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Incidence of Anti-Drug Antibodies to Monoclonal Antibodies in Asthma: A Systematic Review and Meta-Analysis

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Abstract

BACKGROUND: Antidrug antibodies (ADAs) may worsen the efficacy and safety of biologics. However, little is known about the incidence of ADAs associated with the 6 biologics approved for the treatment of asthma in the United States.

OBJECTIVE: To elucidate the incidence of ADAs and their impact on reported clinical outcomes.

METHODS: Systematic review and meta-analyses of randomized controlled trials, open-label extension studies, and non-randomized studies of biologics in patients with asthma indexed in PubMed, Embase, and CENTRAL between January 1, 2000, and July 9, 2022, were carried out. The primary outcomes were treatment-emergent ADAs (incidence) and ADA prevalence.

RESULTS: A total of 46 studies met the eligibility criteria. ADA incidence over follow-up was 2.91% (95% CI, 1.60–4.55) and was highest in the benralizumab studies (8.35%), with a risk ratio of 4.9 (2.69–8.92) when compared with placebo, and lowest in the omalizumab studies (0.00%). Incidence was 7.61% in the dupilumab studies, 4.39% in reslizumab, 3.63% in mepolizumab, and 1.12% in the tezepelumab studies. Incidence of neutralizing antibodies was 0.00% to 10.74% and was highest for benralizumab (7.12%). Incidence of neutralizing antibodies was higher in the benralizumab every 8 weeks (8.17%) versus every 4 weeks arms (5.81%). Results were consistent in subgroup analyses by study type and length of follow-up.

CONCLUSIONS: Approximately 2.9% of individuals in the included studies developed ADAs over study follow-up period. The incidence was highest in the benralizumab group and lowest in

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the omalizumab group. The subcutaneous route and longer dosing intervals were associated with higher ADA development.

Keywords

Antidrug antibodies; Immunogenicity; Asthma; mAbs; Biologics

INTRODUCTION

The treatment options for moderate to severe asthma have increased significantly over the past 2 decades, now including 6 mAb "biologics." These biologics include omalizumab, which inhibits IgE binding to its high-affinity receptors on mast cells and basophils,[1] mepolizumab and reslizumab, which are anti–eIL-5 agents, and a related biologic, benralizumab, which directly targets the IL-5 receptor,[2] dupilumab, an anti–eIL-4 receptor alpha,[3] and the recently approved tezepelumab, which binds to the upstream cytokine, thymic stromal lymphopoietin, and prevents its binding to its receptor.[4] In randomized trials, all these biologics improved asthma-related outcomes and were relatively safe.[5,6] However, as real-world experience and the numbers of these biologics increase, there continues to be increasing interest in their comparative effectiveness and safety.

Despite this growing interest in the comparative effectiveness and safety of these therapies, little research has been done on their immunogenicity. Biologic therapies are however more likely to be immunogenic than conventional small-molecule drugs, leading to the formation of antidrug antibodies (ADAs), which can impact biologic effectiveness and increase the incidence of adverse events.[7,8] ADAs can occur even to humanized biologics,[9] and can limit biologic effectiveness by directly blocking the action of biologics, as in neutralizing antibodies, and/or increase their clearance via the reticuloendothelial system.[10,11] Furthermore, they can lead to the formation of immune complexes, which may lead to the development of autoimmune conditions.[12–14]

Much of the research on ADAs to date has been from patients with rheumatoid arthritis using TNF inhibitors. These studies have confirmed that ADAs may be associated with lower drug trough levels and worse clinical outcomes.[15] There is however sparse evidence on the immunogenicity of the biologics approved for asthma treatment. In this systematic review and meta-analysis, we aimed to elucidate the incidence of ADAs associated with the use of these biologics, and to evaluate the impact of ADA development on reported clinical outcomes and adverse events.

METHODS

We followed the Preferred Reporting Items of Systematic Reviews and Meta-Analyses recommendations,[16] and registered the planned review *a priori* in the International Prospective Register of Ongoing Systematic Reviews, PROSPERO (ID: CRD42022345347).

Search strategy and study selection

We sought relevant articles indexed in PubMed, Embase, and the Cochrane Central Register of Clinical Trials (CENTRAL) between January 1, 2000, and July 9, 2022.

The terms “Benralizumab,” “Dupilumab,” “Mepolizumab,” “Omalizumab,” “Reslizumab,” and “Tezepelumab” were used in combination with “Asthma,” “Anti-drug antibody,” and “Immunogenicity” as the keywords for literature search (see Table E1 in this article’s Online Repository at www.jaci-inpractice.org). We also sought the reference lists of included articles for eligible articles.

Eligible articles included original peer-reviewed reports of randomized controlled trials (RCTs), open-label extension (OLE) studies, and nonrandomized studies of intervention in which ADA prevalence, incidence, or both were reported. Additional outcomes were the effect modification by ADAs of any efficacy or safety outcomes specified by authors. Articles were screened by 2 independent reviewers (M.L.C. and T.N.) and data extracted independently. Discrepancies were resolved by consensus.

Quality assessment

The authors independently assessed the risk of bias in the included trials using the Cochrane Risk of Bias tool 2.0 for RCTs.[17] We assigned each domain, for example, randomization process, as at low risk of bias, some concerns, or at high risk of bias. For non-randomized trials and observational studies, we used the Risk of Bias In Non-randomized Studies of Interventions.[18] We assigned each domain, for example, missing data, as a low, moderate, serious, critical risk of bias, and no information. We resolved any disagreement through discussion.

