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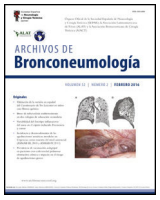

Review Article

Impact of Biologics Administered for Severe Asthma on T2-comorbidities: A Narrative Review

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ABSTRACT

T2-comorbidities including allergic rhinitis, chronic rhinosinusitis with and without nasal polyps, atopic dermatitis, chronic spontaneous urticaria, food allergy, aspirin sensitivity and eosinophilic esophagitis are the most common in severe asthma (SA) patients and have a negative impact on disease outcomes but also an important socio-economic burden. In the era of personalized medicine, treating SA and its comorbidities by one medication is a very exciting possibility for the clinicians. Several biologics used for SA showed benefits on T2-comorbidities but current knowledge regarding the magnitude and consistency of biologics efficacy across these comorbidities as well as the optimal strategies for selecting biologics in multimorbid patients remain limited. In this narrative review, we discuss the available evidence on the efficacy and safety of different biologics currently available as add-on treatment for SA on the most frequent T2-comorbidities, individually or associated, based on randomized controlled trials and real-world studies.

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Abbreviations: AAER, annualized asthma exacerbation rate; Ab, antibody; ACQ, asthma control questionnaire; ACT, asthma control test; AD, atopic dermatitis; AERD, aspirin-exacerbated respiratory disease; AR, allergic rhinitis; AQLQ, asthma quality of life questionnaire; BAS, basophil; BEC, blood eosinophil count; Breg, B regulatory cells; CGRP, calcitonin gene-related peptide; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CSMS, combined symptom and medication score; CSU, chronic spontaneous urticaria; CT, computed tomography; CU-Q_2OL, chronic urticaria quality-of-life questionnaire; DLQI, dermatology life quality index; DNSMS, daily nasal symptom medication score; DSQ, dysphagia symptom questionnaire; EASI, eczema area and severity index; EEsAI, eosinophilic esophagitis symptom activity index; ELSA, esophagitis live symptoms assessment; EOS, eosinophils; EoE, eosinophilic esophagitis; EoE-HSS, EoE-histology scoring system; EoE-IQ, EoE impact questionnaire; EoE-QoL-A, adult eosinophilic esophagitis quality of life questionnaire; EoE-SQ, EoE symptom questionnaire; EREFS, endoscopic reference score; FA, food allergy; FcεRI, high-affinity receptor for the Fc fragment of IgE; FDA, Food and Drug Administration; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GISS, global individual signs score; HADS, hospital anxiety and depression scale; HDM, house dust mite; HRQoL, health-related quality of life; HSS7, weekly hives severity score; IgE, immunoglobulin E antibody; IGA, investigator global assessment; IL, interleukin; IL4Rα, receptor for IL-4 and IL-13, subunit α; IL5R, receptor for interleukin 5; ILC2, innate lymphoid cells type 2; ILCreg, innate regulatory lymphoid cells; (i)NKT, invariant natural killer T cells; ISS, itch severity score; LMS, Lund-Mackay score for sinus CT scan; LoS, loss of smell; LS, least-squares; LT, cysteinyl leukotrienes; LTE_4, leukotriene E_4; MC, mast cell; MEF_{50}, maximal expiratory flow at 50% of forced vital capacity; Mϕ, macrophages; MLK, modified Lund-Kennedy endoscopic scoring system; NAC, nasal allergen challenge; NBS, nasal blockage score; NCS, nasal congestion score; NGF, nerve growth factor; NKT, natural killer T cell; NP, nasal polyps; NPS, nasal polyps' score; NSAIDs, nonsteroidal anti-inflammatory drugs; NSs, nasal corticosteroids; OFC, oral food challenge; OIT, oral immunotherapy; PedsQL, pediatric quality of life inventory; PEF, peak expiratory flow; PGA, physician's global assessment of improvement; PGD_2, prostaglandin D2; PGD_2M, prostaglandin D2 metabolite; PNIF, peak nasal inspiratory flow; POEM, patient-oriented eczema measure; PPI, proton pomp inhibitor; QoL, quality of life; RCTs, randomized controlled trials; ROS, reactive oxygen species; RQLQ, rhinitis quality of life questionnaire; RSOM, rhinosinusitis outcome measurement; RWSs, real-world studies; SA, severe asthma; SAA, severe allergic asthma; SCORAD, scoring atopic dermatitis; SCSs, systemic corticosteroids; SGRQ, St. George's respiratory questionnaire; SIT, specific allergen immunotherapy; SMC, smooth muscle cell; SNOT-22, sino-nasal outcome test-22; SoC, standard of care; T2, type 2 immune response; Tc2, T cytotoxic lymphocyte type 2; Tfh, T follicular helper cells; Th, T helper lymphocytes; TNSS, total nasal symptom score; Treg, T regulatory cells; TSLP, thymic stromal lymphopoietin; UAS7, urticaria activity score over 7 days; UCT, urticaria control test; UPSIT, University of Pennsylvania smell identification test; VAS, visual analog scale.

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Introduction

Severe asthma (SA), affecting 5–10% of asthmatic patients, is associated with a high socio-economic burden due to uncontrolled symptoms, recurrent exacerbations requiring hospitalizations or medical visits, absence from work, and costs for the management of adverse events related to frequent or long-term systemic corticosteroids (SCSs) use [1,2]. "Type 2-high" (T2) asthma, driven by interleukin (IL)-4, IL-5, and IL-13 with eosinophilic inflammation and/or increased fractional exhaled nitric oxide (FeNO) represents ~80% of SA patients [3,4]. T2-inflammation extends beyond the lower airways and underlies a range of comorbidities affecting the upper airway, skin, and gastrointestinal tract, which share overlapping immunopathogenic mechanisms [5]. Fig. 1 summarizes the hypersensitivity reactions involved in T2-inflammatory diseases pathogenesis, while Fig. 2 represents detailed mechanisms of immune responses engaging immunoglobulin E (IgE) antibodies (A), mediated by T2-cells (B), and driven by dysfunctional epithelium following damage (C) [6].

T2-comorbidities, common in SA, include allergic rhinitis-AR (49%), chronic rhinosinusitis-CRS (46%), nasal polyps-NP (21%), atopic dermatitis-AD (10%), chronic spontaneous urticaria-CSU (3.5%), food allergy-FA (3.3%), aspirin sensitivity (1.6%) and eosinophilic esophagitis-EoE (0.5%). Almost 70% of SA patients have at least one T2-comorbidity [7]. These comorbidities adversely affect asthma outcomes, contribute to disease persistence and corticosteroid dependence, increasing the disease burden [2,7–9]. The augmentation in number of comorbidities worsens this negative impact [7]. Therefore, systematic assessment and management of T2-comorbidities is critical for optimizing SA outcomes [10].

The development of biologics targeting key T2-mediators or their receptors has revolutionized the treatment of SA. Randomized controlled trials (RCTs) and real-world studies (RWSs) demonstrated the efficacy of these therapies in terms of exacerbation rate, SCSs use, asthma control, lung function and patients' quality of life (QoL) [1,4]. Several biologics used for SA (e.g. omalizumab, mepolizumab, benralizumab, dupilumab, tezepelumab) proved also benefits on different T2-comorbidities [11–16]. This highlights the systemic nature of T2-inflammation and supports the concept of a unified multimorbidity therapeutic approach.

Despite advances, knowledge regarding the magnitude and consistency of biologics efficacy across SA comorbidities remain limited, whereas the optimal strategies for selecting biologics in multimorbid patients are still unknown [2,4]. The aim of this narrative review is to summarize current data concerning the efficacy of biologics available for SA on T2-comorbidities to help clinicians in choosing the "right treatment for the right patient".

Methodology

For this narrative review, we performed a literature search in PubMed and Medline databases up until November 30th, 2025. The search terms used were: "severe asthma", "biologics" associated with "allergic rhinitis", "chronic rhinosinusitis", "nasal polyps", "aspirin-exacerbated respiratory disease (AERD)", "atopic dermatitis", "eczema", "chronic spontaneous urticaria", "food allergy", and "eosinophilic esophagitis". We selected RCTs, RWSs, systematic reviews, meta-analyses, and case series. Case reports were excluded. A preference was given to more recent articles published in the last five years to have the most up-to-date evidence. Results were limited to publications in English.

Impact of biologics on AR

AR is the most frequent comorbidity of asthma sharing common genetic background, similar epithelial structure and disease characteristics with chronic airway inflammation classically recognized as been mediated by IgE with symptoms related to allergen

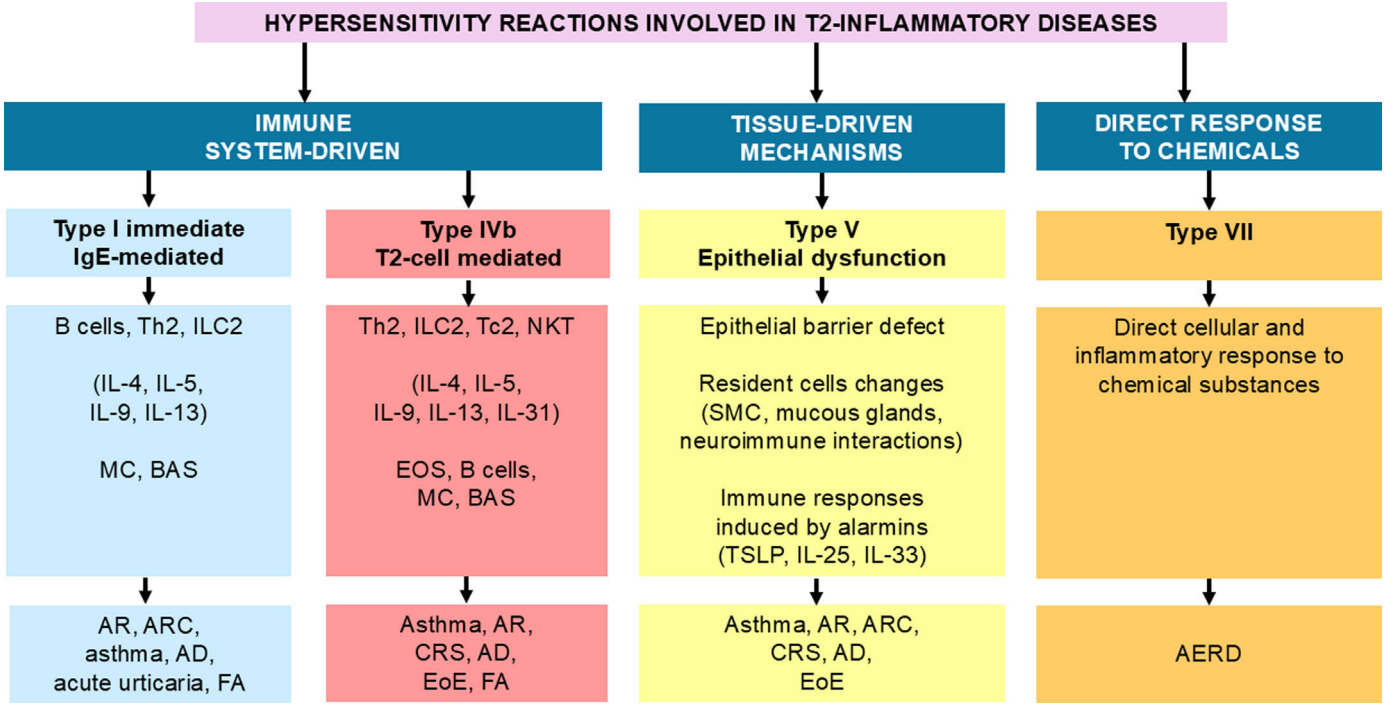


Fig. 1. Summary of hypersensitivity reactions involved in T2-inflammatory diseases. Hypersensitivity reaction is defined as an undesirable, uncomfortable or damaging response that arises from a tissue cell dysfunction or immune system overreaction [6]. T2: type 2 immune response; IgE: immunoglobulin E; Th: T helper lymphocytes; ILC2: innate lymphoid cells type 2; IL: interleukins; MC: mast cell; BAS: basophil; AR: allergic rhinitis; ARC: allergic rhinoconjunctivitis; AD: atopic dermatitis; FA: food allergy; Tc2: T cytotoxic lymphocyte type 2; NKT: natural killer T cell; CRS: chronic rhinosinusitis; EoE: eosinophilic esophagitis; AERD: aspirin-exacerbated respiratory diseases; SMC: smooth muscle cell.

