Review

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Biologics for atopic diseases: Indication, side effect management, and new developments

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Abstract. With the advent of biologicals, more and more therapeutics are available that specifically address specific switch points in the pathomechanism of immunologically dominated diseases. Thus, the focus of diagnostics and therapy (precision medicine) is more on the individual disease characteristics of the individual patient. Regarding the different phenotypes of atopic diseases, severe asthma was the first entity for which biologicals were approved, followed by urticaria, and finally atopic dermatitis and chronic rhinosinusitis with nasal polyps. Experience in the treatment of severe bronchial asthma has shown that the intensity of the response to biological therapy depends on the quality of clinical and immunological phenotyping of the patients. This also applies to different diseases of the atopic form, as patients can suffer from several atopic diseases at the same time, each with different characteristics. Biologics are already emerging that may represent a suitable therapy for allergic bronchial asthma, which often occurs together with severe neurodermatitis, and chronic rhinosinusitis with nasal polyps. In practice, however, the question of possible combinations of biologicals for the therapy of complex clinical pictures of individual patients is increasingly arising. In doing so, the side effect profile must be taken into account, including hypersensitivity reactions, whose diagnostic and logistical management must aim at a safe and efficient therapy of the underlying disease. Increased attention must also be paid to biological therapy in pregnancy and planned (predictable) vaccinations as well as existing infections, such as SARS-CoV-2 infection. Before starting a biological therapy, the immune status should be checked with regard to chronic viral and bacterial infections and, if necessary, the vaccination status should be refreshed or missing vaccinations should be made up

for before starting therapy. Currently, reliable data on the effect of biologicals on the immunological situation of SARS-CoV-2 infection and COVID-19 are not available. Therefore, research and development of suitable diagnostic methods for detection of immunologically caused side effects as well as detection of potential therapy responders and non-responders is of great importance.

Introduction

The increasing elucidation of pathomechanisms of oncological and inflammatory diseases at the cellular and molecular level and the realization that the focus of diagnostics and therapy must no longer be on the disease itself but on the individual patient (precision medicine) has led to the development of targeted therapeutics in recent years (target treatments). The so-called biologicals are substances that imitate actors of the human organism/immune system and can modulate the immune system in different ways.

The biologics that are the subject of this review are mainly composed of active ingredients of the following substance groups: monoclonal antibodies (mAB), cytokines, and fusion proteins. They act specifically via binding to receptors (activation or inhibition) or via the complexation of active structures with the aim of cancelling their effect (cytokine and antibody inhibitors).

The mAB can be chimera, i.e., they consist of human and murine parts. However, due to their relatively high immunogenicity (< 50 – 75% human) and to increase efficiency, more and more humanized or human mAB have been produced and approved.

Fusion proteins are essentially constructs consisting of a soluble protein and an IgG1 antibody fragment (Fc-part) and can thus represent a ligand or a receptor, depending on the construction design, which has a high affinity to the corresponding target.

The fact that biologicals are constructed according to their target structures should not hide the fact that the respective mechanisms of action have not yet been elucidated and understood in detail. The immune-modulating properties are partly responsible for undesired immunological reactions like hypersensitivity reactions, induction of autoimmune diseases, and immunodeficiency, and for some biologicals also non-immunological side effects have become known, e.g., the acneiform exanthema under cetuximab. Among the immunological side effects, the cytokine release syndrome ("cytokine storm") and anaphylaxis are among the most feared.

Inflammatory diseases already successfully treated with biologicals include psoriasis (and psoriatic arthritis), rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, chronic urticaria, asthma, chronic rhinosinusitis with nasal polyps, and atopic dermatitis.

In the following, the biological therapy of atopic diseases is described, and new approvals or expected approvals are briefly described.

Biologics for the treatment of bronchial asthma

Biologics are used to treat patients with certain phenotypes of severe allergic asthma. Omalizumab with this indication was approved in 2005. Other biologics are now available for the treatment of patients with certain forms of asthma. These include antibodies that block IL-5 (mepolizumab, reslizumab), the IL-5 receptor (benralizumab), or the IL-4 receptor alpha chain (dupilumab) [1].

The applications of these biologics are currently reserved for patients with severe asthma. However, there is no single definition of severe asthma. Several different approaches have been published to define the patient group "severe asthma". The main principle of the definitions is the presence of uncontrolled asthma despite high-dose inhaled anti-inflammatory therapy (inhaled corticosteroids) in combination with another controller (e.g., long-acting beta-2 sympathomimetics). Evaluations of insurance and health insurance data suggest that this definition affects ~ 3 – 4% of patients with asthma [2, 3]. Uncontrolled asthma can be objectified by questionnaires (Asthma Control Test or Asthma Control Questionnaire), the presence of acute worsening (exacerbations), inpatient treatment due to exacerbation, and impaired lung function. It is important to distinguish between patients with

"difficult-to-treat" asthma and patients with "severe" asthma [4]. In the majority of patients whose asthma is not controlled despite high-dose ICS therapy, factors can be identified that are the cause of poor symptom control. These factors include inadequate drug intake (e.g., inadequate inhalation technique, lack of adherence), unidentified or untreated comorbidities (e.g., sleep apnea, obesity, reflux, chronic rhinosinusitis), or persistent trigger factors (allergen sources in the environment). In these patients, the management and correction of these factors is of primary importance, and in a large proportion of patients, control of the disease can be achieved without the use of biologicals. If patients remain symptomatic despite evaluation and treatment of the above-mentioned factors, severe asthma is present. These patients should then be evaluated for the possible use of a monoclonal antibody.

National and international guidelines clearly recommend that any antibody therapy [5, 6] should be preferred to treatment with systemic corticosteroids. Prolonged and repeated treatment with systemic corticosteroids also leads to side effects in patients with asthma [3, 7].

The diagnosis asthma includes patients with different clinical manifestations and different immunological alterations. Therefore, good clinical and immunological phenotyping is necessary to identify patients with a high probability of a response to biological treatment. For the phenotypes severe allergic asthma, asthma with eosinophilic inflammatory response and asthma with type 2 inflammation, antibodies are available. Please note that these phenotypes cannot always be clearly separated from each other, but partly overlap considerably.

