida, Tampa, FL, USA; [2]Allergy & Asthma Associates of Southern California, Mission Viejo, CA, USA; [3]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA; [4]Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, MI, USA; [5]Capital Allergy & Respiratory Disease Center, Sacramento, CA, USA; [6]BioPharmaceuticals Medical, AstraZeneca, Wilmington, DE, USA; [7]US Medical Affairs, Amgen, Thousand Oaks, CA, USA; [8]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA

Correspondence: Christopher S Ambrose, AstraZeneca, One MedImmune Way, Gaithersburg, MD, 20878, USA, Tel +1 301-398-4454, Email chris.ambrose@astrazeneca.com

Purpose: Younger age of asthma onset (AAO) has been associated with an allergic phenotype, whereas eosinophilic phenotypes have been associated with older AAO. In randomized trials, biologic efficacy among adults with severe asthma (SA) has varied by age at asthma onset. To determine whether these associations observed in trials apply to real-world outcomes, this study examined biologic effectiveness by AAO and biologic class in a large, real-world cohort.

Patients and methods: CHRONICLE is an ongoing, real-world study of US adults with subspecialist-treated SA receiving biologics, maintenance corticosteroids, or who are uncontrolled on high-dosage inhaled corticosteroids with additional controllers. Patients enrolled between February 2018 and February 2022 who initiated a biologic for SA and had complete data for analysis were included. A locally estimated scatterplot smoothing (LOESS) analysis was used to plot the relationship between percentage exacerbation rate reduction and AAO by biologic class.

Results: Of 578 patients with complete data, 198, 149, and 231 were diagnosed with asthma at age <18, 18–39, and ≥40 years, respectively. Across subgroups, patients were predominantly White (72–78%), female (67–73%), and commercially insured (54–71%). In the LOESS analysis, exacerbation rate reductions were similar for anti-IgE and anti–IL-5/5R and anti–IL-4R subgroups with younger AAO, but the exacerbation rate reduction diminished for patients with older AAO receiving anti-IgE therapy, particularly with asthma onset age ≥40 years.

Conclusion: Clinicians should consider age of onset in biologic treatment decisions, given reduced effectiveness of omalizumab in patients with asthma onset at age ≥40 years.

Clinicaltrials.gov Identifier: NCT03373045.

Keywords: Biologics, severe asthma, anti-interleukin therapy, anti-immunoglobulin E therapy, effectiveness, age of asthma onset

Introduction

Severe asthma (SA) affects 5%–10% of patients with asthma and is heterogeneous. In multiple studies, childhood-onset asthma has been associated with allergic inflammation, whereas adult-onset asthma has been associated with eosinophilic inflammation.[1–5] In randomized, placebo-controlled trials (RCTs) of biologics for SA treatment, exacerbation reduction magnitude varied by age of asthma onset (AAO). Anti-immunoglobulin E (IgE) therapy (approved for allergic asthma) demonstrated a trend of reduced efficacy with AAO >40 years,[6] whereas biologics approved for eosinophilic asthma

Received: 8 May 2024
Accepted: 25 September 2024
Published: 9 October 2024

(anti–interleukin [IL]-5/5 receptor [R] and anti–IL-4R) demonstrated reduced efficacy with AAO <18 years (Supplemental Table 1).[7–10] However, these differences among RCT subgroups are small and could be due to unidentified variables, limited sample size, or chance. To determine whether these efficacy trends are present in real-world outcomes, we examined exacerbation rate reductions with biologic initiation by AAO and biologic class in a large, real-world study cohort of adults with specialist-treated SA.

Methods

CHRONICLE is an ongoing, real-world, observational study of US adults with subspecialist-treated SA who are receiving biologics approved by the US Food and Drug Administration for SA, systemic corticosteroids or other systemic immunosuppressants for ≥50% of the prior 12 months, or are persistently uncontrolled (per European Respiratory Society and American Thoracic Society guidelines) while treated with high-dosage ICS with additional controllers.[11] Included patients are aged ≥18 years at enrollment, treated by pulmonologists or allergist-immunologists, and diagnosed with SA ≥12 months before enrollment; written informed consent for participation and acquisition of medical records was obtained at enrollment.[11] The CHRONICLE study protocol received central institutional review board approval by Advarra (Columbia, MD) on November 3, 2017, and was registered on ClinicalTrials.gov on December 14, 2017 (ClinicalTrials.gov: NCT03373045). The CHRONICLE study is conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guidelines, and applicable regulatory requirements.