exposure, supporting the "one airway, one disease" hypothesis [17]. Increasing evidence exists for the involvement of hypersensitivity type IVb and V reactions in addition to type I hypersensitivity in AR and asthma pathogenesis [6,18] (Figs. 1 and 2). Asthmatic patients with AR have more severe symptoms, frequent exacerbations and medical visits [7,19,20]. In the association AR-asthma, treatment with nasal corticosteroids (NSs) and/or antihistamines for AR improves asthma control and decreases healthcare utilization whereas administration of montelukast or biologics for asthma ameliorates nasal symptoms and patients' QoL [11,17,20–22].

Among biologics, more evidence regarding the impact on AR exists for omalizumab, the first agent approved as add-on therapy for moderate-to-severe allergic asthma. By binding circulating IgE, omalizumab reduces the inflammatory response related to allergen exposure. Both RCTs and RWSs demonstrated the efficacy of omalizumab in patients with seasonal and perennial AR by improving total nasal symptom score (TNSS), endoscopic score, Rhinitis QoL Questionnaire (RQLQ) score and decrease in rescue medication use with a favorable safety profile [11,23–33]. In patients with AR-SA, omalizumab improved sinonasal outcomes, asthma control, exacerbation rates, Asthma QoL Questionnaire (AQLQ) score, and forced expiratory volume in one second (FEV1), enhanced the efficacy and tolerability of specific allergen immunotherapy (SIT) [11,30–33]. Decreases in serum IgE, FeNO levels and blood eosinophil count (BEC) were reported following omalizumab treatment [23,24,34]. These findings have been confirmed by meta-analyses and systematic reviews [35–37].

More recently, the efficacy of dupilumab, an antibody blocking the receptor for IL-4 and IL-13 (IL-4Rα), has been investigated in AR. These cytokines play key role in allergen-specific T-cell responses; therefore, their inhibition may benefit AR outcomes [6,22]. A proof-of-concept study using transcriptome data from nasal brushing showed that 16 weeks of treatment with dupilumab repressed gene signatures of AR disease and after nasal allergen challenge (NAC) [38]. In patients with AR and asthma, dupilumab reduced TNSS and RQLQ score, improved asthma control, exacerbation rate, FEV1 and decreased FeNO and serum IgE levels [22,39]. In a RCT involving patients with AR, adding dupilumab to SIT did not confer superiority over SIT alone with regard to TNSS following NAC [40]. However, a RWS on patients with SA-AR reported improvements in symptom control, QoL, lung function, and airway remodeling on chest CT-scan, with a reduction of FeNO levels after 48 weeks of treatment [41].

The efficacy of anti-IL5 (mepolizumab, reslizumab) and anti-IL5R (benralizumab) antibodies on AR has not been specifically evaluated. A recent RCT involving patients with cat-allergy-related rhinitis showed that addition of tezepelumab, an anti-thymic stromal lymphopoietin antibody, to SIT achieved a greater reduction in TNSS at 52 weeks compared with SIT alone without significant difference when comparing tezepelumab monotherapy vs placebo

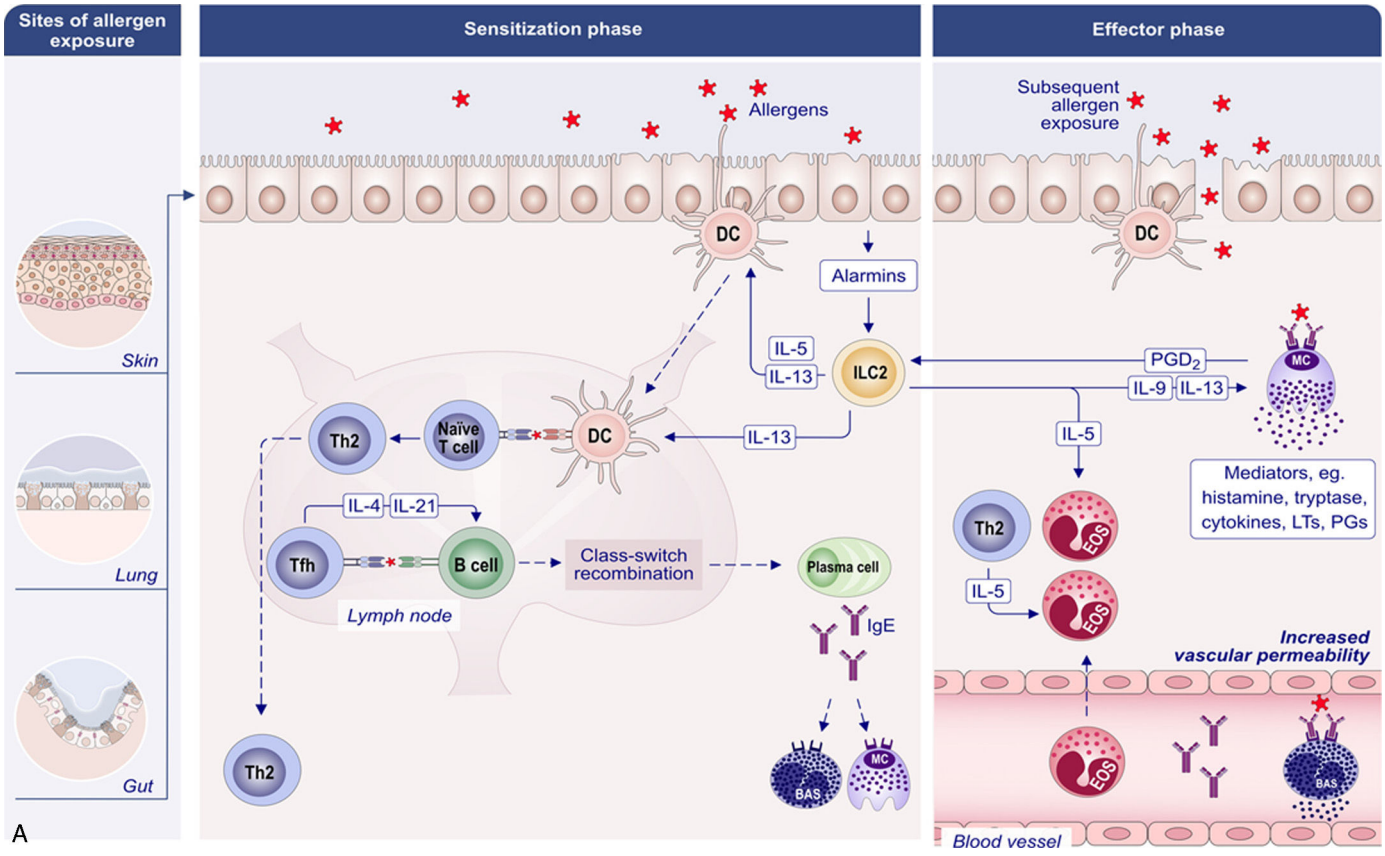
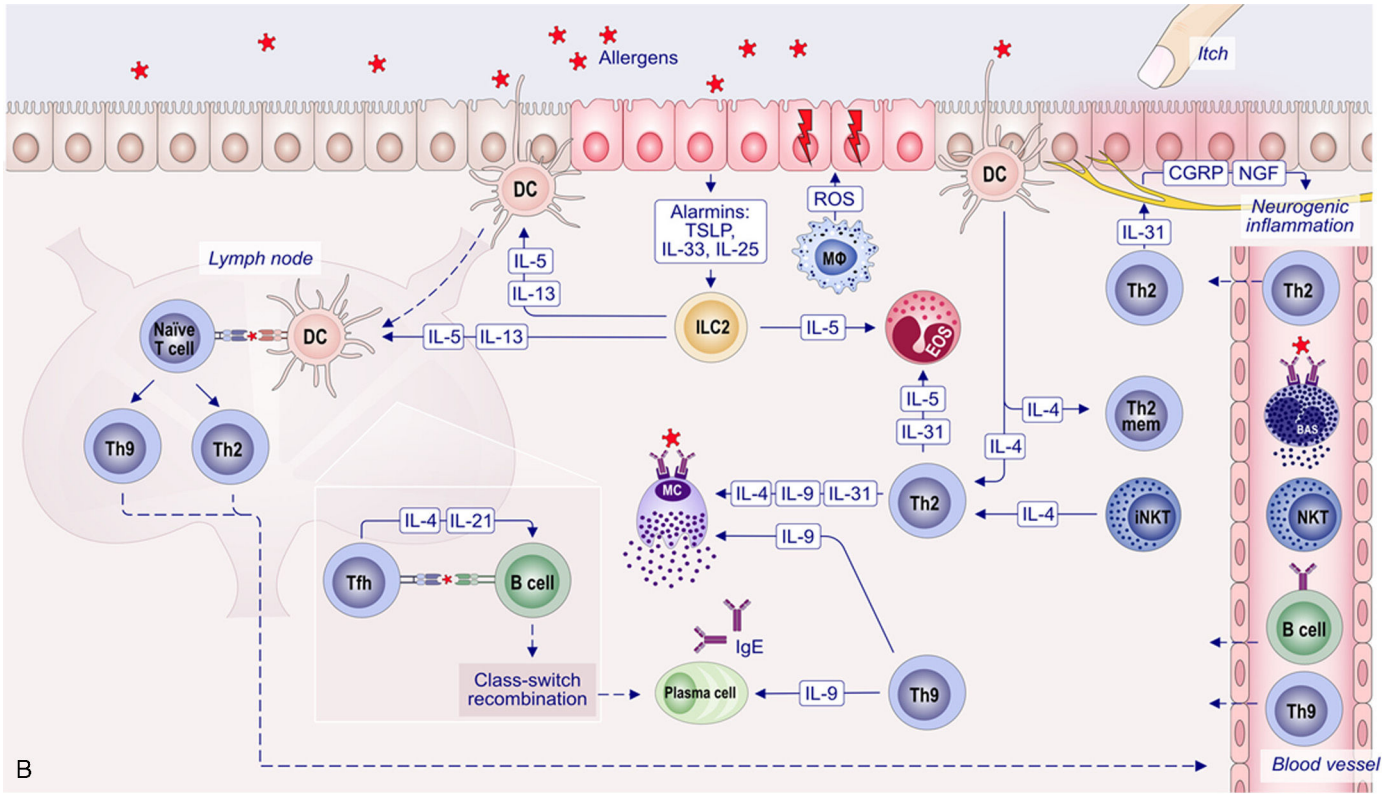