Omalizumab has been approved for patients with severe allergic asthma since 2005. In these patients, treatment with omalizumab can contribute to a reduction in the rate of exacerbation, an improvement in symptoms and quality of life and an improvement in lung function. Omalizumab can also reduce the need for systemic steroid therapy [8]. Recent data also show that omalizumab is effective regardless of the type of inflammation detected. A reduction of acute exacerbations has been shown in patients with and without eosinophilic inflammation [9].

In patients with severe asthma and an inflammatory response with eosinophilic granulocytes, three antibodies against the cytokine itself (IL-5) or against the α-chain of the human IL-5 receptor (IL-5Rα) have now been developed and approved for treatment. Mepolizumab and reslizumab are approved as anti-IL-5 antibodies. Clinical studies on these preparations have shown that patients with the detection of an increased number of eosinophilic granulocytes in peripheral blood under mepolizumab experience a significant reduction in exacerbations, an improvement in asthma control, and also an improvement in FEV1 [10]. Similar results have been reported for benralizumab [11], which binds to IL-5Rα as an antibody, and patients with severe asthma and eosinophilia experience a reduction in exacerbations, improvement in symptoms and quality of life, and a slight improvement in lung function [12].

Particularly important are the effects of mepolizumab and benralizumab in patients who require treatment with a systemic steroid due to their asthma. In controlled studies, it was shown that after administration of anti-IL-5 or anti-IL-5Rα, a reduction of systemic steroids or complete discontinuation was possible in patients with steroid-dependent asthma [10, 13]. Despite the reduced steroid dose, there were fewer exacerbations in the treated groups. Since treatment with systemic steroids can have considerable side effects, these results are of considerable relevance. Dupilumab is also approved as another antibody for patients with severe asthma. Dupilumab binds to the alpha chain of the interleukin-4 receptor (IL-4Rα) and thereby inhibits the binding of IL-4 and IL-13 to the respective receptor. Dupilumab has also been shown to reduce exacerbations, improve quality of life and lung function in patients with uncontrolled asthma in whom eosinophilic inflammation or elevated levels of nitric oxide (FeNO) in exhaled air have been detected [14]. Dupilumab has also been shown to significantly reduce the dose of systemic steroids in patients treated with systemic steroids on a long-term basis; in some cases, it was even possible to discontinue them completely [14].

Omalizumab, mepolizumab, benralizumab, and dupilumab have now been approved for self-administration. Since anaphylactic

reactions to biologicals can occur even after months of successful application [15], self-injection at home is a risk that should not be underestimated.

Treatment should be started by physicians experienced with severe asthma. The effectiveness of the treatment with biologicals should be evaluated after 4 months. If the response is not clearly detectable, the evaluation phase can be extended to 12 months. After the start of treatment with biologicals, the previous inhaled and oral asthma therapy should be maintained for at least 4 weeks and only after this time should it be reduced if necessary under close assessment of asthma control.

It should be noted that all biologicals are an add-on therapy and are not approved for monotherapy. In a number of patients, however, the use of biologicals leads to such an improvement in lung function, asthma control test, and symptoms that patients can – and do – completely avoid the further use of inhaled steroids and long-acting beta-mimetics. Without there being any national or international recommendation for these situations, in these cases, an extension of the injection intervals should be considered. For omalizumab, it has already been described that after reaching a controlled stage, it is possible to significantly extend the injection intervals [16], while a reduction or discontinuation of the biological agent usually led to renewed deterioration. For the other biologics, this procedure also appears possible in individual cases, although not corresponding to the approved description of indications.

Biologics for the treatment of urticaria

In urticaria, one biological agent, omalizumab, is currently approved for therapy, and a number of others are currently undergoing clinical trials.

Urticaria is defined as a disease with the sudden appearance of wheals, angioedema, or both. Chronic urticaria is defined as a disease with a course of more than 6 weeks. It is divided into chronic spontaneous urticaria and chronic inducible urticaria. The latter in turn has various subforms, partly triggered by physical stimuli, e.g., cold urticaria, partly by other exogenous factors, e.g., cholinergic urticaria. In accordance with current international guidelines, all chronic forms of urticaria are treated equally according to one algorithm [17]. In the first stage, this algorithm recommends treatment with a non-sedating antihistamine in the single dose, and in case of non-response, a dose increase up to 4 times the single dose is applied in the second stage. In case of further non-response, the additional administration of omalizumab is recommended in the 3rd stage, and in the 4th stage the administration of cyclosporine A is recommended in case of further non-response. The Urticaria Activity Score (UAS), which has been validated for chronic spontaneous urticaria, has been developed to assess the clinical response of urticaria therapy. Itching is measured on a scale of 0 – 3 and the number of wheals on a scale of 0 – 3. This means that the maximum daily value is 6. Since urticaria fluctuates, for response UAS 7 is calculated, i.e., the sum of the daily values over 1 week. The maximum response therefore is 42. 1 week's UAS 7 of 6 or less is currently considered sufficient, although the actual treatment goal is being symptom-free according to the guideline.

The 3rd stage of the algorithm is the administration of omalizumab as an additional therapy to high-dose antihistamine administration. Omalizumab is a humanized monoclonal antibody against IgE. Its efficacy in chronic spontaneous urticaria has been demonstrated in numerous large studies and is 52 – 90% in antihistamine-refractory patients [18, 19, 20, 21].