Statistical analysis

The primary outcomes were ADA prevalence and treatment-emergent ADAs (TE-ADAs), that is, incidence defined in Table I. These are presented as percentages with associated 95% CI. We subsequently conducted a random-effects meta-analysis pooling the estimates for each biologic. In further analyses, we compared the risk of developing ADA between treatment arms and the placebo arms for RCTs and report results as risk ratio (RR) with 95% CI.

We assessed clinical and methodological heterogeneity by examining participant characteristics, follow-up period, outcomes, and study designs. We then assessed statistical heterogeneity using the I^2 statistic. We conducted a random-effects meta-analysis by the DerSimonian and Laird method,[20] and regarded an I^2 statistic of 0% to 40% as probably unimportant; 30% to 60% moderate heterogeneity; 50% to 90% substantial heterogeneity; and 75% to 100% as considerable heterogeneity.[21] Before pooling, the Freeman-Tukey double arcsine transformation of proportions was used to ensure admissible CIs given its improved estimation of CIs in the presence of 0 events and its more stable estimation of variances.[22–24] The exact method was used for CI computation for pooled estimation of prevalence and incidence. Subgroup analyses, including by study design, drug administration route, drug frequency, frequency of oral corticosteroid (OCS) use, and drug dose, were performed. Sensitivity analyses were performed with exclusion of nonrandomized studies of intervention and OLE studies that had follow-up time longer than the 95% percentile of study follow-up of all included studies.

We assessed publication bias in 2 ways. First, we visually assessed the symmetry of the funnel plot showing each study's effect size plotted against its SE. Second, we used Egger's test to statistically test for asymmetry. Significant asymmetry would indicate the possibility of publication bias or heterogeneity.[25] The meta-analysis was performed using STATA 16.1 (StataCorp, Tex).

RESULTS

Description of search results

We initially identified 1106 records (see Fig E1 in this article's Online Repository at www.jaci-inpractice.org), and 227 duplicated studies were removed. Of the remaining 879 studies, 728 were considered ineligible, and 112 further excluded on the basis of various reasons, with 39 articles left for inclusion. We identified 7 additional studies from ClinicalTrial.gov, which resulted in 46 studies for final review. Three studies were excluded from the meta-analyses: Bel et al[26] because of the reporting of ADA development in the combined intervention and placebo groups, Kavanagh et al,[27] which report ADAs only in nonresponders, and Kornmann et al,[28] which did not report the ADA case numbers. In sensitivity analysis, we excluded studies with greater than or equal to 5% of its study population with history of prior biologics use at baseline: SIROCCO,[29] ZONDA,[30] OSMO,[31] and SOURCE[32] because of the possibility of prior biologics influencing cross-reactive antibodies at baseline. Thus, the total number of studies included in sensitivity analysis was 39. Table E2 in this article's Online Repository at www.jaci-inpractice.org presents the design, baseline characteristics of study population, interventions, and follow-up time of the included studies.

Description of ADA detection method

ADA assessment methodology was reported by 12 publications (13 trials) of the 39 studies (Table E2). The benralizumab studies did not report the ADA detection assay methods. Of the reported assay methods, 4 studies used the electrochemiluminescence immunoassay, which included 1 dupilumab study,[32] and 3 mepolizumab studies.[33–35] As described by Chupp et al,[33] an indirect ligand-binding immunoassay that uses electrochemiluminescence was implemented as the antimepolizumab bridging immunoassay. Pouliquen et al[35] specified the use of Meso Scale Discovery platform. Five studies on omalizumab,[1,36–39] 2 on reslizumab,[40,41] and 1 study on tezepelumab[42] used ELISA as their method of ADA detection. The observed sensitivity of the assays was not reported in any of the studies.

Patient characteristics of included studies

These studies included individuals with moderate to severe asthma. The inclusion criteria of each study's participants were variably defined by baseline treatment and disease severity. The age of included participants ranged from 6 to 82 years (Table E2). Four studies (1 on dupilumab, 2 on mepolizumab, and 1 on omalizumab) were conducted in children aged 6 to 11 years. Most studies included predominantly female participants, and most study participants were White in studies that reported race or ethnicity. From all included populations at study baseline, the mean prebronchodilator FEV_1 ranged from 1.48 to 3.36 L. The mean blood eosinophil count ranged from 242 to 762 cells/mL, and the mean

total IgE level ranged from 179 to 727 IU/mL. About 15% had a history of chronic rhinosinusitis with nasal polyps except in ZONDA, in the oral corticosteroid-sparing study of benralizumab,[30] and in the dupilumab studies, LIBERTY ASTHMA QUEST[42] and LIBERTY VENTURE,[43,44] which had about one-quarter to one-third of participants with a history of chronic rhinosinusitis with nasal polyps at baseline. The median follow-up time was 40 weeks (interquartile range, 24–56).