Fig. 2. Detailed mechanisms involved in type I, type IVb and type V hypersensitivity reactions. (A) Mechanisms of type I hypersensitivity in AR, asthma, AD, urticaria, and FA. Following the first contact with the allergen deposited on the epithelial cells, in the respiratory tract, gut or skin, the sensitization phase occurs. Dendritic cells (DCs) present the antigen to the naïve T cell inducing differentiation into T helper 2 (Th2) cell. Type 2 innate lymphoid cells (ILC2) are activated by epithelial alarmins, such as interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP). Upon activation, they produce large amounts of type 2 cytokines, including IL-5, IL-9 and IL-13, further supporting the T2-cell response. T follicular helper cells (Tfh) help B cells to maturate and produce allergen-specific immunoglobulin E (IgE). Mast cell (MC) and basophil (BAS) possess the high-affinity receptor for the Fc fragment of IgE (FcεRI) and are coated with IgE, thus concluding the sensitization phase. The effector phase occurs upon subsequent exposure to the same allergen. The allergen crosslinks IgE fixed to MC and BAS, triggering degranulation. Preformed mediators inside MC and BAS like histamine, tryptase, leukotrienes (LTs), prostaglandins (PGs) are released into the microenvironment inducing vasodilation, bronchial muscle contraction and increased mucus secretion. Eosinophils (EOS) play a significant role in the delayed allergic response and the persistence of inflammation engaging mechanisms related to type IVb hypersensitivity. The mutual interaction between type I and IVb-related processes is vital to both the sensitization and the chronic phase.



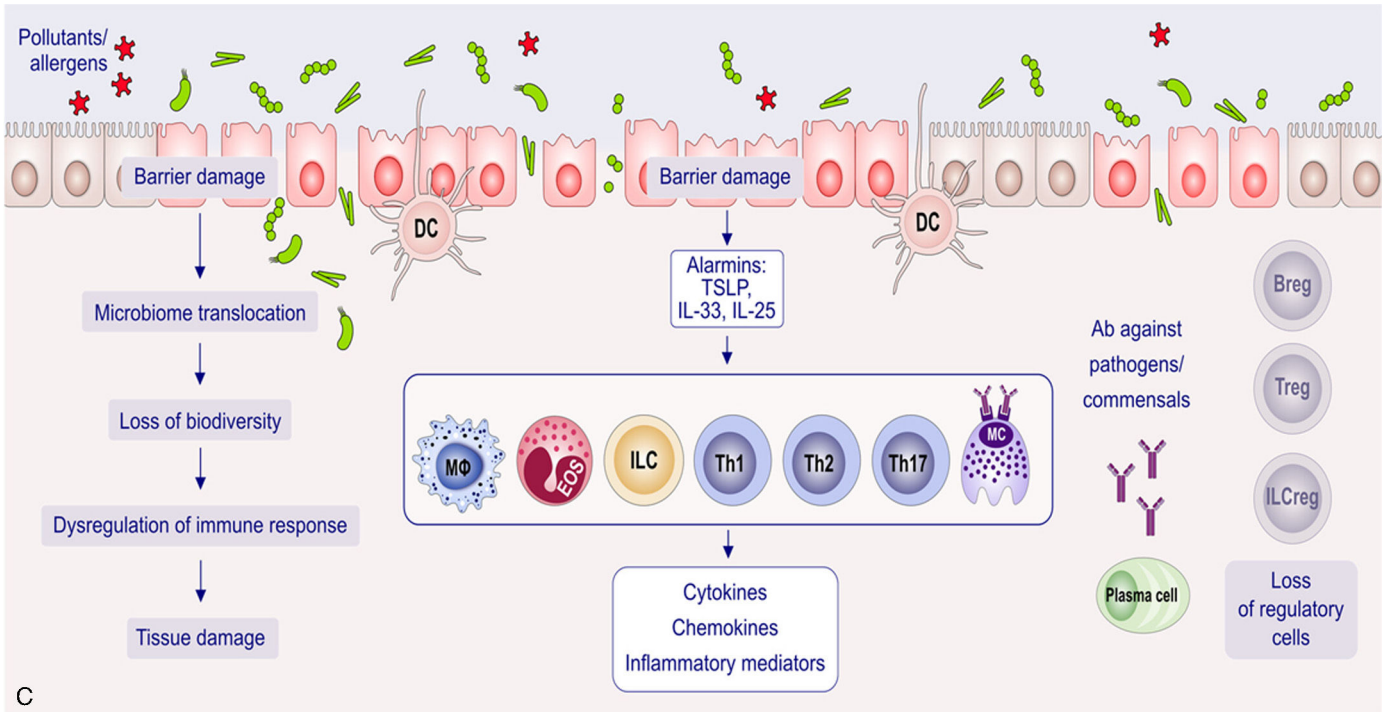


Fig. 2. (B) Mechanisms of type IVb hypersensitivity in AR, asthma, AD, CRS with NP, FA and EoETh2 is the key player in type IVb sensitivity, driven by IL-4, IL-13, IL-5 and IL-31. These cytokines stimulate B cells to produce IgE (IL-4 and IL-13) and activate eosinophils (IL-5) inducing inflammation and tissue damage. IL-31 produced by Th2 activates receptors on sensory neurons with release of calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF) causing neurogenic inflammation and itch. Th9, which differentiate with IL-4 and tumor necrosis factor beta (TGF-β), contribute to this response by promoting IgE production and MC growth. The inflammatory response is enhanced by the ILC2, MC and alternatively activated macrophages (Mϕ). ILC2, DC and Th2 activated by epithelial alarmins cooperate producing cytokines that promote eosinophil and basophil recruitment, modulate DC function and affect epithelial barrier contributing to the chronicity of type IVb reactions. Invariant natural killer T cells-(i)NKT contribute to this response inducing alternative activation in Mϕ by IL-4 and IL-13 production. Migrated to inflammatory sites, eosinophils activate various cytokines and release cytotoxic granules contributing to tissue damage, cell apoptosis and chronic inflammation. At the final stage when IgE synthesis is triggered, type IVb and I hypersensitivity overlap. (C) Mechanisms of type V hypersensitivity in AR, asthma, CRS, AD, and EoE. The epithelial barrier damage and microbial dysbiosis lead to dysregulation of the immune response, including extensive activation of T1 (mediated by T helper 1 [Th1] cells), T2 (mediated by Th2) and T3 (mediated by T helper 17 [Th17]) responses combined with the loss of T regulatory cells (Treg), B regulatory cells (Breg) and innate regulatory lymphoid cells (ILCreg). Increased microbiome translocation induces aberrant immune response to opportunistic pathogens and commensals like *Staphylococcus aureus* with IgE antibody (Ab) production against them. Additionally, activation of Mϕ, EOS, innate lymphoid cells (ILC), MC and BAS by epithelial alarmins with release of proinflammatory cytokines and chemokines (e.g. histamine, LT, reactive oxygen species- ROS) enhances the local inflammatory response and tissue damage.
The figure was reproduced with permission (License Number 6150051257285) from Ref. [6].

[42]. Incoming study TEZARS (NCT06189742) evaluates the efficacy of tezepelumab in patients with AR and asthma. Subgroups analyses from large clinical studies showed comparable efficacy of tezepelumab and mepolizumab in improving asthma outcomes in SA patients with or without AR [43,44].

Overall, evidence supports a high level of efficacy for omalizumab and dupilumab on AR as comorbidity of SA. Findings from representative studies are summarized in Table 1.

Impact of biologics on CRS with and without NP

CRS and asthma often coexist sharing the same immunological processes involved in their pathogenesis with epithelial barrier dysfunction and cell-mediated inflammation (hypersensitivity type IVb and V) [6,18,20] (Figs. 1, 2B and 2C). While T2-inflammation is predominant in patients with NP, T1 and T3 inflammatory signatures are more frequent in patients with CRS without NP (CRSsNP) [45]. Clinical characteristics of patients with asthma-CRS include older age at diagnosis, longer duration of nasal symptoms, poor symptom control, high risk of exacerbation requiring SCSs, airflow obstruction, worse sinus CT and endoscopy scores, increased frequency of sinonasal surgeries and impaired QoL. Treatment of CRS with NSs or surgery may improve asthma outcomes, whereas several asthma medications (e.g. montelukast, macrolides, biologics) demonstrated benefits on CRS scores [20].

Previous data showed increased local production of IgE in NP independent of the presence of allergy [46]. In this context, the efficacy of omalizumab has been evaluated in NP. RCTs showed significant improvement in nasal polyps score (NPS), TNSS, sinonasal outcome test-22 (SNOT-22) score, with decrease in needs for surgery after 24 weeks of treatment with omalizumab compared to placebo allowing for its approval as add-on therapy in patients with uncontrolled severe NP [46,47]. The benefits of treatment are also reported in patients with recurrent NP and maintained at one year [48,49]. The positive impact of omalizumab on NP and its favorable safety profile were confirmed by metanalyses and systematic reviews involving RCTs and RWSs [50,51]. Regarding the association SA-NP, RCTs and RWSs demonstrated omalizumab efficacy in improving both conditions outcomes from 16 weeks to 2 years of treatment, by increasing patients' QoL, reducing T2-inflammation and therapeutic pressure [46,52–57]. In contrast, the effects of omalizumab in patients with CRSsNP were disappointing, with only modest improvement in SNOT-22 scores without significant differences compared to placebo concerning sinonasal symptoms and imaging after 6 months of treatment [58].