It's safety profile is also very good. In the clinical trials, the rate of side effects was comparable to placebo. The most commonly reported adverse events included nasopharyngitis, sinusitis, and colds without likely relation to the drug [20, 21, 22, 23]. Anaphylactic reactions have been reported in asthma patients, but these were not observed in the treatment of urticaria, and the drug is now approved as a ready-to-use subcutaneous syringe for self-application. A major advantage of the safety of omalizumab is that no preliminary studies are required, such as the exclusion of tuberculosis in TNF-alpha antagonists and the fact that no antibodies blocking the action of omalizumab have been described. This allows a flexible han-

dling of the drug. The approval documents a fixed dose of 300 mg s.c., which corresponds to two 150-mg syringes, to be administered every 4 weeks. Recent real-life results show, however, that under certain circumstances, if there is no treatment response, it may be appropriate to either shorten the interval or increase the dose [24, 25]. In particular, overweight patients may benefit from an upward dose adjustment. On the other hand, the absence of blocking antibodies allows patients who respond fully to treatment to stop taking the medication after a period of 3 – 6 months without any risk of reducing the effectiveness of the medication when it is reapplied. Although not yet noted in the algorithm in the current guidelines, there is now well-established scientific evidence that in those patients who do not respond to omalizumab 300 mg at 4-weekly intervals, a dose increase to initially 450 mg and possibly also to 600 mg will increase the response rate. A general distinction is made between fast and slow response in different patients. In some patients, the response is almost complete 24 hours after the first dose. Other patients show only a slow improvement of UAS7 over the first 3 months of omalizumab therapy. Although it is not possible to predict with certainty whether a fast or slow response will be observed in individual patients, it is generally true that patients with very low total IgE respond less well or not at all. For those patients who do not respond to omalizumab, the algorithm of the international guideline recommends the administration of cyclosporine A [17]. In practice, however, cyclosporine A can also be combined with omalizumab.

Omalizumab has revolutionized the treatment of chronic spontaneous urticaria but is also effective in the treatment of chronic inducible urticaria [22, 26]. Study results – or at least case series – are now available for most forms of inducible urticaria.

Due to the efficacy of omalizumab, the first commercially available anti-IgE antibody, the significance of IgE-antibodies directed against endogenous structures has become more evident. Not only is total IgE elevated on average in patients with urticaria, but anti-dsDNA, anti-thyroid globulin, and anti-thyroid peroxidase IgE are also found in a number of patients [27, 28]. Against this background, further biologics have been developed and are currently in various stages of clinical testing. The most advanced are the phase 3 studies on ligelizumab, a humanized IgG1 antibody directed against the Ce3 domain of IgE. Compared to omalizumab, it shows significantly higher inhibition of IgE binding to the high-affinity IgE receptor but lower inhibition of IgE binding to the low-affinity receptor CD23 [29].

Biologics for the treatment of atopic dermatitis

The first biological agent approved for the treatment of atopic dermatitis is dupilumab, a recombinantly produced human IgG4 monoclonal antibody. The antibody specifically targets the common IL-4Rα subunit of type 1 and type 2 IL-4 receptors and thus blocks not only interleukin 4 but also interleukin 13 and thus two key cytokines of atopic inflammation. Dupilumab was approved by the European Medicines Agency (EMA) at the end of 2017 for adults with moderate to severe atopic dermatitis after an extensive study program with two successful placebo-controlled phase 3 studies [30], a long-term study over 1 year in which topical corticosteroids were allowed to be used in the comparative arm [31]. In autumn 2019, approval was granted for children from 12 years of age and adolescents, after a placebo-controlled study was successfully completed in this age group as well [32]. A phase 3 study in the age group of 6- to 11-year-old children has been completed, but has not yet led to an extension of the approval [33].

The approval of dupilumab for the indication of atopic dermatitis represents a milestone in the treatment of moderate to severe forms of this disease, since apart from corticosteroids, which, according to the guidelines, should only be used as an interventional therapy for a maximum of 3 weeks in adults, until then only cyclosporine for the treatment of atopic dermatitis from the age of 16 had been approved. In the updated AWMF guideline for the systemic treatment of atopic dermatitis, dupilumab was included in the 2020 recommendations [34].

The neurodermatitis registry TREAT-germany recorded a correspondingly large number of patients with moderate to severe

atopic dermatitis who have been treated with the antibody since then, while according to registry data cyclosporine and other "off-label" immunosuppressants have been used significantly less frequently for the indication atopic dermatitis since then [35]. Under "real-life conditions" of the German neurodermatitis registry TREATgermany, the efficacy under treatment with dupilumab in terms of improvement of severity and subjective symptoms was in a similar spectrum as in the previously published phase 3 studies [36].

The main side effects of dupilumab occur in the eye, with non-allergic conjunctivitis and other changes in the eye occurring exclusively as a side effect in patients with atopic dermatitis (and not in patients with allergic bronchial asthma or chronic rhinosinusitis with nasal polyps). There are a number of speculations on the pathomechanism, each of which sounds plausible, but which have not been verified to date [37]. Fortunately, most patients who develop (peri-)orbicular changes (~ 10 – 15% of all patients on dupilumab therapy) are able to continue therapy with symptomatic treatment [38].

In view of the ongoing SARS-CoV-2 pandemic, two meta-analyses on the frequency of infections under dupilumab therapy are important to show that there has been no increase in systemic infections under therapy with the antibody in controlled studies. Herpes infections of the skin were also not observed in controlled studies. With regard to the dreaded Eczema herpeticatum, even a clear protection could be achieved by effective therapy with dupilumab (OR 0.34), the same applies to bacterial skin infections (OR 0.54) [39, 40].

Fortunately, the antibody was also approved in 2019 for the treatment of allergic bronchial asthma, which often occurs together with severe neurodermatitis, so that in this case, two atopic diseases can now be treated with one antibody. With chronic rhinosinusitis with nasal polyps (see below), dupilumab was recently approved for another disease that often occurs together with atopic dermatitis.

Hardly any other disease is currently so much in the focus of ongoing clinical studies with innovative drugs as atopic dermatitis. In the last 1.5 years alone, phase 2 studies with 6 further monoclonal antibodies were published as full papers [summarized under 41]. The most advanced clinical developments are the antibodies tralokinumab (anti-IL-13) and nemolizumab (anti-IL-31R), which have been shown to be effective in both eczema severity and subjective symptoms, especially pruritus. Lebrikizumab, another anti-IL-13 antibody, also showed convincing efficacy in a recently published phase 2 study, while fezakinumab (anti-IL-22), etokimab (anti-IL-33), and tezelumab (anti-TSLP) have only been the subject of smaller proof-of-concept studies for the indication atopic dermatitis [summarized in 41].