Results of primary outcomes

Prevalence.—Data from 26 studies (9 benralizumab studies, 5 mepolizumab, 5 tezepelumab, 4 omalizumab, 2 reslizumab, and 1 dupilumab study) with a total of 11,271 participants were analyzed for prevalence. The pooled prevalence of ADA at study baseline across all biologics was 1.59% (95% CI, 0.80–2.61). The prevalence between biologics was significantly different (heterogeneity between groups: $P < .001$) (see Fig E2 in this article's Online Repository at www.jaci-inpractice.org). The pooled prevalence of ADAs at any point during follow-up (including those with baseline preexisting antibodies) was higher in the biologics groups (4.66%; 95% CI, 3.25–6.29) than in the placebo group (2.74%; 95% CI, 1.41–4.42) (see Figures E3 and E4 in this article's Online Repository at www.jaci-inpractice.org). ADA prevalence in the intervention arms over the period of follow-up was highest in the benralizumab group (12.03%; 95% CI, 9.97–14.25) (Fig E3) followed by 6.92% (95% CI, 4.22–10.19) in the reslizumab group, 5.70% (95% CI, 2.53–10.00) in the dupilumab group, 4.08% (95% CI, 1.98–6.80) in the mepolizumab group, and 3.71% (95% CI, 2.68–4.88) in the tezepelumab group, and was the lowest in the omalizumab group (0.00; 95% CI, 0.00–0.12).

Incidence.—A total of 31 studies (9 benralizumab studies, 6 mepolizumab, 6 tezepelumab, 7 omalizumab, 2 reslizumab, and 1 dupilumab study) with a total of 12,379 participants were included. During the treatment period, the overall incidence of TE-ADAs in all biologics groups was 2.91% (95% CI, 1.60–4.55) and 1.00% (95% CI, 0.12–2.41) in the placebo groups (Fig 1; see Fig E5 in this article's Online Repository at www.jaci-inpractice.org). The incidence of TE-ADAs between biologics was significantly different ($P < .001$). ADA incidence was highest in the benralizumab groups (8.35%; 95% CI, 5.60–11.57), followed by dupilumab groups (7.61%; 95% CI, 6.51–8.84), reslizumab groups (4.39%; 95% CI, 2.88–6.20), mepolizumab groups (3.63%; 95% CI, 0.39–9.15), and tezepelumab groups (1.12%; 95% CI, 0.11–2.77), and was the lowest in omalizumab groups (0.00%; 95% CI, 0.00–0.15). A total of 18 studies with 9654 participants with neutralizing antibody (Nab) data available were analyzed for NAb incidence. Development of NAbs was mostly seen in benralizumab groups, with an incidence of 7.12% (95% CI, 4.05–10.94) (Fig 2). Across all biologics, the overall pooled incidence of NAbs from studies in which this was reported was 1.16% (95% CI, 0.05–3.23) in the intervention arms and 0.55% (95% CI, 0.01–1.57) in the placebo arms (see Fig E6 in this article's Online Repository at www.jaci-inpractice.org).

RRs comparing intervention arms versus placebo arms

Only 9 studies with 4847 individuals (4 benralizumab studies and 4 tezepelumab studies) presented data on development of TE-ADAs or NAbs for both intervention and placebo

groups. Individuals in the benralizumab arms had approximately a 5-fold statistically significant increase in the risk of TE-ADAs compared with the placebo arms (RR, 4.90; 95% CI, 2.69–8.92) and a 4-fold increase in NAbs (RR, 3.93; 95% CI, 2.27–6.82) (Fig 3, A and B).

Effect modification of biologics efficacy and safety by ADA status

Of the 46 included studies, 13 studies (28%) reported the effect of ADAs on efficacy outcomes, whereas 23 studies (50%) reported safety outcomes related to ADAs. These were mostly reported qualitatively with specific numbers not provided. Most studies reported that there was no meaningful effect of ADAs on efficacy or safety outcomes, by demonstrating that the efficacy and safety profile of ADA-positive patients did not differ from that noted in the ADA-negative patients or the overall population.

ADA status by the biologics dose and interval

We explored possible dose-response relationship by stratifying on dose or drug interval. We excluded the omalizumab studies from this stratified analysis because of very low ADA prevalence and incidence. Among the benralizumab studies, we excluded Nowak et al[45] because of evaluation of a single dose, and stratified the remaining studies on the basis of drug interval into 30 mg every 4 weeks (Q4W) versus 30 mg every 8 weeks (Q8W). We found that ADA incidence in benralizumab studies was slightly higher in the Q8W arms (12.15% in RCTs and 5.16% in OLE studies) than in the Q4W arms (10.77% in RCTs and 4.96% in OLE studies). ADA prevalence (14.20% in Q8W vs 11.62% in Q4W arms; $P = .184$) and NAb incidence (8.17% vs 5.81%; $P = .399$) were also slightly higher in the Q8W arms although not statistically significant. The results were comparable after excluding Bleecker et al[29] (SIROCCO), which had reported more individuals having NAbs (11) than having TE-ADAs (10).

We stratified dupilumab studies into 200 mg every 2 weeks (Q2W) versus 300 mg Q2W and found that the prevalence of ADA in the 300 mg study arms (4.99%) was comparable to that in the 200 mg arms (4.81%). But in dupilumab RCTs, ADA prevalence was significantly higher in the 200 mg group (4.81%; 95% CI, 3.49–6.32) than in Q4W 300 mg group (2.23%; 95% CI, 1.23–3.48; $P = .008$). These studies did not report TE-ADAs.