As most of NP in Caucasian population exhibit eosinophilic inflammation driven by IL-4, IL-5 and IL-13, biologics targeting these cytokines and their receptors have been extensively evaluated. The anti-IL5 antibody, mepolizumab reduced NPS, visual analog scale (VAS) symptom score, SCSs use and risk for sinus surgery in patients with refractory, recurrent NP compared to placebo allowing for its reimbursement for this indication [59–61]. Large metanalyses of RCTs and RWSs confirmed these findings and demonstrated good tolerability of the treatment [51,62,63]. Post-hoc analyses from RCTs showed similar benefits of mepolizumab on asthma outcomes in SA patients with and without NP [64]. Data from real-world cohort REDES suggested even higher efficacy of mepolizumab in improvement of asthma symptoms, annualized exacerbation rate (AAER), FEV1 and SCSs use in patients having this association compared to other SA patients after one year of treatment [65]. Multiple RWSs involving patients with SA and NP demonstrated the efficacy of mepolizumab on both conditions at 6 and 12 months of treatment with decrease in eosinophilic inflammation [66–69].

More limited data exists for the effects of reslizumab in the association SA-NP. Post-hoc analyses from RCT including 150 patients with SA-NP showed that reslizumab decreased AAER by 83% vs placebo with concomitant improvement in FEV1, asthma control and AQLQ score (all $p < 0.001$) after 52 weeks of treatment [70]. In a subgroup analysis from RWS, including 14 patients with SA-NP, reslizumab reduced AAER, needs for surgery and BEC with increased asthma control and FEV1 (all $p < 0.02$). Thirty-six percent of patients reported improvement in smell, although changes in NPS were not significant at one year of treatment [71].

The efficacy of benralizumab inducing eosinophil depletion, was also evaluated in patients with NP. A large RCT showed improvements in NPS, nasal blockage and sense-of-smell in patients receiving benralizumab compared to placebo at 40 weeks of treatment (all $p \leq 0.003$) without significant benefits on SNOT-22 score, time to first surgery and SCSs use. Patients with asthma experienced greater effects on NPS than the others [72]. A metanalysis including RWSs confirmed the positive impact of benralizumab on NP and its good tolerability [51]. In a subgroup analysis from a RCT involving 153 patients with SA-NP, significant improvements were found in the group benralizumab vs placebo after 24 weeks of treatment on SNOT-22 score ($p = 0.018$), AAER, asthma control, FEV1 and St. George's Respiratory Questionnaire (SGRQ) score (all $p < 0.001$) [73]. Numerous RWSs confirmed benralizumab efficacy in the association SA-NP regarding symptoms, AAER, lung function, SNOT-22 score, NPS, sinus imaging, eosinophilic inflammation, SCSs use and needs for surgery [69,74–78]. Despite benefits sustained up to 3 years [74], benralizumab is not currently approved as an add-on treatment of NP.

Very limited data exists concerning the impact of anti-IL5/R antibodies on CRSsNP. A RWS including 36 patients with SA-CRSsNP showed significant improvements on sinus imaging, BEC and serum IgE levels after treatment [79].

Dupilumab proved high efficacy in improving sinonasal outcomes in patients with NP in RCTs and RWSs. Analyses from RCTs showed decreases of NPS, nasal congestion, loss-of-smell, TNSS, SCSs use and needs for surgery with improvements of SNOT-22 score, sinus imaging and patients' QoL after 24, respectively 52 weeks of treatment versus placebo with a favorable safety profile (all $p < 0.001$) [80–83]. These results allowed to its approval as add-on therapy for adults with severe NP. Numerous RWSs confirmed sustained benefits up to 3 years [51,84–91]. In a metanalysis including RWSs, 90% of patients respond to treatment with at least three of five criteria defined in current guidelines [51]. Response appeared independent of the number of prior sinus surgery, comorbidities, or baseline levels of T2-inflammation [90]. Concerning the association SA-NP, dupilumab administered for ≥16 weeks, proved its efficacy on sinonasal outcomes with concomitant improvement of AAER, asthma control, lung function, patients' QoL, FeNO and serum IgE levels, regardless of treatment indication, in RCTs and RWSs [15,80,91–95]. The benefits persist up to 30 months of treatment [94]. Regarding the impact of dupilumab on the association SA-CRS, an one-year study involving 50 patients showed similar efficacy of treatment in patients with and without NP in terms of exacerbations, hospitalizations, asthma control, anosmia, FEV1, BEC and SCSs use. A greater improvement in SNOT-22 scores was found in the group with NP compared to the group with CRSsNP (26.5 ± 12.5 vs 15.1 ± 9.4, $p \leq 0.001$) [96]. Dupilumab-induced blood eosinophilia probably represents the most feared effect for clinicians due to potential complications. Although nearly half of treated patients develop blood eosinophilia within six months of treatment, most of them are asymptomatic and BEC typically declines by 12 months [97–99]. Hypereosinophilia (BEC $\geq 1.5 \times 10^9$ cells/L) occurs in 15%

Table 1
Efficacy of biologics in patients with AR.

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary Outcomes
Omalizumab	RCT [23]	251	Effects of omalizumab in patients with birch-pollen induced seasonal AR	Significant improvement in average daily nasal symptom severity score in the group omalizumab vs placebo ($p < 0.001$) after 8 weeks of treatment	Improvement in the RQLQ score and decrease in rescue medication use in the omalizumab group vs placebo (both $p < 0.001$)
Omalizumab	RCT [24]	536	Efficacy of omalizumab for prophylaxis of symptoms in patients with seasonal AR	Decrease in average nasal symptom severity score during 12 weeks of treatment with omalizumab vs placebo ($p = 0.002$)	Improvement in the RQLQ score ($p = 0.008$) and reduction in rescue antihistamine use ($p = 0.001$) in the omalizumab group vs placebo
Omalizumab	RCT [25]	289	Impact of omalizumab in patients with perennial AR	Decrease in mean daily nasal symptom severity score in the omalizumab group vs placebo at week 16 ($p < 0.001$)	Reduction in rescue antihistamine use and improvement of RQLQ score (both $p \leq 0.005$) with omalizumab vs placebo
Omalizumab	RCT [26]	100	Efficacy and safety of omalizumab in patients with Japanese cedar pollen-induced AR	Significant reduction in DNSMS and nasal rescue medication use (both $p \leq 0.002$) in the omalizumab group vs placebo after 12 weeks of treatment	Decrease in daily ocular symptom score and local rescue medication use in the omalizumab group vs placebo (both $p < 0.001$) with good tolerability
Omalizumab	RCT [27]	337	Superiority of omalizumab + SoC vs SoC patients with cedar pollinosis induced AR	Decrease in TNSS including sneezing, rhinorrhea, nasal congestion during 12 weeks of treatment in the group omalizumab + SoC vs SoC ($p < 0.001$)	Concomitant improvement in the mean ocular symptom score and RQLQ score (both $p < 0.001$) in the omalizumab group vs control
Omalizumab	RCT [28]	31	Efficacy of preseason omalizumab administration in patients with seasonal AR	Reduction in mean daily CSMS ($p < 0.001$) during the pollen period in the omalizumab group vs control	Decrease in average daily medication score with improvement of RQLQ score (both $p \leq 0.04$) during the pollinosis with omalizumab treatment
Omalizumab	Open label study [29]	64	Preventive efficacy of omalizumab in patients with seasonal AR	Improvement in daily CSMS during the pollen period with omalizumab compared to the forepassed pollen season without omalizumab ($p < 0.001$)	
Omalizumab	RWS [30]	60	Change of TNSS and RQLQ score in patients with seasonal AR treated with omalizumab	Significant improvement in TNSS and RQLQ scores after 6 months of treatment (both $p < 0.001$)	Concomitant increase in the ACT scores in patients with coexisting asthma ($p < 0.001$)
Omalizumab	RCT [31]	130	Superiority of omalizumab + SIT vs SIT alone in patients with seasonal AR and asthma	Reduction in daily nasal 'symptom load' by 39% ($p = 0.046$) and symptom severity score ($p = 0.004$) in the group omalizumab + SIT vs SIT after 18 weeks of treatment	Improvement of ACT ($p = 0.030$) and AQLQ ($p = 0.029$) and RQLQ scores ($p = 0.054$) in the combination therapy vs SIT alone
Omalizumab	RCT [11]	405	Efficacy of omalizumab in patients with moderate-to-severe asthma and AR	Decrease in AAER in the omalizumab group vs placebo (20.6% vs 30.1%, $p = 0.02$) with improvement in AQLQ and RQLQ scores (both $p < 0.001$) at week 28	Concomitant improvement in asthma symptom control ($p = 0.023$) and total rhinitis symptom score ($p < 0.001$) in the omalizumab group vs placebo
Omalizumab	Open label study [32]	11	Effects of omalizumab in patients with SA and persistent AR	Reduction in total nasal symptom VAS score, turbinate hypertrophy, and FeNO levels with improvement of ACT score (all $p < 0.05$) after 28 weeks of treatment	
Omalizumab	RWS [33]	10	Efficacy of omalizumab in patients with SA and persistent AR	Significant improvement in total nasal symptom VAS score, MLK score, ACT score, FEV1 (all $p \leq 0.01$) after 36 months of treatment with decrease of serum IgE level	
Dupilumab	Post-hoc analysis RCT [39]	241	Change of SNOT-22 and AR-associated symptoms in patients with asthma and perennial AR treated with dupilumab	Improvement in SNOT-22 score and AR-symptoms (all $p < 0.01$) after 24 weeks of treatment with dupilumab (300 mg/2 weeks) vs placebo	Concomitant reduction in AAER and increase of FEV1 (both $p < 0.04$) in the dupilumab group vs placebo
Dupilumab	Post-hoc analysis RCT [22]	814	Efficacy of dupilumab in patients with moderate-to-severe asthma and perennial AR	Improvement in RQLQ score, ACQ score, FEV1 with decrease of AAER, FeNO and IgE serum levels (all $p \leq 0.04$) at week 12 of treatment in the dupilumab group (200 mg/2 weeks) vs placebo	

Table 1 (*Continued*)

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary Outcomes
Dupilumab	RCT [40]	103	Change of TNSS after NAC in patients with seasonal AR receiving dupilumab + SIT vs SIT monotherapy	No significant difference by adding dupilumab to SIT on TNSS after NAC at week 17 of treatment ($p = 0.719$)	Fewer withdrawals in the group dupilumab + SIT vs SIT alone ($p = 0.022$)
Dupilumab	RWS [41]	41	Efficacy of dupilumab + HDM SIT in patients with asthma and AR	Improvement in ACQ, AQLQ, RQLQ scores, FEV1 after 48 weeks of treatment with decrease of FeNO level, wall thickness and airway wall area percent on chest CT scan (all $p < 0.05$)	
Tezepelumab	RCT [42]	121	Superiority of tezepelumab + SIT vs tezepelumab and placebo in patients with perennial AR based on TNSS after NAC	Decrease in TNSS after NAC in the group tezepelumab + SIT vs SIT alone significant at week 52 ($p = 0.028$) but not at week 104 ($p = 0.314$)	No difference in TNSS between tezepelumab and placebo groups ($p = 0.139$ at week 52, respectively $p = 0.558$ at week 104)

AAER: annualized asthma exacerbation rate; ACQ: asthma control questionnaire; ACT: asthma control test; AQLQ: asthma quality of life questionnaire; AR: allergic rhinitis; CSMS: combined symptom and medication score; CT: computed tomography; DNSMS: daily nasal symptom medication score; FEV1: forced expiratory volume in one second; FeNO: fractional exhaled nitric oxide; HDM: house dust mite; IgE: immunoglobulin E; MLK: modified Lund-Kennedy endoscopic scoring system; NAC: nasal allergen challenge; RCT: randomized controlled trial; RWS: real-world study; RQLQ: rhinitis quality of life questionnaire; SA: severe asthma; SNOT-22: 22-item sino-nasal outcome test; SIT: specific immunotherapy; SoC: standard of care; TNSS: total nasal symptom score; VAS: visual analog scale.

of patients, but the incidence of eosinophilic complications remains low (<1%) [97,99–101]. A practical algorithm was developed for the management of dupilumab-induced blood eosinophilia [101].