Biologics for the therapy of chronic rhinosinusitis with nasal polyps

The prevalence of chronic rhinosinusitis (CRS) is ~ 10 – 15% of the population in developed countries, which means a significant cost to health systems and economies [42, 43]. While the current phenotype classification is based on endoscopic examination of the nasal cavity or imaging techniques and divides CRSs into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) [42, 44, 45], the focus of interest is increasingly shifting to the causative inflammatory pathomechanisms, according to which an endotype classification could be undertaken as soon as there is an internationally accepted consensus, and easy-to-identify and reliable biomarkers are developed [46].

Several studies have investigated the anti-IgE-antibody omalizumab in CRSwNP [47, 48, 49, 50]. A significant reduction of the nasal polyp score was shown in a randomized, double-blind placebo-controlled (DBPC) study in patients with CRSwNP and comorbid asthma [51]. Here, omalizumab therapy showed an effect on polyp scores comparable to a 3-week oral steroid treatment.

A phase 2 study investigated the effect of omalizumab on CT morphological shading in the anterior ethmoid bone and maxillary sinus (polyp CT score) [52]. Two parallel double-blind, placebo-controlled phase 3 studies with omalizumab in CRSwNP (POLYP 1 and POLYP 2) investigated efficacy

and tolerability in a large number of patients [53]. Compared to placebo, omalizumab showed statistically significant reductions in nasal polyp scores, nasal obstruction and other symptoms of CRSwNP.

Omalizumab has been approved in Germany in 2020 as an adjunct therapy to intranasal corticosteroids (INCS) for the treatment of adults with severe CRSwNP in whom therapy with INCS does not provide adequate disease control.

Two different strategies are available to block the IL-5-mediated inflammatory response: elimination of circulating IL-5 and blockade of the IL-5 receptor (IL-5R) on eosinophils and basophils [54, 55, 56].

In the treatment of steroid-refractory CRSwNP with mepolizumab, a significant improvement of polyp scores in CT and endoscopy and an improvement of olfactory function could be demonstrated even in the long-term effect 9 months after end of therapy [57]. A further study with mepolizumab to avoid the need for surgical sinus surgery using mepolizumab vs. placebo is currently still pending [58], as is the publication of the results of the pivotal phase 3 study [59].

The IL-5 antibody reslizumab has been tested in several placebo-controlled studies in asthma patients with comorbid nasal polyps and has been shown to improve quality of life [60, 61]. Also for the sole indication CRSwNP, promising results were obtained [62] with regard to polyp scores in CT of the paranasal sinuses and symptoms.

Anti-IL5- and anti-IL-5R biologics such as benralizumab and TPI ASM8 [63] have not been used in nasal polyposis, but a DBPC phase 3 study to evaluate benralizumab in patients with CRSwNP is currently being completed (OSTRO study) [64].

Studies with anti-IL-4/anti-IL-13 antibodies aim to reduce pro-inflammatory markers of the Th2-mediated inflammatory response. The receptors of both cytokines share a common subunit (IL-4Rα), therefore blocking this subunit and thus both cytokines is a promising option [65, 66, 67]. In the indication CRSwNP, the monoclonal anti-IL-4Rα antibody dupilumab was evaluated in a DBPC phase 2 study over a treatment period of 4 months with significant improvements under dupilumab therapy for the primary endpoint of endoscopic polyp score [68].

In two phase 3 clinical trials (SINUS-24 and SINUS-52) with large patient numbers, dupilumab treatment in severe CRSwNP resulted in a statistically significant reduction in polyp size, reduction of shadows in the CT of the paranasal sinuses and improvement of disease symptoms [69].

Dupilumab has been approved in Germany since 2019 as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP that cannot be adequately controlled with systemic corticosteroids and/or surgery.

Biologics for the treatment of hereditary angioedema

In hereditary angioedema (HAE), recurrent edema of the skin and mucous membranes occurs in attacks. The prevalence of HAE is ~ 1 in 50,000 [70]. The cause of autosomal-dominantly inherited HAE type 1 and type 2 is a genetic defect in chromosome 11 that leads to a deficiency or malfunction of the C1 inhibitor (C1-INH). Other C1-INH-independent types are caused by mutations of factor XII, plasminogen, or angiopoetin. In addition, there appear to be other, as yet unidentified mutations [70, 71]. The kallikrein-kinin system, C1-INH, and bradykinin play an important pathophysiological role. In addition to the administration of C1-INH preparations, drugs that act on the bradykinin system are now also used therapeutically in HAE [71]. Depending on the frequency and severity of the attacks, a distinction must be made in the care of HAE patients between acute treatment, short-term and long-term prophylaxis [71].

In early 2019, lanadelumab, a new drug for the long-term prevention of HAE, became available on the German market. Lanadelumab is a recombinant, fully humanized immunoglobulin G1-kappa light chain monoclonal antibody [72]. Subcutaneous administration is performed regularly every 14 days; an extension of the dose intervals is possible. Due to the highly potent and specific inhibition of plasma kallikrein, lanadelumab leads to a sustained inhibition of plasma kallikrein activity [72]. The efficacy and safety of lanadelumab for the long-term prevention of HAE attacks in patients with confirmed

C1-esterase-inhibitor-induced HAE aged 12 years and older has been investigated in several studies. The studies showed a significant reduction in the attack rate of HAE in the actively treated groups compared to placebo and an increase in the percentage of patients without attacks. Treatment with lanadelumab was generally safe and well tolerated, with local reactions at the injection site being the most common treatment-related adverse events [73, 74, 75]. Garadacimab (CSL132, NCT03712228), a human IgG4 antibody for subcutaneous administration, is another biological agent in clinical trials for use in HAE. Garadacimab binds and inhibits activated factor XIIa, thereby inhibiting bradykinin formation and preventing the development of HAE attacks. In a phase 2 study in 32 patients with C1-INH-dependent HAE, a significant reduction in the number and severity of attacks was achieved in the three actively treated groups compared to placebo. Mild local reactions were observed in 12.5% [76].