For mepolizumab, we categorized the doses studied as medium (100 mg subcutaneously [SC] or 125 mg SC or 75 mg intravenously [IV]) or high (250 mg SC or 250 mg IV or 750 mg IV). The incidence of ADA was significantly higher in the medium-dose group (5.17%; 95% CI, 2.91–7.91) than in the high-dose group (0.00%; 95% CI, 0.00–0.82; $P < .001$) although follow-up was also longer in the medium-dose group (median follow-up, 40 weeks; interquartile range, 24–60 weeks) versus the high-dose group (all 20 weeks). Similarly, the ADA prevalence was significantly higher in the medium-dose group (4.35%) than in the high-dose group (0.00%; $P < .001$).

We categorized the reslizumab studies to 0.3 mg/kg IV Q4W group, 3.0 mg/kg IV Q4W group, and 110 mg SC Q4W group. The ADA prevalence was the highest in 0.3 mg/kg IV group (11.54%), followed by the 110-mg SC group (8.49%), and then 3.0 mg/kg IV group (5.77%) ($P = .215$).

We compared tezepelumab studies with low-dose use (70 mg Q4W) to those with medium-dose use (210 mg Q4W or 280 mg Q2W) to those with high-dose use (700 mg IV Q4W). The low-dose group had the highest ADA incidence (3.62%), then the medium-dose group (0.89%), and finally the high-dose group the lowest (0.00%). This pattern was similar for ADA prevalence, which was highest in the low-dose group (4.35%), followed by medium-dose (4.08%) and high-dose (0.00%) groups.

ADA status by the route of administration of biologics

We stratified ADA outcomes by route of administration (SC vs IV). In the mepolizumab studies, the incidence of ADAs was observed mostly in the SC group (6.36%; 95% CI, 4.01–9.15) versus (0.00%; 95% CI, 0.00–0.13) in the IV arms ($P < .001$). The prevalence was also significantly higher in the SC group (5.36%; 95% CI, 3.63–7.37) than in the IV group (0.15%; 95% CI, 0.00–2.76) ($P = .008$). When compared with 75 mg IV only, the 100-mg SC group demonstrated higher ADA incidence (5.8% vs 0.0%) and prevalence (4.92% vs 1.92%).

In the reslizumab studies, we found that the SC group had higher ADA prevalence (8.49%; 95% CI, 5.63–11.85) than the IV group (6.63%; 95% CI, 3.56–10.51) ($P = .422$) though not statistically significant. Similar results were discovered in the tezepelumab studies, in which the ADA incidence was 1.24% (95% CI, 0.15–3.03) in the SC group and 0.00% (95% CI, 0.00–20.59) in the IV group ($P = .949$).

Impact of prior biologic exposure on estimates

After excluding studies composed of more than 5% of population with previous biologic use, the overall ADA incidence decreased from 2.91% to 2.47% (95% CI, 1.16–4.16). The incidence of NAbs also decreased from 1.16% to 0.73% (95% CI, 0.00–2.76). RRs of ADA development decreased from 2.08 to 1.44 (95% CI, 0.22–9.59), but NAb development changed from 3.93 to 5.55 (95% CI, 2.11–14.61) (see Figures E7–E9 in this article's Online Repository at www.jaci-inpractice.org).

Impact of study design on estimates

We evaluated the outcomes in RCTs or OLE studies separately, and further excluded the Korn et al[46] (MELTEMI) study and the Khatri et al[34] (COLUMBA) study because of long follow-up time (4.6 and 5 years, respectively). In general, the results were consistent with the main analysis. Compared with RCTs, OLE studies had a slightly higher baseline prevalence of ADA at 2.91% (95% CI, 0.39–7.47) versus 1.58% (95% CI, 0.88–2.45) and higher ADA prevalence at any time at 6.34% (95% CI, 3.23–10.33) versus 4.75% (95% CI, 3.07–6.74). ADA incidence at 3.42% (95% CI, 1.39–6.21) versus 3.33% (95% CI, 1.34–6.03) and NAb incidence were however comparable between OLE studies (1.14%; 95% CI, 0.00–6.79) and RCTs (1.68%; 95% CI, 0.03–5.07) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Study follow-up time did not appear to modify either ADA prevalence or incidence estimates.

Impact of OCS use on ADA status

We compared ADA incidence and prevalence in the studies that included only OCS-dependent patients to other studies. Four of the included studies included only OCS-dependent patients (see Figures E10–E12 in this article's Online Repository at www.jaci-inpractice.org). Ten studies reported less than 15% of participants on maintenance OCS at baseline, and 7 studies 15% to 30%. No studies reported use between more than 30% but less than 100%. For benralizumab, which had the highest ADA incidence, the ADA rate was lower in ZONDA (7.59%; 3.85%–13.17%) than in studies in which OCS use was reported and was less than 15% (11.25%; 8.35%–14.5%) (Figure E10).

Assessment of risk of bias and publication bias

Most of the RCTs were at low risk of bias for both random sequence generation and allocation concealment. Some concerns arose from measurement of the outcomes. This included studies where ADA was examined in the intervention group only and studies comparing interventions with different routes (outcome assessors may be aware of the intervention received by study participants). We noted that there may be possible high risk of bias from the study by Nowak et al[45] because only 73% completed the study. We deemed all the nonrandomized studies of intervention at moderate risk of bias at the best (see Tables E4 and Table E5 in this article's Online Repository at www.jaci-inpractice.org). Visual inspection of the funnel plots for the primary outcomes demonstrated approximately symmetry (see Figure E13 in this article's Online Repository at www.jaci-inpractice.org). There was no strong evidence of publication bias for the ADA RRs (Egger's test, $P = .245$) or in NAb RRs ($P = .265$).