As thymic stromal lymphopoietin (TSLP) is an upstream key driver of multiple inflammatory cascades, the efficacy of tezepelumab targeting this alarmin has been assessed in patients with NP. In a large RCT, tezepelumab administered for 52 weeks improved NPS, nasal-congestion, loss-of-smell, TNSS, SNOT-22 score, and sinus imaging while reducing surgery and SCSs needs compared to placebo (all $p < 0.001$) with good tolerability, supporting recent approval as add-on therapy in severe NP. Patients with comorbid asthma receiving tezepelumab had greater improvement in disease control vs placebo [15]. Subgroup analyses from RCTs and RWSs in SA-NP confirmed benefits of tezepelumab regarding AAER, asthma control, lung function, SNOT-22 score, and T2-biomarkers at weeks 24 and 52 [102–104]. In the PASSAGE RWS, patients with SA-NP had greater reduction in AAER than those with SA-CRSsNP (by 85% [65,93] vs 65% [52,75]) with higher improvement in SNOT-22 scores from baseline at 24 weeks (−26.1 [−34.6, −17.6] vs −12.6 [−16.1, −9.0]). The rate of response to treatment (improvement in the SNOT-22 score by ≥8.9) was 79% in the group NP and 55% in the group CRSsNP [104].

Indirect comparisons and metanalyses (mostly based on RCTs) assessing biologics efficacy on NP suggest a superiority of dupilumab (strongest evidence) and tezepelumab in improving sinonasal outcomes [105–111]. A RWS ($n = 85$) showed greater efficacy of dupilumab compared to mepolizumab at 3 and 6 months of treatment in NPS, improving smell, peak nasal inspiratory flow (PNIF) and sniff-test with higher rate of response to treatment (70% vs 37%) [112]. The first head-to-head RCT comparing the efficacy of dupilumab and omalizumab in 360 patients with NP and asthma was recently published. Dupilumab was superior to omalizumab at 24 weeks of treatment across all endpoints including NPS, smell test score, nasal congestion, TNSS, SNOT-22 score, PNIF, rhinosinusitis severity, asthma control, FEV1, forced expiratory flow 25–75%, and AQLQ (all $p \leq 0.013$) [113]. A recent metanalysis of RCTs in SA-NP suggests greater efficacy of tezepelumab for AAER and asthma control, benralizumab for FEV1 and mepolizumab for SNOT-22 score [114]. RWSs in SA-NP reported comparable efficacy of anti-IgE, anti-IL5/R and anti-IL4R antibodies on asthma outcomes at 4–6 months of treatment with more benefits on sinonasal disease for dupilumab [15,69,115,116]. A systematic review showed that biologics use in patients with SA-NP is associated with significant improvements in lung function and QoL [117]. Analyses from the largest worldwide adult SA registry showed that patients with CRS ± NP or NP alone may have greater benefits from biologics than those without these comorbidities [8,118].

Strong evidence supports the efficacy of dupilumab, tezepelumab, mepolizumab and omalizumab in NP as a comorbidity of SA, with currently greater benefits reported for dupilumab and tezepelumab. Results from key studies are summarized in Table 2. Limited data is currently available regarding the efficacy of biologics in the SA-CRSsNP association.

Impact of biologics on aspirin-exacerbated respiratory disease (AERD)

AERD associates asthma, NP and sensitivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). A prevalence of 14.9% is reported in SA [119]. Disease course is typically severe with numerous exacerbations requiring intubation, treatment-refractory NP, frequent needs for SCSs and sinus surgery [20,120]. In patients with AERD, ingestion of aspirin or NSAIDs increases production of cysteinyl leukotrienes (LT) and prostaglandin D2 (PGD_2) inducing bronchoconstriction, mucosal oedema and T2-airway inflammation (hypersensitivity type VII reactions) [6,119,120]. Traditional management includes optimized treatment of SA and NP, along with as aspirin desensitization [17,20]. Biologics targeting T2-inflammation represent a promising therapeutic option for AERD.

Omalizumab administration for at least 16 weeks in patients with AERD suppresses LTE_4 and PGD_2 overproduction with improvement in sinonasal and respiratory symptoms, AAER, hospitalization rates, NPS, FEV1, SNOT-22 scores, SCSs and asthma rescue medication use in RCTs and RWSs [121–124]. Omalizumab pretreatment increased the tolerability during aspirin desensitization compared with placebo [121,125]. No significant differences in sinonasal and asthma outcomes were observed between patients with AERD and those aspirin-tolerant with SA-NP receiving omalizumab for 24 weeks [47,54].

Treatment with mepolizumab for 3 months decreased IL5-mediated signaling in mast cells, eosinophils and nasal epithelial cells in patients with AERD resulting in reductions of BEC and urinary LTE_4 levels (all $p < 0.04$) [126]. Subgroup analysis of the SYNAPSE RCT showed decrease in NPS and nasal congestion in

Table 2
Efficacy of biologics in patients with NP.

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary outcomes
Omalizumab	RCT [46]	265	Efficacy and safety of omalizumab in patients with NP	Significant decrease in NPS and NCS from baseline at week 24 in the omalizumab group vs placebo (all $p < 0.02$)	Improvement in SNOT-22 score, UPSIT score, TNSS, sense of smell, postnasal drip, and runny nose with reduction in need for surgery and increase of AQLQ score in the subgroup of patients with asthma in the omalizumab group vs placebo (all $p < 0.05$) with favorable tolerability
Omalizumab	RCT [47]	24	Impact of omalizumab treatment on the association NP and asthma	Significant reduction in NPS in the omalizumab group vs placebo after 16 weeks of treatment ($p = 0.001$)	Improvement in NCS, anterior rhinorrhea, LoS, wheeze, dyspnea, LMS and AQLQ score in the omalizumab group vs placebo (all $p < 0.05$) without significant changes in lung function parameters
Omalizumab	RWS [53]	22	Effects of omalizumab in patients with NP and asthma	Improvement in NPS, total nasal symptom VAS score, SNOT-22 score, ACT score, LMS, PEF and BEC after 24 weeks of treatment	
Omalizumab	RWS [54]	24	Efficacy of omalizumab on sinonasal and asthma outcomes in patients with SAA and NP	Decrease in nasal symptoms, asthma attacks, exacerbation rate, acute sinusitis number, ACT score, BEC, asthma rescue medication use, with improvement of sinus CT imaging and FEV1 (all $p \leq 0.02$) at 6 months	
Mepolizumab	RCT [59]	407	Efficacy and safety of mepolizumab in patients with recurrent, refractory severe NP	Significant improvement in NPS and nasal obstruction VAS score (both $p < 0.001$) from baseline to 49–52 weeks in the mepolizumab group compared to placebo	Improvement in total nasal symptom VAS score and SNOT-22 score, PNIF, decrease in needs for surgery, BEC and SCSs use in the mepolizumab group vs placebo (all $p \leq 0.02$) with favorable safety profile
Mepolizumab	RWS [66]	55	Effects of mepolizumab in patients with NP and comorbid asthma	Improvement in all sinonasal parameters (all $p < 0.001$) with increase of ACT score, decrease of FeNO levels, BEC, and SCS use (all $p < 0.05$) during 6 months of treatment	
Mepolizumab	RWS [67]	44	Benefits of mepolizumab on sinonasal and asthma outcomes in patients with SA and NP	Decrease in NPS, SNOT-22 score, AAER, BEC, nasal eosinophil count, and SCS use at 6 months (all $p < 0.01$), persistent up to one year, with improvement of ACT score ($p < 0.01$) and FEV1 ($p < 0.01$ only at 12 months) without significant effect on FeNO levels	
Reslizumab	RWS [71]	14	Impact of reslizumab on olfaction in patients with SA and NP	Improvement in olfaction in 36% of patients after one year of treatment	Concomitant reduction in AAER, BEC, needs for surgery with increase of ACT score and FEV1 (all $p < 0.02$) but no significant effect on NPS
Benralizumab	RCT [72]	413	Efficacy of benralizumab in patients with NP	Reduction in NPS and NBS in the benralizumab group vs placebo (both $p \leq 0.005$) at 40 weeks of treatment	Improvement in the sense of smell in the benralizumab group vs placebo ($p = 0.003$) without significant impact on SNOT-22 score, time to first surgery, and SCSs use
Benralizumab	RWS [76]	58	Impact of benralizumab on sinonasal and asthma outcomes in patients with SA and NP	Decrease in AAER, hospitalization number, SCS use with improvement of asthma control, FEV1, SNOT-22 score, VAS nasal score (all $p < 0.001$) at 12 months of treatment	
Benralizumab	RWS [78]	233	Effects of benralizumab on sinonasal and asthma outcomes in patients with SA and NP	Significant improvement in NPS and SNOT-22 score (both $p < 0.05$) during 12 months of treatment with reduction in AAER and increase of asthma control	
Dupilumab	RCT [80]	724	Efficacy and safety of dupilumab in patients with NP despite previous treatment with SCS, surgery, or both	Significant improvement in NPS, NCS and LMS (all $p < 0.001$) at 24 and 52 weeks of treatment in the dupilumab group vs placebo	Concomitant improvement in TNSS, UPSIT score, and SNOT-22 score in the dupilumab group vs placebo (all $p < 0.001$) with favorable safety profile
Dupilumab	Post-hoc analysis RCT [92]	428	Impact of dupilumab on sinonasal and asthma outcomes in patients with NP and asthma	Improvement in NPS, NCS, VAS score, SNOT-22 score, ACQ score, LMS, PNIF, FEV1, and HRQoL after 24 weeks of treatment in the group dupilumab vs placebo (all $p < 0.001$)	

Table 2 (*Continued*)