Biologics for the treatment of food allergy

IgE-mediated food allergy is a potentially life-threatening disease for the treatment of which there is no approved biological agent yet. Based on the pathophysiology of the disease or the mechanism of action of omalizumab, it is believed that this substance is effective in IgE-mediated food allergy. Accordingly, numerous case series and individual controlled prospective studies with a limited number of cases, mostly in children, show that omalizumab is effective as monotherapy or in combination with oral immunotherapy.

Monotherapy with anti-IgE can raise the tolerance threshold of the food allergen in question. Most cases have been reported with peanuts [77, 78], but other foods such as cow's milk [79] and hen's egg have also increased the maximum tolerated dose after several months of treatment with anti-IgE [80]. A recent study investigated the efficacy of anti-IgE treatment in children who were allergic to several foods [81]. The results of the study show that the group treated with omalizumab was significantly more likely to reach 2 g protein in more than 2 of the food allergies compared to placebo.

These data show that even in patients with several food allergies, omalizumab can improve the efficacy of oral immunotherapy.

Another therapeutic approach is to reduce the rate of side effects or to enable a faster dosage of the food allergen by administering anti-IgE during oral immunotherapy. Again, the study results show efficacy of omalizumab in peanut-allergic children [82] as well as in patients with multiple food allergies compared to placebo-treated patients [83, 84].

In summary, the data available to date are promising with very good tolerability, but there are still open questions such as the optimal dose and the treatment regimen.

The next-generation anti-IgE ligelizumab is of future interest. It has already shown very good results in the treatment of chronic spontaneous urticaria. Due to its biological properties, it will be an interesting new molecule for the treatment of food allergy in the future.

Dupilumab also has potential for clinical use in food allergy due to its ability to downregulate the IgE response during treatment. First studies have started, and the results are eagerly awaited. Ultimately, the great hope is that safe and effective new biologically active substances for food allergy will be available for therapy to effectively treat patients with potentially life-threatening diseases [85].

Hypersensitivity reactions to biologicals

Among the adverse effects of biologicals, the "cytokine storm" and the IgE- and non-IgE-mediated anaphylactic/anaphylactoid reaction are the most feared. Pichler [86] classified the side effects of biologicals into five types (alpha, beta, gamma, delta, epsilon) and thus made the sometimes very unusual adverse events clinically more comprehensible in terms of diagnostics, therapy, and prevention. Only the alpha- and beta-type reactions will be discussed in more detail here.

Type alpha reactions are based on a direct effect on immune stimulation by cytokine release. They are direct substance-dependent, dose-dependent effects right from the first application. They are among the most fre-

quent reactions and decrease again in the course of therapy.

Type beta reactions are hypersensitivity reactions, including allergies of type I – IV, i.e., immune reactions to the therapeutic protein. They are unpredictable, do not occur during first application apart from the anaphylaxis due to cetuximab (see below), and are rather independent of the dose.

Both types of reaction can be life-threatening and may produce symptoms that meet the anaphylaxis criteria. To date, the non-IgE-mediated response and the "cytokine storm" are not fully pathophysiologically/mechanistically understood, making classification difficult [87]. These reactions are important not only because they can be life-threatening, but also because their symptomatology generally leads to the termination of the triggering biological therapy, which is very detrimental to patients with regard to their underlying disease. Therefore, the goal must be to understand these reactions fundamentally and to diagnose them more reliably in order to derive a better management of these severe side effects in favor of a safe and efficient therapy of the underlying disease.

On the other hand, the therapy of the cytokine release syndrome is different from that of anaphylaxis!

A temporary discontinuation of the biological therapy and a new start with slower infusion rate as well as premedication with antihistamines and glucocorticoids can be helpful. In case of anaphylaxis, premedication does not help causally. Furthermore, the risk of subsequent anaphylaxis is high [87]!

However, a comprehensive review of databases and scientific literature has shown that, on the one hand, the nomenclature of hypersensitivity reactions to biologicals is not harmonized, so that data on the prevalence and incidence of "real" allergic and anaphylactic reactions to the various biologicals cannot be reliably collected [88, 89]. Furthermore, the symptomatology of anaphylaxis may vary between different biologicals [87]. Only the careful characterization of patients with such reactions in registries will be able to remedy this situation.

The immunogenicity of biologics depends mainly on the degree of their humanization: Chimeric monoclonal antibodies, such as cetuximab and infliximab, which are produced in a mouse hybridoma cell line (SP2/0), have immunogenic murine components. The now best-known IgE epitope is the disaccharide alphaGAL, which was discovered by anaphylaxis due to cetuximab after initial application with detection of pre-existing IgE antibodies against this structure and is also responsible for the delayed anaphylaxis due to mammalian meat. The main sensitization pathway is now considered to be tick bites, in the USA the species *Amblyomma americanum* is responsible [90]. Another association with anti-alphaGal IgE has only been described for infliximab [91]. There are reports of IgE antibody detection against biologicals that triggered anaphylactic reactions (summarized by Joshi and Khan, 2019 [87]). A group of Italian authors showed that patients with IgE against the relevant biological in serum and/or skin tests with this biological reacted more rapidly (3rd dose) and more severely [92, 93]. To date, there is no routine procedure available for this. (The detection of antibodies directed against biologicals in sera of treated patients is routinely performed only for the detection of neutralizing antibodies, which are mostly of the IgG type).

However, the fact that the degree of humanization of biologicals reduces their immunogenicity does not exclude the formation of anti-drug antibodies (ADA) against non-self sequences of fully human therapeutic antibodies [86].

Anti-infliximab IgG is detectable in sera of patients with anaphylaxis due to infliximab during infusions [92, 94] as well as IgM, but the clinical relevance of IgM remained unclear. Matucci et al. [93] and Hwang et al. [95] described the possibility of using anti-infliximab antibody detection to assess the risk of developing a reaction.

For patients living in endemic areas with a high prevalence of alphaGAL sensitization, the determination of IgE antibodies against alphaGAL prior to cetuximab administration is useful [90, 96]. For this purpose, alphaGAL is available in the form of bovine thyroglobulin in the ImmunoCAP (ThermoFisher Scientific/Phadia, Freiburg, Germany).