DISCUSSION

We conducted a systematic review and meta-analysis of studies of biologics approved for the treatment of asthma evaluating the prevalence or incidence of ADAs. We synthesized both quantitative and qualitative information from 46 RCT, OLE, and nonrandomized studies that met the inclusion criteria, of which 43 studies were included in the meta-analysis. The effect of ADAs on efficacy and safety outcomes was extracted for review. We deemed the studies included as low risk of bias in general. We found that the incidence of ADAs (TE-ADAs) is low, occurring in less than 3% of individuals who initiated these therapies. However, patients in the benralizumab studies (8.35%) and in the dupilumab studies (7.61%) had the highest incidence of ADAs, with patients in the omalizumab studies consistently having less than 1% of participants who developed ADAs. However, the benralizumab studies included 2 OLE studies with patients with preexisting ADAs at baseline. To address these limitations, we conducted multiple sensitivity analyses. The results of the sensitivity analyses were consistent with the main analyses. In addition, we found that the subcutaneous route of administration was associated with a higher incidence of ADAs than the intravenous routes, and that longer dosing intervals were associated with a higher incidence of ADAs. Interestingly, despite excluding studies whose study population had more than or equal to 5% with history of prior biologics use at baseline, a certain percentage of individuals, albeit low, was reported as having ADAs even before the initiation of these biologics (across all biologics: 1.5%) and some patients in the placebo groups developed ADAs over the

course of follow-up (0.76%). In the benralizumab-ZONDA study, which had recruited only OCS-dependent patients, ADA incidence was lower than in other benralizumab studies. However, for reslizumab, the reported prevalence was higher in the OCS-dependent study, but the incidence of neutralizing antibodies was low in all studies. There were no reports of effect modification of safety and efficacy by ADA status, although this conclusion was drawn mostly from qualitative reports in the included studies and not from quantitative assessment.

Several systematics review and meta-analyses have demonstrated the clinical effectiveness and acceptable safety profile of biologics in the treatment of asthma.[2,47–54] However, these analyses mostly included randomized trials with relatively short follow-up periods. To date, little information has been presented on the immunogenicity of these biologics and its impact on clinical outcomes. This information could however be helpful as we evaluate the real-world effectiveness and safety of these biologics given that biologics are more likely than small-molecule drugs to trigger an immune response.[8] Although the immunogenicity of biologics has improved significantly over the past decades as biologics have become more humanized, there is ample evidence that ADAs can still develop even to humanized biologics.[9] In studies of patients with rheumatoid arthritis using adalimumab, a fully human TNF-inhibitor, around 31% of patients developed ADAs over the course of therapy.[15] This is higher than the average percentage of patients who develop ADAs on infliximab (17.4%), a chimeric TNF-inhibitor,[15] thus suggesting that humanized biologics can lead to the generation of ADAs.

Our findings are consistent with a previous review that showed that ADA prevalence in patients with asthma was approximately 16% in patients with benralizumab, 5% with reslizumab, 3% with mepolizumab, and 0% with omalizumab.[10] For tezepelumab, surprisingly, we noted a higher incidence of antibodies in the placebo group both at baseline and over the course of follow-up although the incidence was less than 5% in both the intervention and placebo arms. However, this raises questions not only on assay specificity but also on other issues such as batch effects or whether ADAs were evaluated in the intention-to-treat versus per-protocol populations. These are however beyond the scope of this study.

In further analyses, we found that a longer drug interval or a lower dose was associated with a higher incidence of ADA development. In a previous study of risankizumab, an IL-23 inhibitor used in the treatment of psoriasis, patients receiving a higher dose were more likely to develop ADAs but had a lower incidence of NAbs.[55,56] Similarly, in previous studies of patients with psoriasis receiving adalimumab, dose spacing, including lengthening when superior effectiveness is already demonstrated from standard dosing interval, or shortening the interval to improve effectiveness, has been investigated as a way of optimizing therapy.[57–60] These studies and others have shown that lengthening of the dosing interval may increase the risk of ADA development,[61,62] and that once ADAs are formed, dose interval shortening is less likely to lead to improvements in effectiveness.[62,63]

Few of the included studies explicitly evaluated effect modification of efficacy or safety by ADA status. When evaluated,[32,39] there was no clinically significant impact of ADA

on treatment-emergent adverse events or on safety. These findings suggest that ADA development may not be clinically relevant in most patients. However, there was low ADA incidence and prevalence and statistical power to detect any differences may have been low. Furthermore, the relatively short follow-up period of these studies may have failed to capture the development of ADAs in patients who developed ADAs outside the follow-up period. Other factors that may have influenced ADA rates include the characteristics of the study population. The higher ADA incidence in the benralizumab studies may be related to the inclusion of patients with higher peripheral eosinophil counts in the study given prior evidence that higher eosinophil counts may be associated with a higher risk of developing ADAs.[30,64] However, some studies showed comparable blood eosinophil counts between ADA-positive and ADA-negative patients.[65–67] It is also possible that receptor-blockade, such as by benralizumab and dupilumab, may be associated with higher immunogenicity than cytokine blockade, for example, blockade of IL-5 by mepolizumab or reslizumab. However, more research is needed in this area. For effect modification of efficacy, in BORA, an open-label extension trial of 2 benralizumab studies, there was a slight decrease in eosinophil-depleting activity when there were high ADA titers.[68] Another study evaluated ADAs to benralizumab in patients who demonstrated a less than 50% reduction in either exacerbation frequency or daily OCS dose.[27] The presence of ADAs in 28% of these nonresponders offered a potential explanation for their suboptimal drug response given the pooled ADA prevalence of less than 10% in most benralizumab studies.