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary outcomes
Dupilumab	RWS [94]	38	Efficacy of dupilumab on sinonasal and asthma outcomes in patients with NP and asthma	Improvement in NPS, NCS, total nasal symptom VAS score, SNOT-22 score, LMS and ACT score with decrease of FeNO levels over 30 months of treatment (all $p < 0.001$)	
Dupilumab	RWS [15]	34	Impact of dupilumab on sinonasal and asthma outcomes in patients with SAA and NP	Reduction of asthma and sinonasal symptoms, exacerbation rate, number of acute sinusitis, rescue medication use, total nasal symptom VAS score, NPS and LMS with increase of ACT score (all $p < 0.001$) and FEV1 ($p = 0.004$) without significant changes in BEC at 6 months of treatment	
Tezepelumab	RCT [16]	408	Efficacy and safety of tezepelumab in patients with NP	Significant decrease in NPS and NCS in the tezepelumab group vs placebo (both $p < 0.001$) after 52 weeks of treatment	Improvement in sinonasal symptoms, LoS, SNOT-22 score, UPSIT score and LMS, with decrease in needs for surgery and SCSs in the tezepelumab group vs placebo (all $p < 0.001$); concomitant reduction of ACQ score and increase of FEV1 in patients with coexisting asthma
Tezepelumb	Post-hoc analysis RCT [102]	1059	Effects of tezepelumab in SA patients with and without NP	Improvement in AAER, ACQ-6 score, FEV1, HRQoL, BEC, FeNO and serum IgE levels in patients with and without NP receiving tezepelumab vs placebo, with decrease of SNOT-22 score in patients with NP at week 52	
Tezepelumab	RWS [104]	208	Impact of tezepelumab on asthma outcomes in SA patients with and without NP	Greater decrease in AAER in patients with NP than in the entire study population (85% vs 76%) after 24 weeks of treatment with concomitant improvement of SNOT-22 score (LS mean change from baseline −26.1 [−34.6, −17.6])	

ACQ: asthma control questionnaire; ACT: asthma control test; AQLQ: asthma quality of life questionnaire; BEC: blood eosinophil count; CT: computed tomography; FEV1: forced expiratory volume in one second; FeNO: fractional exhaled nitric oxide; HRQoL: health-related quality of life; IgE: immunoglobulin E; IL: interleukin; LS least-squares; LoS: loss of smell; LMS: Lund-Mackay score for sinus CT scan; NBS: nasal blockage score; NCS: nasal congestion score; NPS: nasal polyps score; PEF: peak expiratory flow; PNIF: peak nasal inspiratory flow; RCT: randomized controlled trial; RWS: real-world study; SAA: severe allergic asthma; SA: severe asthma; SNOT-22: 22-item sino-nasal outcome test; SCS: systemic corticosteroid use; TNSS: total nasal symptom score; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analog scale.

patients with AERD receiving mepolizumab compared to placebo at week 52 without significant benefits on olfaction [127]. Improvements in SNOT-22 scores, asthma control and BEC were also reported after 3 months of treatment with mepolizumab in patients with AERD in a RWS [128]. Small series suggest that mepolizumab may not prevent NP recurrence or aspirin-induced reactions during desensitization [129,130]. Post-hoc analyses of RCT showed similar efficacy of reslizumab administered 52 weeks on asthma outcomes in patients with SA-NP with or without aspirin sensitivity [70]. Data from RCT and RWS demonstrated comparable efficacy of benralizumab in patients with AERD and those with NP or SA after at least 4 months of treatment in terms of sinonasal and asthma outcomes [72,131].

In patients with AERD, dupilumab improves nasal symptoms (particularly olfaction), asthma control, NPS, PNIF, sinus imaging, lung function, SCSs use and patients' QoL in RCTs and RWSs [132–137]. The benefits, evident after one month of treatment, are attributed to reduced IL-4Rα signaling on respiratory tissue granulocytes, epithelial cells, and B cells, leading to decreased nasal and urinary LTE_4 levels, even in patients with inadequate response to anti-IL5/R antibodies [134,138]. As perioperative treatment, dupilumab reduces the risk of NP recurrence [139]. Pretreatment with dupilumab for 6 months increases aspirin tolerance in more than half of patients [140]. In a RWS, greater perceived efficacy was reported by patients with AERD receiving dupilumab compared to other biologics [141].

NP tissues from patients with AERD expressed high levels of TSLP, which induces PGD_2 production by mast cells suggesting its involvement in disease pathogenesis [142]. In a subgroup analysis of the WAYPOINT RCT, tezepelumab demonstrated similar efficacy regarding NPS and nasal congestion vs placebo at 52 weeks in patients with NP ± AERD [16]. A post-hoc analysis of the NAVIGATOR trial, including 43 patients with AERD, showed a 79% decrease in AAER in patients receiving tezepelumab for 52 weeks compared to placebo, with improvement in asthma control, patients' QoL and FEV1. A complete response was achieved in 71.4% of patients treated with tezepelumab [143].

Overall, biologics targeting T2-inflammation are effective in AERD, with more evidence for dupilumab, tezepelumab and omalizumab. Some subgroup analyses from studies on patients with SA and/or NP suggest also benefits of reslizumab and benralizumab in this population. The key findings from relevant studies are summarized in Table 3.

Impact of biologics on skin T2-comorbidities

CSU, characterized by wheals, angio-oedema, or both ≥6 weeks, is considered a T2-disease, at least the endotype driven by IgE autoantibodies (half of cases). CSU is associated with impaired QoL and performance at work/school, comorbidities and substantial economic burden. Other T2-conditions (e.g. AR, AD, asthma) are present in up to 20-30% of patients with CSU. One quarter of patients have uncontrolled disease despite up-dosing of antihistamines [144].

Omalizumab was approved as add-on treatment for CSU following RCTs showing significant improvement in symptoms and QoL vs placebo with a favorable safety profile [12,145–148]. These findings were confirmed in RWSs [149–151]. Dupilumab also showed benefits on CSU activity and symptoms in RCTs and RWSs [152,153].

Table 3
Efficacy of biologics in patients with AERD.

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary outcomes
Omalizumab	RCT [121]	16	Efficacy of omalizumab against aspirin hypersensitivity, LTE_4 overproduction, and symptoms during oral aspirin challenge test in patients with AERD	Significant reduction in urinary LTE_4 concentration during oral aspirin challenge test in the omalizumab group vs placebo ($p < 0.001$) during 3 months of treatment	Decrease in urinary PGD_2M level during oral aspirin challenge test with aspirin tolerance (up to 930 mg) achieved in 62.5% of patients receiving omalizumab with concomitant improvement of dyspnea, wheezing, cough, nasal congestion, rhinorrhea, anosmia, asthma control, FEV1 and SNOT-22 vs placebo (all $p < 0.05$)
Omalizumab	Open label study [122]	21	Impact of omalizumab in patients with AERD	Significant decrease in nasal congestion, rhinorrhea, anosmia, dyspnea, wheezing, cough, AAER, hospitalization, SCSs use, urine LTE_4 and PGD_2M (all $p < 0.025$) without significant impact on FEV1 after one year of treatment	
Omalizumab	Open label study [123]	16	Efficacy of omalizumab in patients with AERD	Improvement in VAS nasal congestion, rhinorrhea, hyposmia, facial pain, RSOM-31 score, NPS, ACT score, and FEV1 with decrease of therapeutic pressure for asthma control during 9 months of treatment (all $p < 0.05$)	
Mepolizumab	Subgroup analysis RCT [127]	108	Impact of mepolizumab in patients with AERD	Higher proportion of patients with improvement ≥1 point in NPS in the mepolizumab group vs placebo (51.1% vs 20.6%) and >3 points in nasal obstruction VAS score (64.4% vs 30.2%) during weeks 49–52	Increased proportions of patients with significant improvement of overall symptom VAS score, loss of smell VAS score, SNOT-22 score and decrease in SCSs use in the mepolizumab group vs placebo
Mepolizumab	RWS [128]	14	Efficacy of mepolizumab in patients with AERD	Decrease in SNOT-22 score ($p = 0.005$) and BEC ($p = 0.001$) with increase of ACT score ($p = 0.002$) but no significant impact on FEV1 at 3 months	No patients requiring sinus surgery or SCS use
Dupilumab	Post-hoc analysis RCT [133]	204	Efficacy of dupilumab in patients with NP with and without AERD	Improvement in NPS, olfaction, NCS, TNSS, LMS, SNOT-22 score, rhinosinusitis severity VAS score, PNIF, and ACQ score with dupilumab vs placebo (all $p < 0.001$) in patients with AERD at week 24 with greater benefits in this group than those without AERD for NCS, TNSS, SNOT-22 score, and PNIF (all $p < 0.05$).	
Dupilumab	Open label study [134]	22	Impact of dupilumab in patients with AERD	Improvement in UPSIT score, NPS, SNOT-22 score, PNIF, ACQ score, FEV1 and FVC (all $p < 0.005$) after 1 month of treatment, sustained at 3 months, with decrease of nasal and urinary LTE_4 levels and increase of nasal PGE_2 levels (all $p < 0.03$)	
Dupilumab	Open label study [140]	30	Effects of dupilumab on clinical outcomes and oral aspirin challenge test results in patients with AERD	Significant improvement in NPS, TNSS, UPSIT score, SNOT-22 score, ACT score, FEV1 and MEF_{50} (all $p < 0.05$) during 6 months of treatment with complete aspirin tolerance achieved in 23% of patients and partial aspirin tolerance in 33% of patients	
Tezepelumab	Subgroup analysis RCT [16]	408	Efficacy of tezepelumab on NPS and NCS in patients with NP with and without AERD	Improvement in terms of LS mean NPS (−2.0 [−2.8, −1.2] vs −2.1 [−2.4, −1.7]) and NCS (−1.1 [−1.5, −0.7] vs −1.0 [−1.2, −0.8]) compared to placebo in patients with AERD and NP without AERD at 52 weeks of treatment	
Tezepelumab	Post-hoc analysis RCT [143]	43	Benefits of tezepelumab in patients with AERD	Reduction of AAER by 79%, improvement in ACQ score, AQLQ score, SGRQ score, SNOT-22 score and FEV1 at week 52 in patients receiving tezepelumab compared to placebo with complete response achieved in 71.4% of patients	

AAER: annualized asthma exacerbation rate; ACQ: asthma control questionnaire; ACT: asthma control test; AQLQ: asthma quality of life questionnaire; BEC: blood eosinophil count; FEV1: forced expiratory flow in one second; FVC: forced vital capacity; LS: least-squares; LTE_4: leukotriene E_4; LMS: Lund-Mackay score for sinus CT scan; MEF_{50}: maximal expiratory flow at 50% of forced vital capacity; NCS: nasal congestion score; NPS: nasal polyps score; PNIF: peak nasal inspiratory flow; PGD_2M: prostaglandin D2 metabolite; PGE_2: prostaglandin E2; RCT: randomized clinical trial; RWS: real-world study; RSOM: rhinosinusitis outcome measurement; SNOT-22: 22-item sino-nasal outcome test; SCSs: systemic corticosteroids use; SGRQ: St Georges's Respiratory Questionnaire; TNSS: total nasal symptom score; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analog scale.