However, additives such as polysorbate, mannitol, albumin, latex, trometamol, and papain [89, 97] can also cause allergic reactions to biologicals and should be included in the allergological investigation.

Table 1. Published reports on the frequencies of hypersensitivity reactions to biologics.

Biologic	Target	Author	Year	HSR	IR	ISR	Urticaria	Anaphylaxis
Omalizumab	IgE	Cox et al. [136]	2007	< 0.2		–	–	0.09
		Di Bona et al. [137]	2017	–		3.4	1.0	0
		FDA [138][a]	2019	–		12.0 – 45.0	0.2	0.1
		FDA [138][b]	2019	–		0.6 – 2.7	–	–
		EMA [139]	2019	–		1.0 – 10.0	0.1 – 1.0	0.2
Ligelizumab	Cε3 domain of IgE	Gauvreau et al. [140]	2016	–		12.5–25.0	0	0
		Maurer et al. [141]	2019	–		4.0–7.0	–	0
Mepolizumab	IL-5	Pavord et al. [142]	2012	≤ 1.0	5.0 – 12.0	–	–	0
		Lugogo et al. [143]	2016	< 1.0	< 1.0	3.0	–	0
		Khatri et al. [144]	2019	2.0	–	12.0	–	0
		FDA [145]	2019	1.0 – 4.0	–	8.0 – 15.0	–	–
		EMA [146]	2019	1.0 – 10.0	1.0–10.0	1.0 – 10.0	–	0.1 – 0.01
		Chapman et al. [147]	2019	< 1.0	–	3.0	< 1.0	0
Reslizumab	IL-5	Castro et al. [60]	2015	–	–	1.0 – 2.0	–	< 1.0
		Murphy et al. [148]	2017	< 1.0	< 1.0	< 1.0	< 1.0	0
		FDA [149]	2019	–	–	–	–	0.3
		EMA [150]	2019	0.19	0.19	–	–	0.19
		Bernstein et al. [151]	2020	0	–	6.0 – 11.0	–	–
Benralizumab	IL-5Rα	Castro et al. [152]	2014	–		16.0	–	–
		Park et al. [153]	2019	–		0	0 – 2.0	–
		Liu et al. [154]	2019	–		2.6 – 17.5	–	–
		FDA [155]	2019	3.0		2.2	3.0	3.0
		EMA [156]	2019	1.0 – 10.0		2.2	–	?
		Bourdin et al. [157]	2019	0 – 3.2		3.2 – 6.5	–	–
Dupilumab	IL-4Rα	Ou et al. [158]	2018	–		13.2	–	–
		EMA [159]	2019	3.0 – 4.3		16.0 – 20.1	0.5 – 1.3	0.2
		FDA [160]	2020	< 1.0		10.0	< 1.0	< 1.0
Lanadelumab	Plasma kallikrein	FDA [161]	2018	1.0		45 – 57.0	–	–
		EMA [162]	2020	1.2		52.4	–	–
Lebrikizumab	IL-13	Hanania et al. [163]	2015	0 – 0.9		11.1 – 20.5	–	0 – 0.9
		Hanania et al. [164]	2016	–		6 – 10.0	–	< 1.0
		Simpson et al. [117]	2018	–		1.3	–	0
		Korenblat et al. [165]	2018	–		2.9	–	1.0
Tralokinumab	IL-13	Wollenberg et al. [166]	2019	–		5.2	–	–
		Panettieri et al. [167]	2018	–		4.0 – 5.4	–	0
		Busse et al. [168]	2019	–13.2 – 25.9		15.7	–	0
		Carlsson et al. [169]	2019			–	< 1.0	0
Secukinumab	IL-17A	EMA [170]	2015	6.5–11.2		5.6	< 1.0	0
		Blauvelt [171]	2016	–		0.7	–	–
		Deodhar et al. [172]	2019	2.4		0.8 – 1.3	–	–
		FDA [173]	2020	–		–	0.6 – 1.2	–
		EMA [174]	2020	–		–	0.1 – 1.0	< 0.1
		Grace et al. [175]	2020	–		25.0	–	–
Fezakinumab	IL-22	–	–	–	–	–	–	–
Nemolizumab	IL-31Rα	Nemoto et al. [176]	2016	–	–	–	–	0
		Kabashima et al. [120]	2018	–	–	2.0	2.0–6.0	–
		Silverberg et al. [177]	2020	–	–	1.8 – 3.5	–	–
		Ständer et al. [178]	2020	–	–	3.0	–	–
Etokimab	IL-33	Chen et al. [121]	2019	–	–	25.0	16.7	–
		Chinthrajah et al. [179]	2019	–	–	26.7	6.7	0
Ustekinumab	IL-12/IL-23	Ghosh et al. [180]	2019	< 1.0	0.1	–	< 1.0	0
		FDA [181]	2020	0.08	–	1.0 – 2.0	< 1.0	0.1
		EMA [182]	2020	0.1 – 1.0	0.1	0.1 – 1.0	–	0.01 – 0.1

[a]Results of clinical studies with asthma in FDA 2019 label; [b]results of pooled Chronic Idiopathic Urticaria trials in FDA 2019 label. HSR = hypersensitivity reaction; IR = infusion reaction, substance-specific; ISR = injection-site-reaction.

For the biologicals listed in this overview under the various indications for the therapy of atopic diseases, the frequency of hypersensitivity reactions is shown in Table 1 and Figure 1 according to the research on data bases. Recently, the case of a serum disease-like reaction to dupilumab was described [98].

Table 2. Laboratory tests before administration of immunosuppressive or immunomodulating drugs.