Our results should be interpreted with caution. First, differences in assay sensitivity, specificity, timing of sample collection, concomitant medications, and underlying comorbidities make direct comparisons of ADA incidence between studies challenging.[7] Second, the assays, especially for the benralizumab studies, may have been overly sensitive given the prevalence of ADAs at baseline and ADA detection in placebo groups. However, we also considered incidence, which evaluates individuals who newly developed ADAs while on treatment. Third, the baseline use of standard-of-care drugs was not well reported; thus, how the differences in baseline asthma severity and permitted concomitant drugs could potentially influence ADA formation was not elucidated. Furthermore, reports of effect modification of safety and efficacy by ADA status and/or intra-subject comparisons on treatment responses before and after ADA development were drawn mostly from qualitative reports, and not from quantitative assessment. Finally, although the formation of ADAs is a component of the immunogenicity of these therapies, additional work is needed in understanding the whole spectrum of their immunogenicity.

In summary, this review and meta-analysis found that less than 3% of individuals enrolled in the trials of the biologics currently approved for asthma treatment developed ADAs over the course of follow-up, and that lower dose, the subcutaneous route, and longer dosing intervals may be associated with higher ADA development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used

ADA	antidrug antibody
IV	intravenous/intravenously
NAb	neutralizing antibody
OCS	oral corticosteroid
OLE	open-label extension
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
RCT	randomized controlled trial
RR	risk ratio
SC	subcutaneous/subcutaneously
TE-ADA	treatment-emergent ADA

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What is already known about this topic?

mAbs are more likely to be immunogenic than small-molecule drugs and can lead to the development of antidrug antibodies (ADAs). ADAs may worsen drug efficacy and safety.

What does this article add to our knowledge?

ADA incidence was about 8% in patients in the benralizumab and dupilumab studies, and less than 5% for other biologics. The subcutaneous route, lower doses, and longer dosing intervals were associated with higher risk of ADA development. Few studies reported ADA's effect on safety and efficacy.

How does this study impact current management guidelines?

Longer dosing intervals, such as imposed by gaps in treatment, and biologics blocking receptors may be associated with a higher risk of ADAs to respiratory biologics.