Table 4
Biologics efficacy in patients with CSU and AD.

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary outcomes
Omalizumab	RCT [146]	335	Safety and efficacy of omalizumab in patients with moderate-to-severe CSU symptomatic despite antihistamine and/or antileukotrienes therapies	Favorable safety profile with significant improvement in ISS at week 12 in the omalizumab group vs placebo sustained to week 24 (both $p < 0.001$)	Improvement in UAS7, CU-Q_2OL score, DLQI from baseline to week 12 in the omalizumab group vs placebo, sustained to week 24 (all $p < 0.001$)
Omalizumab	Open label study [151]	117	Impact of omalizumab in patients with CSU antihistamine refractory	Significant improvement in UAS7 ($p < 0.001$) at 3 months of treatment	Concomitant improvement in UCT score, CU-Q_2OL score and DLQI from baseline to 3 months, sustained at 6 months (all $p < 0.001$)
Mepolizumab	Open label study [156]	10	Efficacy of mepolizumab in antihistamine-refractory CSU	Only 30% of patients with ≥95% reduction in baseline UAS7 after 10 weeks of treatment	
Benralizumab	RCT [154]	155	Clinical efficacy of benralizumab in patients with antihistamine-refractory CSU	No significant differences in change of ISS7 from baseline to week 12 and 24 between the benralizumab group and placebo	No significant changes in UAS7 and HSS7 in patients receiving benralizumab vs placebo at week 12 and 24
Dupilumab	RCT [152]	246	Efficacy and safety of dupilumab in patients with symptomatic CSU despite antihistamines	Significant changes in ISS7 from baseline to week 24 in the dupilumab group (pretreated or not with omalizumab) vs placebo ($p < 0.05$)	Improvements in UAS7 and HSS7 in the dupilumab group vs placebo at week 24 (all $p < 0.05$) with significant changes in UCT score only in omalizumab-naïve patients ($p < 0.001$) and good tolerability
Dupilumab	RWS [153]	7	Benefits of dupilumab in patients with omalizumab-refractory CSU	Significant improvement in UAS7 after 16 weeks of treatment in patients with omalizumab-refractory CSU ($p < 0.001$)	
Tezepelumab	RCT [155]	183	Efficacy of tezepelumab in patients with antihistamine-refractory CSU	No significant change in UAS7 between the tezepelumab group and placebo from baseline to week 16	
Omalizumab	RCT [167]	62	Efficacy of omalizumab in pediatric population with severe AD	Significant improvement in SCORAD from baseline to week 24 in the omalizumab group vs placebo ($p \leq 0.02$)	Concomitant improvement in EASI and DLQI (all $p < 0.05$)
Mepolizumab	RCT [169]	40	Effects of mepolizumab in AD	No clinical success on PGA score in the mepolizumab group vs placebo after 2 weeks of treatment	No significant changes in SCORAD and pruritus score between groups
Benralizumab	RCT [170]	194	Impact of benralizumab on moderate-to-severe AD symptomatic despite topical therapy	No significant difference in IGA score between the benralizumab group vs placebo at week 16	No significant benefits on EASI, pruritus score, SCORAD, DLQI, and POEM score in the benralizumab group vs placebo
Dupilumab	RCT [160]	1379	Efficacy of dupilumab in patients with moderate-to-severe AD inadequately controlled by topical treatment	Higher proportions of patients with significant improvement in IGA score at week 16 in the dupilumab group vs placebo (36–38% vs 8–10%, all $p < 0.001$)	Concomitant improvements of EASI, SCORAD, pruritus score, GISS, DLQI, POEM score, and HADS in the dupilumab group vs placebo (all $p < 0.001$)
Dupilumab	RWS [161]	27	Efficacy of dupilumab in patients ≥12 years-old with moderate-to-severe AD	Significant reduction in EASI, pruritus score, sleep disturbances, and DLQI from baseline to week 24 (all $p < 0.001$)	
Dupilumab	Post-hoc analysis RCT [165]	2444	Efficacy of dupilumab in patients with AD and asthma, NP or both conditions	Concomitant improvement in EASI, pruritus, ACQ and SNOT-22 scores (all $p < 0.05$) at week 16 in the group receiving dupilumab vs placebo	
Dupilumab	Post-hoc analysis RCT [166]	162	Impact of T2-comorbidities on the response to dupilumab in young children with AD	Higher proportions of patients achieving improvement in AD scores in the dupilumab group vs placebo at week 16 in children aged 6 months to 5 years with or without T2-comorbidities such as FA, asthma and AR (all $p < 0.05$)	
Tezepelumab	RCT [171]	113	Efficacy of tezepelumab in patients with moderate-to-severe AD	No significant difference in EASI between the tezepelumab group and placebo at week 12	No differences in terms of IGA score and SCORAD between groups
Omalizumab	RWS [168]	310	Impact of omalizumab in adult patients with SAA and T2-comorbidities	Significant improvement in ACT score, SCSs use, FEV1 and FeNO after 12 months of treatment (all $p \leq 0.003$) with benefits on skin conditions reported by 85.7% of patients with CSU and 82.1% of patients with AD	

ACQ: asthma control questionnaire; ACT: asthma control test; CU-Q_2OL: chronic urticaria quality-of-life questionnaire; DLQI: dermatology life quality index; EASI: eczema area and severity index; FEV1: forced expiratory flow in one second; FeNO: fractional exhaled nitric oxide; GISS: global individual signs score; HSS7: weekly hives severity score; HADS: Hospital Anxiety and Depression Scale; IGA: investigator global assessment; ISS: itch severity score; POEM: patient-oriented eczema measure; PGA: physician's global assessment of improvement; RCT: randomized controlled trial; RWS: real-world study; SCORAD: scoring atopic dermatitis; SNOT-22: 22-item sino-nasal outcome test; SCSs: systemic corticosteroids use; UAS7: urticaria activity score (UAS) over 7 days; UCT: urticaria control test.

Table 5
Efficacy of biologics on IgE-mediated FA and EoE.

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary outcomes
Omalizumab	RCT [174]	180	Efficacy and safety of omalizumab in pediatric population with multiple FA	67% of patients receiving omalizumab for 16 weeks able to ingest ≥600 mg peanuts without dose-limiting symptoms compared to 7% in the group placebo ($p < 0.001$)	Higher proportions of patients able to ingest ≥1000 mg milk, egg or cashew without dose-limiting symptoms in the omalizumab group compared to placebo (all $p < 0.001$) with good tolerability
Omalizumab	RCT [176]	20	Impact of omalizumab on food allergen thresholds in children with FA	Higher proportion of children with increased thresholds by ≥2-steps in the omalizumab group vs placebo after 3 months of treatment (10% vs 33.3%, $p = 0.003$)	Increased threshold up to 44,000 mg after treatment with omalizumab vs 13–443 mg before treatment
Omalizumab	Open label study [175]	14	Kinetics of clinical response to omalizumab in patients with peanut allergy	Significant increase in the threshold during OFC at week 8 and 24 of treatment with omalizumab compared to baseline (both $p \leq 0.005$)	
Omalizumab	RWS [179]	15	Effects of omalizumab on food threshold tolerability in children treated for SA	Increase in the allergen threshold from a mean 1012.6 ± 1464.5 mg protein to 8727 ± 6463.3 mg after 4 months of treatment ($p < 0.001$)	Complete tolerance during OFC obtained in 70.4% of patients with significant improvement of PedsQL score after 4 months of treatment ($p < 0.001$)
Omalizumab	RCT [181]	37	Efficacy of omalizumab in conjunction with peanut OIT in patients with peanut allergy	Increased peanut tolerated dose after 12 weeks of treatment with omalizumab vs placebo (250 vs 22.5 mg, $p < 0.001$)	Higher proportion of patients receiving omalizumab with tolerance of 2000 mg of peanut protein at week 20 compared to placebo (73.9% vs 12.5%, $p < 0.01$)
Dupilumab	Open label study [184]	24	Proportion of patients achieving tolerability of ≥444 mg peanut protein during OFC on treatment with dupilumab	Only 8.3% of patients achieving tolerability of ≥444 mg peanut protein during OFC after 24 weeks of treatment	
Dupilumab	RCT [185]	148	Effects of dupilumab added to OIT in pediatric patients with peanut allergy	A 20.2% increase in the number of patients achieving tolerability to 2044 mg of peanut protein in the group dupilumab + OIT vs placebo + OIT ($p < 0.05$) at weeks 28–40	
Omalizumab	RCT [192]	30	Impact of omalizumab on symptoms and tissue eosinophil count in patients with EoE	No differences between the omalizumab group and placebo concerning dysphagia score and tissue eosinophil count after 16 weeks of treatment	
Omalizumab	Open label study [193]	15	Efficacy of omalizumab in patients with EoE	Improvement in symptom score, endoscopy findings, tissue IgE and eosinophil levels after 12 weeks of treatment (all $p < 0.05$) with full remission in 33% of patients	
Mepolizumab	RCT [194]	66	Impact of mepolizumab on dysphagia and tissue eosinophil count in adolescents and adults with EoE	No significant difference on EEsAI between the mepolizumab group and placebo after 3 and 6 months of treatment	Significant decrease in tissue eosinophil counts and higher rates of histological responses (all $p \leq 0.02$) in the mepolizumab group vs placebo
Reslizumab	RCT [196]	227	Efficacy of reslizumab in children and adolescents with EoE	No significant improvement in the PGA score in the reslizumab group vs placebo after 12 weeks of treatment despite decrease of tissue eosinophil counts ($p < 0.001$)	
Benralizumab	RCT [197]	211	Effects of benralizumab in adult patients with EoE	No difference between the benralizumab group and placebo in the DSQ score at week 24 despite a higher rate of histological response (87.4% vs. 6.5%, $p < 0.001$)	No substantial differences between groups in EREFS and patients' QoL scores
Dupilumab	RCT [187]	321	Efficacy of dupilumab in adolescent and adult patients with EoE non-responsive to PPI	Significant improvements in DSQ score, EoE-HSS, EREFS with higher rates of histological responses in the dupilumab group vs placebo at 24 and 52 weeks of treatment (all $p < 0.001$)	Positive impact of dupilumab on patients' QoL measured by EoE-IQ and EoE-SQ scores compared to placebo

Table 5 (*Continued*)

Biologic	Design	Population	Endpoints	Primary outcomes	Secondary outcomes
Dupilumab	RCT [188]	102	Impact of dupilumab in children 1 to 11 years of age with active EoE refractory to PPI	Higher rates of histological remission in the dupilumab group vs placebo at 16 weeks of treatment (58-68% vs 3%, $p < 0.001$)	Concomitant decrease in tissue eosinophil counts, Eo-HSS score and EREFS in the dupilumab group vs placebo (all $p < 0.001$)
Dupilumab	RWS [190]	46	Efficacy of dupilumab in patients with severe and fibrostenotic EoE	Improvement in symptoms, EREFS, stricture diameter, and tissue eosinophil count with high rate of histological response (all $p < 0.001$) after 6 months of treatment	
Dupilumab	RWS [191]	9	Efficacy of dupilumab in patients with asthma and EoE	Improvement in digestive and asthma symptoms, ELSA score, EREFS, EoE-QoL-A score and FeNO levels after 6 months of treatment	

DSQ: dysphagia symptom questionnaire; EREFS: endoscopic reference score; EoE-QoL-A, Adult eosinophilic esophagitis quality of life questionnaire; EoE-HSS: EoE-histology scoring system; EoE-IQ: EoE impact questionnaire; EEsAI: EoE symptom activity index; EoE-SQ: EoE symptom questionnaire; ELSA, esophagitis live symptoms assessment; FeNO: fractional exhaled nitric oxide; OFC: oral food challenge; OIT: oral immunotherapy; PedsQL: pediatric quality of life inventory; PGA: physician's global assessment of improvement; PPI: proton pomp inhibitor; QoL: quality of life; RCT: randomized controlled trial; RWS: real-world study; SA: severe asthma.