This analysis evaluated patients enrolled between February 2018 and February 2022 who initiated a biologic and had complete data for 6 months before and after biologic initiation for estimating annualized exacerbation rates. Exacerbations were events requiring ≥3 days of oral corticosteroids (OCS) or a temporary increase in OCS dose for those receiving maintenance OCS, ≥1 corticosteroid injection, or inpatient hospital admission lasting ≥24 hours. Study sites report all exacerbations for 12 months before enrollment and every 6 months thereafter. Patients were required to have no biologic use during the pre-initiation period and complete data for the pre- and post-initiation periods to enable a self-controlled cohort analysis of exacerbation reduction with biologic initiation.

A locally estimated scatterplot smoothing (LOESS) analysis was conducted to plot the relationship between percentage reduction in exacerbation rate and AAO for each biologic class. In this analysis, the percentage reduction in exacerbation rate is only calculable for patients who had at least 1 exacerbation during the 6 months prior to biologic initiation. LOESS regression is a nonparametric method that generates a smooth curve through data in a scatterplot using local weighted regression. LOESS was used to fit a curve to a scatterplot of percentage exacerbation rate reduction by AAO. Two biologic classes (ie, anti-IgE and anti–IL-5/5R/4R) were selected a priori at CHRONICLE study start as the primary biologic classes of interest based on biologic usage at the time. To account for changes in the usage of biologics since that time, a sensitivity analysis was conducted with 3 biologic classes: anti-IgE, anti–IL-5/5R, and anti–IL-4R. Additionally, to support the primary LOESS analysis, annualized patient exacerbation rates were calculated and compared by AAO category (<18, 18–39, ≥40 years) for the pre- and post-initiation periods for each biologic class (ie, anti-IgE and anti–IL-5/5R/4R).

Results

Among 578 patients with complete data, 198 were diagnosed with asthma at age <18 years, 149 were diagnosed at 18–39 years, and 231 were diagnosed at ≥40 years. Across AAO subgroups, patients were predominantly White (73%–78%), female (67%–73%), and commercially insured (54%–71%) (Table 1). Pre-initiation, a slightly smaller proportion of patients treated with anti–IL-5/5R/4R versus anti-IgE had allergic rhinitis, whereas overall more had rhinosinusitis, nasal polyps, and higher blood eosinophil counts (Supplemental Table 2).

Across subgroups, exacerbation rates were reduced following biologic initiation. LOESS plot curves showed similar rate reductions between anti-IgE and anti–IL-5/5R/4R subgroups at younger AAO. However, the anti-IgE exacerbation reduction diminished (effectiveness decreased) steadily with increasing AAO, particularly with AAO ≥40 years (Figure 1). The sensitivity analysis showed similar rate reductions for anti–IL-5/5R and anti–IL-4R biologics across AAO groups (Supplemental Figure 1).

Table 1 Characteristics of Patients at Enrollment by Age of Asthma Onset

Characteristics	Age of Asthma Onset		
	<18 years (n = 198)	18–39 years (n = 149)	≥40 years (n = 231)
Age at enrollment, median (IQR)	48.0 (38.0, 60.5)	47.0 (38.0, 58.0)	61.0 (54.0, 68.0)
Age at diagnosis, median (IQR)	6.0 (3.0, 11.0)	28.0 (24.0, 35.0)	50.0 (45.0, 59.0)
Female, %	67.2	72.5	67.1
Race, %			
White	78.3	72.5	74.9
Black	16.2	20.1	17.3
Other[a]	5.1	4.1	4.3
Not reported	0.5	3.4	3.5
Hispanic or Latino ethnicity, %	4.0	11.4	7.4
Insurance, %			
Commercial	66.2	70.5	54.1
Medicaid	13.1	10.7	8.7
Medicare	18.2	14.1	30.3
Uninsured	1.0	0	0.4
Other[b]	1.5	4.0	6.5
Missing	0	0.7	0
Comorbidities, %			
Allergic rhinitis	62.1	55.7	64.1
Gastro-esophageal reflux disease	34.3	38.9	42.9
Sleep apnea	18.7	22.8	26.4
Anxiety	19.7	14.1	14.7
Depression	18.2	17.4	16.0
Rhinosinusitis	9.6	16.8	17.7
Chronic obstructive pulmonary disease	10.1	8.7	13.4
Nasal polyps	7.1	10.7	5.2
Highest blood eosinophil count while not on biologics or mSCS (cells/mcL)			
Patients with available data, n	123	104	155
<150, %	25.2	26.9	27.1
≥150 and <300, %	22.8	18.3	18.7
≥300 and <450, %	22.8	23.1	16.8
≥450, %	29.3	31.7	37.4
Highest IgE while not on biologics or mSCS (IU/mL)			
Patients with available data, n	87	69	110
<150, %	46.0	47.8	52.7
≥150 and <400, %	27.6	29.0	29.1
≥400, %	26.4	23.2	18.2

Notes: [a]"Other" includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander; [b]"Other" includes other government insurance.