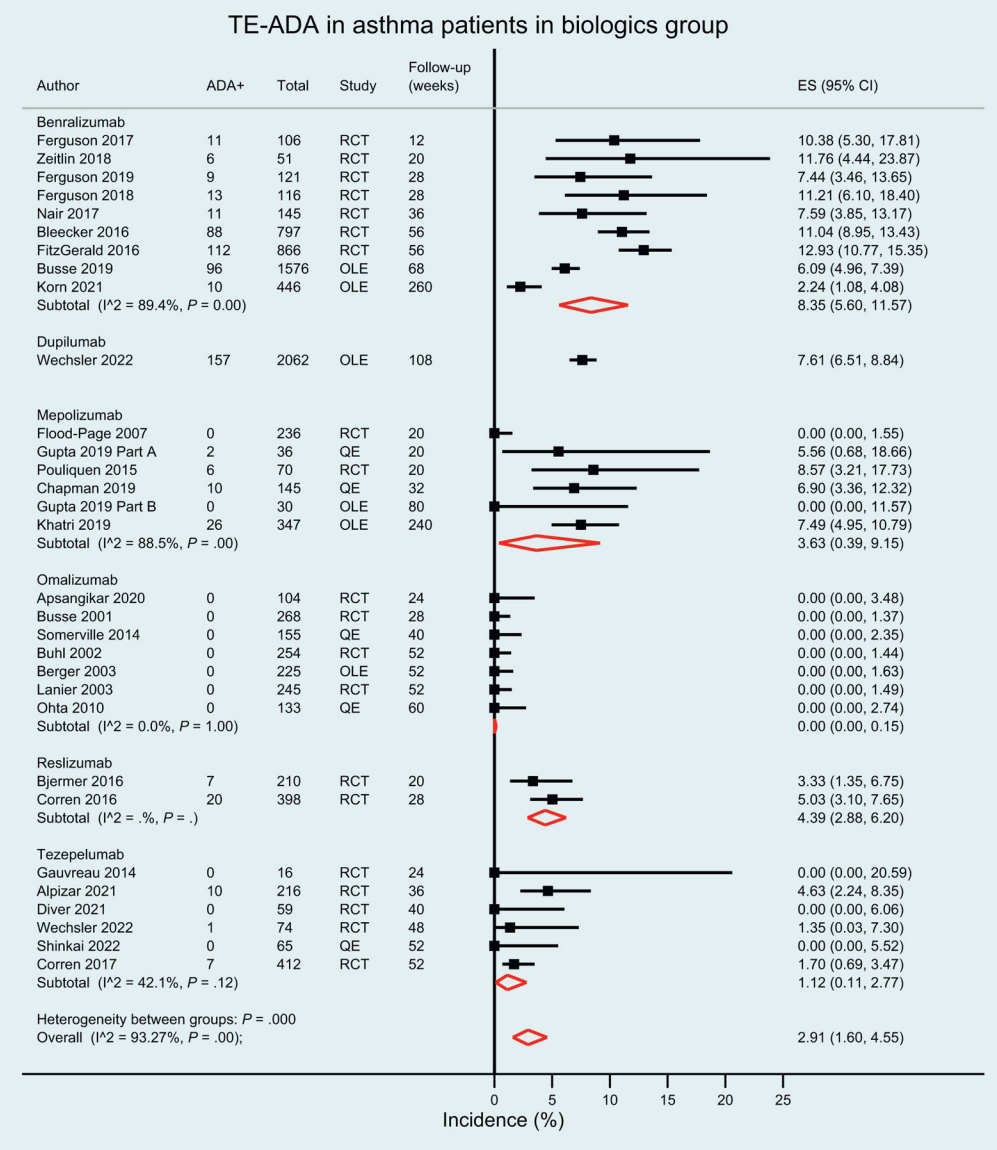

FIGURE 1.

TE-ADAs in patients with asthma in the biologic treatment arms. *Showing results from studies in which this outcome was reported.

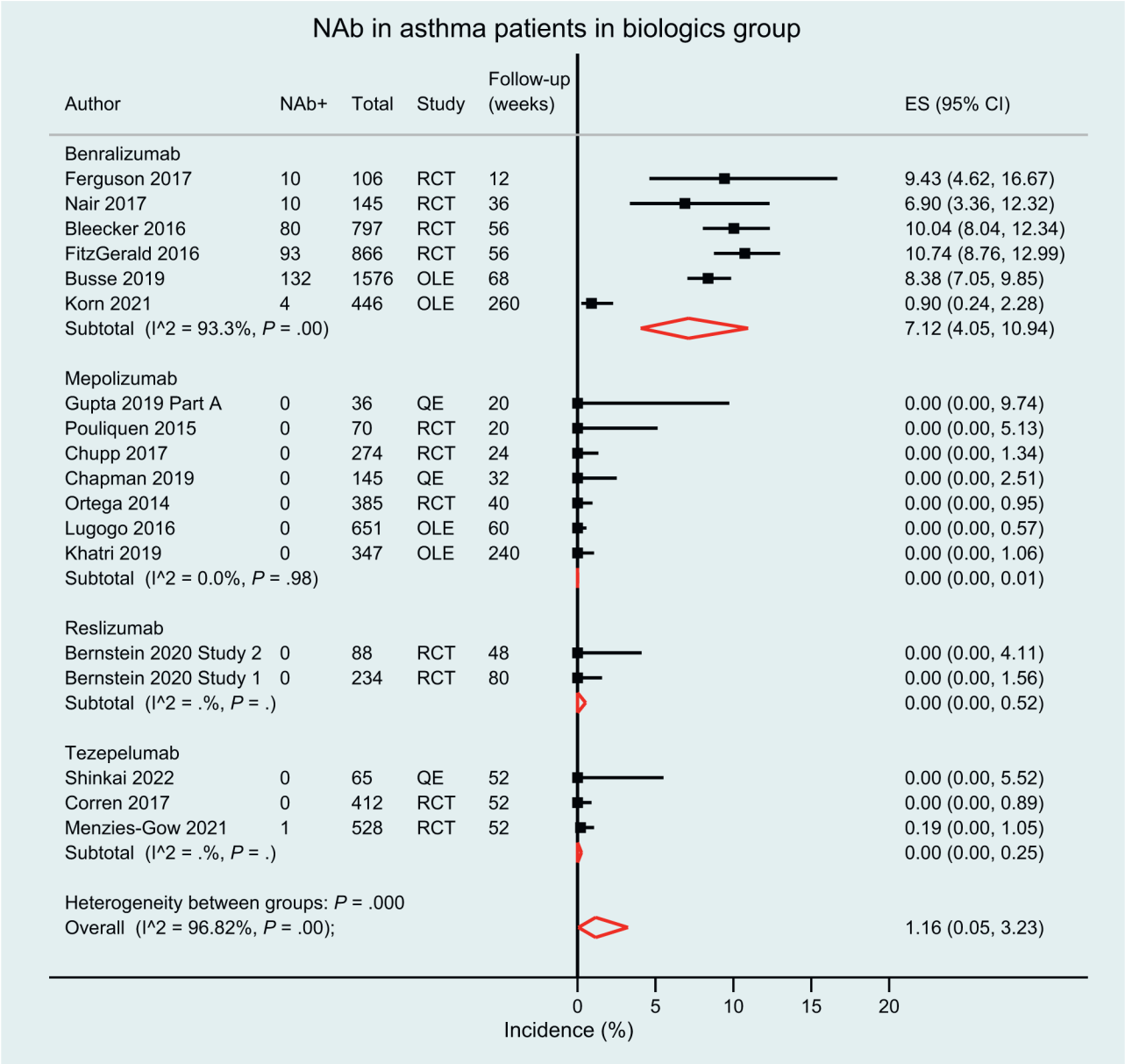

FIGURE 2.

Incidence of NAbs in patients with asthma in the biologic treatment arms. *Showing results from studies in which this outcome was reported.