Virus	Test
Hepatitis B virus	– Anti-HBS quantified – HBs antigen, anti-HBs, and – Anti-HBc
Hepatitis C virus	(Anti-hepatitis C)
Hepatitis A virus	(Anti-HAV IgG)
Epstein-Barr virus	Anti-EBV
Cytomegalovirus	Anti-CMV IgG and IgM
Herpes virus	Anti-HSV q and 2: IgG and IgM
Varizella-Zoster virus	Anti-VZ IgG
Syphilis	VDRL or TPPA

The diagnostic measures to detect a rather rare IgE-mediated adverse reaction are, in addition to the medical history (occurrence and progression of the reaction in the course of therapy, relative independence from the administered dose, method of application, duration of therapy and therapy pause, if applicable life in an alphaGAL sensitization endemic area, mammalian meat allergy), the prick and intradermal test with the suspected biological, which, however, corresponds to an off-label use about which the patient should have been informed and given written consent. In general, allergy diagnostics should be performed within 4 – 6 weeks after the event to be meaningful [89].

According to our own data, antibody-based diagnostics of biological hypersensitivity reactions should be expanded in order to detect pre-existing antibodies before starting a biological therapy or to detect their development during the course of therapy [99, 100] and to exclude possible allergen or epitope similarities between the biological that causes undesirable immunological side effects and the one to be switched to. This way, the change to a safe and efficient biological therapy can be largely ensured in the future.

Treatment with biologics and vaccinations

Biologics therapy massively interferes with immune regulation. The question always arises whether this has an effect on the defense against infectious agents, i.e., bacteria, viruses, fungi, and parasites. Specifically, the question is whether the respective biological therapy increases the readiness for infection. Parallel to this, vaccination programs are being carried out very successfully against many pathogens today. Here the question arises whether patients under biological therapy also benefit from vaccinations (inactivated or attenuated vaccines), or whether – especially through the administration of attenuated vaccines – there is an increased risk of a flare-up or development of a corresponding infectious disease under biological therapy.

Biologics therapy has been in use for the longest time and is most widely used in the context of rheumatoid arthritis. Biologic therapy, especially with TNF antagonists, has revolutionized the treatment of rheumatoid arthritis. This is why most experience in this field is available in terms of infection risks and vaccination responses. Anti-TNF therapy has been described as having increased rates of infection with Varicella zoster virus (this is a reactivation), chronic hepatitis B virus infection and CMV infection. For this reason, the immune status with regard to these pathogens (and also other infections) should be examined before therapy with TNF antagonists. There is a pragmatic suggestion for this in the literature [101], and it can also be transferred to a therapy with biologicals for allergy and asthma (Table 2). Therefore, it is recommended to check the immune status with regard to these important viruses (and bacteria) before starting a biological therapy and, if necessary, to refresh vaccinations or make up for missing vaccinations before initiating a biological therapy.

In the case of bacterial diseases, the focus is on tuberculosis, especially with regard to biological therapy for autoimmune diseases. Here it could be shown that therapy with TNF antagonists leads to an increased risk of a mycobacterial infection flaring up. On the other hand, there is no increased risk with a biological therapy directed against CD20, IL-6 receptor, IL-12/IL-23, and CD80/CD86 [102].

Vaccination data are also available for some biologics that are now approved for allergy and asthma therapy. With regard to vaccinations against bacterial pathogens, the tetanus vaccination is worth mentioning. Here, it could be shown for the therapy with dupilumab (inhibition of the IL-4 and IL-13 signaling pathways) that there is no