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; mSCS, maintenance systemic corticosteroids.

In the secondary descriptive analyses of exacerbation reductions by AAO category and biologic class, overall patients treated with anti-IgE and anti–IL-5/5R/4R biologics had 48% and 55% fewer exacerbations, respectively. Exacerbation reductions were similar for anti-IgE and anti–IL-5/5R/4R in patients with AAO <18 years (52% and 45%, respectively) and 18–39 years (64% and 55%, respectively). However, among patients with AAO ≥40 years, annualized exacerbation rate reductions were 61% for anti–IL-5/5R/4R versus 25% (P=NS) for anti-IgE (Supplemental Figure 2).

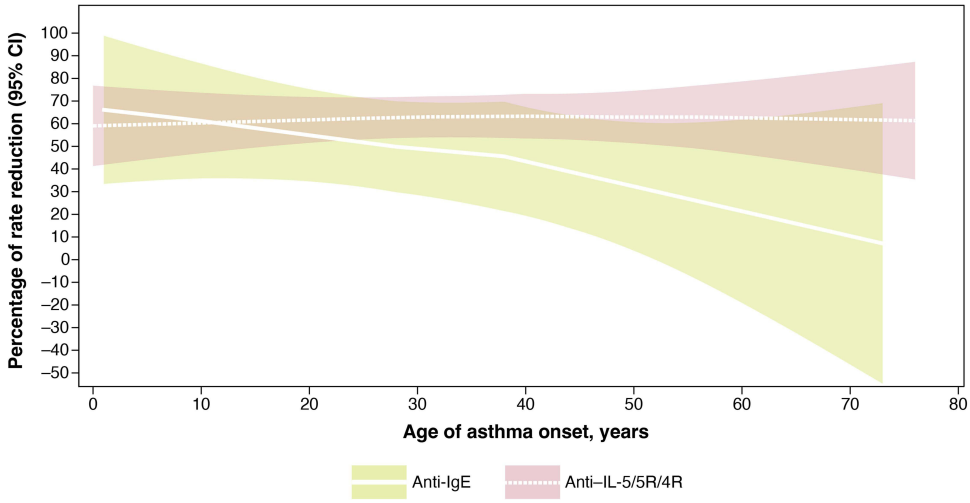

Figure 1 Exacerbation rate reductions 6 months pre- and post-initiation of anti-IgE and anti–IL-5/5R/4R biologics by age of asthma onset The percentages of rate reduction were calculated only among patients with ≥1 exacerbation 6 months pre-biologic initiation (anti-IgE: n = 64; anti–IL-5/5R/4R: n = 198).
Abbreviations: CI, confidence interval; IgE, immunoglobulin E; IL, interleukin; R, receptor.

Discussion

To our knowledge, the observation of differential biologic outcomes by biologic class and AAO is novel in the real-world setting. These results align with post hoc analyses of clinical trials that suggest differential efficacy based on AAO and mechanism of biologic therapy (ie, anti-IgE vs anti–IL-5/5R/4R).[6–10] The overall reductions in exacerbations after biologic initiation support the effectiveness of biologics for SA in general and align with previous real-world analyses.[12,13] The diminished exacerbation rate reduction with anti-IgE use in patients with adult-onset asthma, which was most dramatic with AAO ≥40 years, aligns with the trend observed in RCTs of omalizumab and raises the question of whether these patients may be better treated with other biologics. Anti-IgE treatment may have reduced effectiveness with adult-onset asthma because adult-onset asthma is less likely to be driven by allergy and IgE.[3–5] It is possible that the smaller sample size and lower pre-initiation exacerbation incidence for anti-IgE therapy recipients with AAO ≥40 years might have impacted the observed results; however, a major impact seems unlikely as both the sample size and pre-treatment exacerbation incidence were comparable to those in the anti-IgE cohort with AAO <18 years, in which robust effectiveness was demonstrated.

Despite consistent trends in RCTs of anti–IL-5/5R/4R biologics demonstrating diminished exacerbation reductions (reduced efficacy) in individuals with AAO <18 years compared with AAO ≥18 years, a meaningful decrease in effectiveness with younger AAO was not observed in the current analysis. This difference may be due to patient selection by subspecialists, as anti–IL-5/5R/4R recipients were a more highly eosinophilic subset of patients with childhood-onset disease, which should lead to improved real-world outcomes with anti–IL-5/5R/4R use. Additionally, given the historical order of biologic approval, anti–IL-5/5R/4R recipients may have been enriched for those with insufficient previous response to anti-IgE.