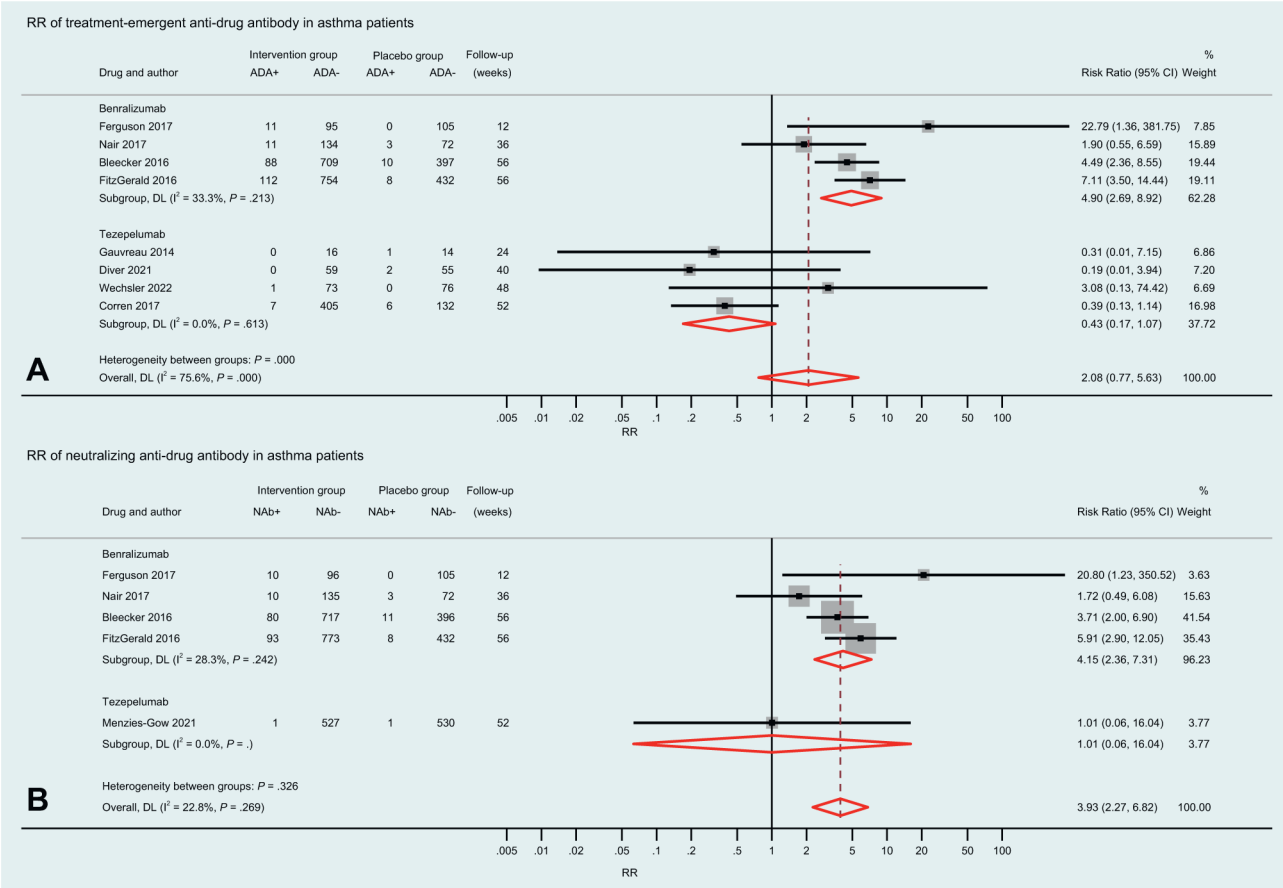

FIGURE 3.

RR of (**A**) TE-ADAs and (**B**) NAbs in the treatment arms vs the placebo arm. *Showing results from studies in which this outcome was reported. Weights and between-subgroup heterogeneity test are from random-effects model (continuity correction applied to studies with 0 cells).

Table I.

Definition of terminology[19]

Definitions for terms applied in the descriptions of immunogenicity in our study are described below:	
ADA	Biologic drug-reactive antibody, including preexisting host antibodies that are cross-reactive with the administered biologic drug (baseline ADA). It comprises neutralizing and nonneutralizing ADAs. Synonyms include antitherapeutic antibody, antiproduct antibody, or antibiologic antibody
NAb	ADA that inhibits or reduces the pharmacological activity of the biologic drug molecule, as determined by an *in vitro* test or animal-based bioassay method as defined by each study, regardless of its clinical relevance
Baseline ADA	We used this term to refer to antibodies reactive with the biologic drug that are present in subjects before treatment, or before initiation of a clinical study, or at the baseline assessment of an OLE study. Analogous to “preexisting ADA”
ADA prevalence	The proportion of all individuals having ADAs (including baseline antibodies) at any point in time throughout the study
TE-ADA	Synonymous with “ADA incidence,” which is the sum of both treatment-induced and treatment-boosted ADA-positive response subjects as a proportion to the total evaluable subject population. Treatment-induced ADA-positive is defined as ADA-negative at baseline and postbaseline ADA-positive. Treatment-boosted ADA-positive is defined as baseline-positive ADA titer that was boosted to a 4-fold or higher-level following treatment

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