The effects of other T2-biologics on CSU have been disappointing [154–157].

AD is the most common chronic inflammatory skin disease, characterized by eczematous lesions with intense pruritus, causing important socioeconomic burden, particularly in patients with moderate-to-severe disease. Its pathogenesis is complex involving skin barrier dysfunction and immune-mediated inflammation [158]. As part of the "atopic march", AD is frequently associated with AR, asthma, and FA [159]. For long time, treatment options were limited to topical and systemic immunosuppressive agents but recently developed biologics revolutionized AD management [158].

In patients with AD aged ≥6 months, dupilumab improved symptoms and QoL with favorable tolerability in RCTs and RWSs, allowing for its approval as add-on medication to topical treatment in this indication [14,160–163]. Its effects are rapid and persist over time [163,164]. Post-hoc analyses of RCTs including adult patients with asthma, NP and both conditions associated with AD demonstrated concomitant improvements in asthma control, sinonasal and AD outcomes [165]. Dupilumab proved similar effects on AD in children aged 6 months to 5 years with and without T2-comorbidities such as asthma, AR, and FA [166]. Positive impact on AD was also reported for omalizumab in pediatric population [167]. In SA adult patients receiving omalizumab for one year, benefits on AD and CSU were observed in >80% of cases alongside improvement of asthma outcomes [168]. Other T2-biologics showed disappointing results on AD [169–171].

Currently omalizumab and dupilumab are the most effective biologics for CSU. Dupilumab is probably the best therapy for the association AD-SA and should be the first therapeutic choice, while omalizumab represents a good option for treating these patients. Key study results are summarized in Table 4.

Impact of biologics on food-related T2-comorbidities

FAs are hypersensitivity reactions to food allergens that may be IgE-mediated, non-IgE mediated (e.g. EoE) or mixed types (I, IVb and V). Common food allergens include milk, eggs, peanuts, soy, wheat, fish and shellfish [159,172]. In IgE-mediated FA, symptoms occur during the first 2 h after exposure including cutaneous, gastrointestinal, respiratory manifestations and, in severe cases, anaphylaxis [172]. Patients with EoE experience dysphagia, regurgitation, vomiting, food impactions and abdominal pain between 1 and 24 h after ingestion [159,173]. The gold standard for diagnosis of IgE-mediated FA is the oral food challenge (OFC) test and for EoE – the biopsy. Dietary elimination is recommended in both conditions with oral immunotherapy (OIT) for the first one, proton pomp inhibitors and SCSs for the EoE [172]. As FA and asthma frequently coexist and share common pathogenic mechanisms, T2-biologics were tested for FA treatment [159,172].

In patients with IgE-mediated FA, omalizumab significantly increased the tolerated dose of multiple foods and reduced allergic reactions during ingestion in RCTs and RWSs [174–178]. Improvements in FA-related symptoms, food tolerance, and QoL were reported in patients with SA-FA receiving omalizumab in RWSs [179,180]. In association with OIT, omalizumab raises the tolerated dose and the chances for successful desensitization [178,181,182]. Based on these results, the FDA approved omalizumab as add-on therapy for FA. A large post-hoc analysis of RCTs and RWSs showed a comparable efficacy of omalizumab on asthma outcomes in patients with and without FAs [183]. In contrast, dupilumab provided only modest increase in OIT efficacy in children with peanut allergy without any protection against OIT-related anaphylaxis [184,185].

In EoE, dupilumab improved symptoms, endoscopic scores, histology and QoL in RCTs and RWSs, leading to its approval for children and adults in this indication [13,186–190]. In patients with asthma-EoE, improvements in both diseases' outcomes were found after 6 months of treatment with dupilumab [191]. Omalizumab showed limited efficacy in patients with EoE while other biologics showed disappointing results [192–197].

Current evidence suggests that omalizumab should be the preferred treatment for SA patients with IgE-mediated FA and dupilumab for those with EoE. Findings from relevant studies are summarized in Table 5.

Fig. 3 represents the current knowledge on the efficacy of biologics on T2-conditions associated with SA.

Safety and tolerability of biologics available for SA treatment

Systematic reviews and analyses using VigiBase, the World Health Organization global pharmacovigilance database, confirmed the good safety of biologics currently available as treatment for SA in children and adults [198–200]. The most frequently reported drug-related adverse events are injection-site reactions, hypersensitivity, headache, fatigue, upper respiratory tract infections, and pyrexia [199,200]. These are well-known adverse effects related to biologic therapies but other associations, such as malignancies or cardiovascular events, are also reported requiring further assessment and investigation [199]. More limited data is available for tezepelumab as it is the most recently developed. Table 6 sum-

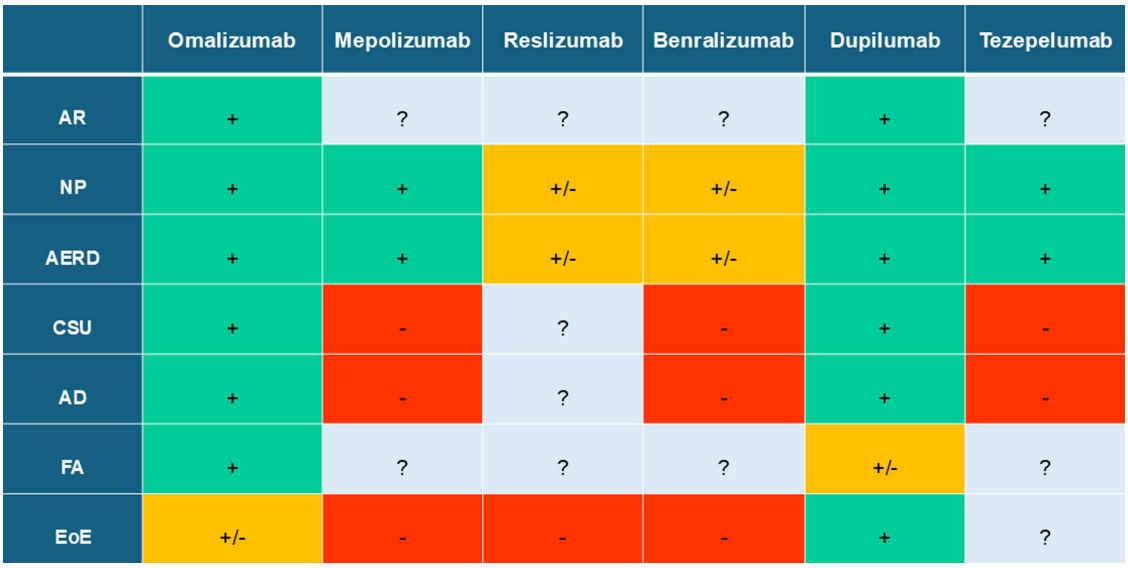


Fig. 3. Current evidence regarding the efficacy of biologics on T2-conditions associated with SA. AR: allergic rhinitis; NP: nasal polyps; AERD: aspirin-exacerbated respiratory disease; CSU: chronic spontaneous urticaria; AD: atopic dermatitis; FA: food allergy; EoE: eosinophilic esophagitis; green (+): undeniable benefits; red (−): absence of benefits; orange (+/−): some benefits; light blue (?): unknown.

Table 6
Safety profile of biologics used as add-on treatment for SA.

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Injection-site reactions	+	+	+	+	+	+
Anaphylaxis	+	+	+	+	+	+
Headache	+	+	+	+	−	−
Pyrexia	+	+	+	+	+	−
Fatigue	+	+	−	−	−	?
Infections and infestations	+	+	+	+	+	−
Skin reactions	+	+	+	+	+	+
Eye disorders	+	+	+	+	+	?
Ear disorders	+	+	+	+	+	?
Blood eosinophilia	−	−	−	−	+	−
Respiratory disorders	+	+	+	+	+	?
Cardiovascular disorders	+	+	+	+	+	?
Endocrine disorders	+	+	+	+	+	?
Gastrointestinal disorders	+	+	+	+	+	?
Hepatobiliary disorders	+	+	+	+	+	?
Renal disorders	+	+	?	+	+	?
Musculoskeletal manifestations	+	+	+	+	+	+
Metabolic diseases	+	+	+	+	+	?
Neurological disorders	+	+	+	+	+	?
Reproductive system disorders	+	+	?	+	+	?
Psychiatric disorders	+	+	+	+	+	?
Malignancies	+	+	+	+	+	?

(+): present; (−): absent; (?): unknown.

marizes current evidence on safety and tolerability of biologics currently used as add-on treatment for SA.

Conclusion

T2-comorbidities are frequent in SA patients and have negative impacts on asthma outcomes, so their management is mandatory to reduce disease burden. Biologics available for the SA treatment proved benefits on T2-comorbidities, and the presence of CRS ± NP, or NP alone may enhance their efficacy on asthma outcomes. This underscores the importance of systematic assessment of comorbidities before initiating biologic therapy. The spectrum of biologics efficacy on T2-comorbidities varies according to their mechanisms of action and should be considered in the choice of biologic for each patient. While choosing the most appropriate therapy in SA patients with a comorbidity for which one biologic proved superior efficacy (e.g. omalizumab for FA, dupilumab for EoE or AD) is evident, the decision-making process becomes more complex in multimorbid patients or those having a comorbidity with multiple treatment options (e.g. NP). Discussion by multidisciplinary team of these cases may be useful. More comparative analyses currently exist for the association SA-NP. Future directions should include more head-to-head trials to better assess the efficacy of biologics across T2-disease outcomes in other associations and SA patients with multiple comorbidities, but also studies evaluating socio-economic burden and patient-reported satisfaction to help physicians in their clinical practice.

Authors' contributions

AT was the promoter of the project. All the authors contributed to the writing and reviewing the manuscript. All the authors approved the submission.

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