Differences in patient characteristics by biologic class highlight an important strength as well as limitation of this analysis of patient outcomes with biologics as prescribed by US specialists. Our patient–self-controlled analyses of exacerbation reductions accurately describe the patient experience within each biologic class but cannot describe what outcomes would occur if patients who received one biologic class were instead treated with the alternative class. However, RCT results suggest improved outcomes with anti–IL-5/5R/4R biologics versus anti-IgE therapy for adults with SA and AAO ≥40 years.[6–10]

Strengths of this study include the large real-world sample of patients with SA and the novelty of results stratified by AAO. General limitations of the CHRONICLE study have been previously described and include inherent limitations of any real-world descriptive study, differences in clinical practice across study sites, and lack of probabilistic site selection.[11] CHRONICLE is limited to US adults with SA receiving subspecialist care and may not be completely generalizable to the broader SA population in the US or globally.[11] Follow-up time for capturing exacerbations was limited to 6 months before and after biologic initiation due to the available sample, as many fewer patients had complete data for 12 months before and

after biologic initiation. Previous analyses have demonstrated similar results when using 6 months or 12 months before and after biologic initiation.[14,15] Further analyses with follow-up duration of ≥12 months would be ideal to characterize long-term exacerbation risk. The analysis cannot rule out that the observed differences by AAO are due to other factors; however, this appears less likely given the comparable findings in RCTs and the well-established age association with the allergic asthma phenotype. This analysis did not examine outcomes by specific biologics within the anti–IL-5/5R class due to concerns regarding sample size for individual biologics, and because RCTs have demonstrated similar effects of AAO on efficacy for each of these biologics.[8–10] The ongoing CHRONICLE study may provide real-world insight into these concerns and outcomes for anti-thymic stromal lymphopoietin therapy in future analyses.

Conclusions

In conclusion, our analysis of this large real-world cohort of US adults with SA showed that exacerbation reductions with biologic use varied by patient AAO and by biologic class. Although exacerbation rate reductions were similar across biologic classes at younger AAO, the anti-IgE exacerbation reduction was diminished among those with AAO ≥40 years, a finding consistent with RCT results. Clinicians should consider AAO in biologic treatment decisions, particularly with use of anti-IgE in patients with AAO ≥40 years.

Abbreviations

AAO, age of asthma onset; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; IQR; interquartile range; LOESS, locally estimated scatterplot smoothing; mSCS, maintenance systemic corticosteroid; OCS, oral corticosteroid; RCT, randomized, placebo-controlled trial; SA, severe asthma.

Data Sharing Statement

CHRONICLE is an ongoing study; individual de-identified participant data cannot be shared until the study concludes. The full study protocol is available upon request of the corresponding author. Individuals who were or were not involved in the study may submit publication proposals to the study's Publication Steering Committee by contacting the corresponding author.

Ethics Approval and Informed Consent

The CHRONICLE study protocol received central institutional review board (Advarra, Columbia, MD) approval on November 3, 2017, and was registered on ClinicalTrials.gov on December 14, 2017 (NCT03373045). A signed informed consent form is obtained at enrollment for study participation and to acquire medical records from other providers, including pharmacy records.

Acknowledgments

The authors wish to thank Wenjiong Zhou, PhD, of ClinChoice, Inc. (Fort Washington, PA, USA), for data analysis support. Medical writing support was provided by Karen Kurtyka, MPH, and Priyanka D Pinky, PhD, of Oxford PharmaGenesis (Newtown, PA, USA), which was in accordance with Good Publication Practice (GPP 2022) guidelines and funded by AstraZeneca (Wilmington, DE, USA).

Portions of this paper were presented at the American College of Allergy, Asthma & Immunology Annual Scientific Meeting, November 9–13, 2023 in Anaheim, CA as a poster presentation with interim findings. The poster's abstract was published in *Annals of Allergy, Asthma & Immunology*: https://doi.org/10.1016/j.anai.2023.08.148.

Funding

This work was supported by AstraZeneca, and the CHRONICLE study is funded by the same.

Disclosure

DKL: Consultant and speaker – AstraZeneca, Genentech/Roche, GlaxoSmithKline, Novartis, and Sanofi/Regeneron; Grant support – AstraZeneca. Royalties – Taylor and Francis and Wolters Kluwer Health; Contributing editor to Ask the

Expert - American Academy of Allergy, Asthma & Immunology. **WWC**: Speaker – AstraZeneca, Boehringer Ingelheim, Regeneron, Sanofi, and Teva; Consultant – Aerocrine, Alcon Laboratories, AstraZeneca, Baxalta, Boehringer Ingelheim, Circassia, CSL Behring, Genentech, GlaxoSmithKline, Greer Laboratories, Grifols, Horizon Pharma, Kaleo, Meda, Mylan, Novartis, Optinose, Pfizer, Regeneron, Sanofi, Shire, Teva, and Valeant Pharmaceuticals. **WCM**: Advisory boards and grant support – Areteia Therapeutics; AstraZeneca; Genentech; GlaxoSmithKline; National Heart, Lung, and Blood Institute; Sanofi Regeneron; and Teva, and GlaxoSmithKline. **NLL**: Advisory board and consultant – Amgen, AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron, Sanofi, and Teva; Grant support – Amgen, AstraZeneca, Avillion Life Sciences, Gossamer Bio, Genentech, GlaxoSmithKline, Janssen, Regeneron, Sanofi, and Teva. **AM**: Personal fees from Verona Pharma, outside the submitted work. **BC**: Personal fees from AstraZeneca, Regeneron, and Sanofi Genzyme, outside the submitted work. **ARM**: Employee and shareholder – AstraZeneca. **AWL**: Employee and shareholder – Amgen. **JS** and **CSA**: Employees and shareholders – AstraZeneca. The authors report no other conflicts of interest in this work.

References

1. Pakkasela J, Ilmarinen P, Honkamaki J, et al. Age-specific incidence of allergic and non-allergic asthma. *BMC Pulm Med*. 2020;20(1):9. doi:10.1186/s12890-019-1040-2
2. Tan DJ, Walters EH, Perret JL, et al. Age-of-asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. *Expert Rev Respir Med*. 2015;9(1):109–123. doi:10.1586/17476348.2015.1000311
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated July 2023. Accessed 25, Jul 2024. Available from: https://ginasthma.org.
4. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18:716–725. doi:10.1038/nm.2678
5. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010;181:315–323. doi:10.1164/rccm.200906-0896OC
6. Rogers L, Holweg CT, Pazwash H, Ko J, Louie S. Age of asthma onset does not impact the response to omalizumab. *Chron Respir Dis*. 2023;20:14799731231159673. doi:10.1177/14799731231159673
7. Busse WW, Paggiaro P, Munoz X, et al. Impact of baseline patient characteristics on dupilumab efficacy in type 2 asthma. *Eur Respir J*. 2021;58(4):2004605. doi:10.1183/13993003.04605-2020
8. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *Eur Respir J*. 2018;52(4):1800936. doi:10.1183/13993003.00936-2018
9. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulm Pharmacol Ther*. 2017;43:39–45. doi:10.1016/j.pupt.2017.01.011
10. Lemiere C, Taillé C, Lee JK, et al. Impact of baseline clinical asthma characteristics on the response to mepolizumab: a post hoc meta-analysis of two Phase III trials. *Respir Res*. 2021;22(1):184. doi:10.1186/s12931-021-01767-z
11. Ambrose CS, Chipps BE, Moore WC, et al. The CHRONICLE study of US adults with subspecialist-treated severe asthma: objectives, design, and initial results. *Pragmat Obs Res*. 2020;11:77–90. doi:10.2147/POR.S251120
12. Bousquet J, Humbert M, Gibson PG, et al. Real-World Effectiveness of Omalizumab in Severe Allergic Asthma: a Meta-Analysis of Observational Studies. *J Allergy Clin Immunol Pract*. 2021;9(7):2702–2714. doi:10.1016/j.jaip.2021.01.011
13. Charles D, Shanley J, Temple SN, Rattu A, Khaleva E, Roberts G. Real-world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: a systematic review and meta-analysis. *Clin Exp Allergy*. 2022;52(5):616–627. doi:10.1111/cea.14112
14. Panettieri RA Jr, Ledford DK, Chipps BE, et al. Biologic use and outcomes among adults with severe asthma treated by US subspecialists. *Ann Allergy Asthma Immunol*. 2022;129(4):467–474.e3. doi:10.1016/j.anai.2022.06.012
15. Panettieri RA Jr, Lugogo N, Moore WC, et al. Real-world effectiveness of benralizumab in US subspecialist-treated adults with severe asthma: findings from CHRONICLE. *Respir Med*. 2023;216:107285. doi:10.1016/j.rmed.2023.107285