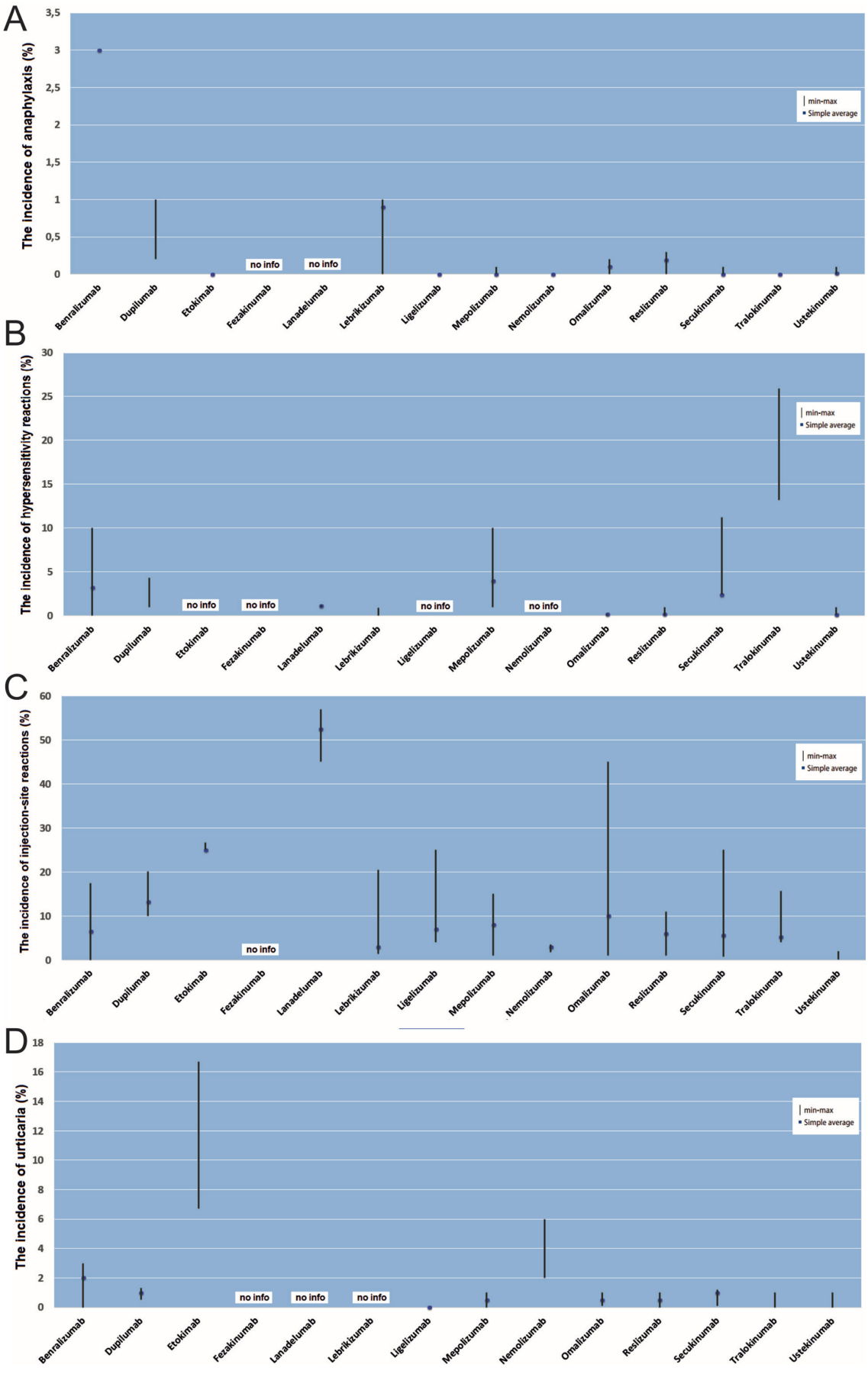

Figure 1. Incidences of different hypersensitivity reactions to biologics.

impairment of the development of a tetanus titer response [103] or a bactericidal response detectable in serum. It can therefore be concluded that patients treated with this biological agent can also receive inactivated or attenuated vaccines at the same time. With regard to viral infections, influenza vaccination is of particular importance, especially since patients with asthma have an increased risk of a (severe) influenza infection. In this context, therapy with a monoclonal anti-IL-5 receptor antibody (benralizumab) has been shown to not limit the antibody response under seasonal influenza vaccination in adolescents and young adults with moderate to severe asthma [104].

However, it has to be emphasized that it is not possible to draw conclusions from one vaccine to the other in principle, as vaccinations against different pathogen classes (viruses and bacteria) also activate or use different immunological strategies when using drugs with completely different configurations (e.g., attenuated and inactivated vaccines, significance of the added adjuvant). Therefore, there is still a considerable need for studies (regarding the number of vaccinated patients under biological therapy, the use of different vaccines against different pathogens and regarding the long-term course). Only then can a conclusive and comprehensive picture be drawn on this important topic.

Biologics in pregnancy and childhood

Most scientific publications and studies on biologicals in pregnancy refer to autoimmune or inflammatory chronic diseases, such as rheumatoid arthritis, lupus erythematosus, or psoriasis vulgaris. Active autoimmune diseases involve an increased risk of adverse maternal and fetal events such as preeclampsia, miscarriage, intrauterine growth disorders, preterm birth, or low birth weight [105]. For example, the treatment goal for rheumatoid arthritis is to have little or no pre-conception activity, as negative effects of steroids and non-steroidal anti-inflammatory drugs must be considered [106]. Experiences from case reports and registry data with TNF antagonists, which have been approved for many years for the treatment of rheumatological diseases and psoriasis vulgaris, have so far shown no evidence of an increased number of spontaneous abortions or malformations [107]. As a result, the use of TNF inhibitors such as infliximab, adalimumab, and etanercept is recommended in pregnancy up to week 20. A newer antibody, certolizumab, has been shown to be safe for the entire pregnancy [108, 109, 110]. There is limited data on the newer biologics, such as ustekinumab, secukinumab, ixekizumab, and brodalumab, and their use in pregnancy is currently not recommended, mainly as a precaution [110]. Omalizumab, which has been approved and used for the longest time in allergology, was investigated in the “Expect Study” [111]. In this study, 250 women with asthma who received omalizumab during pregnancy were examined. The data show no evidence of an increased risk of congenital malformations. However, there are still no recommendations in the international guidelines. The other antibodies used in allergology, such as benralizumab, reslizumab, and dupilumab, are not recommended for use in pregnancy due to lack of data. However, due to their mechanism of action, no increased risk can be assumed, and on the other hand, unstable chronic diseases have to be considered in the context of increased use of, for example, oral corticosteroids. In the future, further register-based data or case-control studies will be required to establish the evidence for the safe use of biologicals in pregnancy also in allergology.

Biologics in patients with uncertain SARS-CoV-2 infection status

The pandemic SARS-CoV-2 infection, which is still being researched pathophysiologically, has caused uncertainty for potential risk groups of patients regarding the therapy regimen of chronic inflammatory and oncological diseases, i.e., especially those diseases that are treated immunosuppressively and/or with biologicals. This concerns acute care as well as the treatment of chronically ill patients. Up to now, only little is known about the immune response after SARS-CoV-2 infection and could be

changed favorably or unfavorably by a therapy with monoclonal antibodies. The current study situation [cited in 112] does not provide evidence of an increased risk of allergic patients for a more severe COVID-19 disease course, but reliable data are lacking. Numerous patients receive biologicals that inhibit type 2 immune responses via different mechanisms. A selective literature search was carried out in Pubmed, Livivo, and on the World Wide Web for the past 10 years (period 05/2010 – 04/2020). The current German-language publications not included in this search were analyzed and a position paper with recommendations for treatment with biologicals in patients with allergic and atopy-associated diseases in the COVID-19 pandemic was compiled [112]. Until study data are available, all patients under therapy with a biological agent directed against type 2 immune reactions who are suffering from COVID-19 should be registered and well characterized. In this way, the basis for experience- and data-based instructions for action can be created. The position paper recommends the continuation of therapy of bronchial asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps and spontaneous urticaria with biologicals during the SARS-CoV-2 pandemic in patients without suspected or proven SARS-CoV-2 infection [112]. The aim is to optimally control difficult-to-control allergic and atopic diseases through appropriate medication-as-needed and add-on therapy and to avoid the need for systemic glucocorticosteroids. Since there is no reliable knowledge about the effect of the biologicals on the immunological situation of SARS-CoV-2 infection and COVID-19, the therapy should be decided on individually together with the patient after a risk-benefit analysis in case of justified suspicion or proof of an infection with SARS-CoV-2.

New biologics – this could be what we can expect in the next few years

Biologics have also revolutionized therapy in the field of allergic diseases in recent years. Currently, several promising biologicals for different indications are being studied in clinical trials. An excerpt from the diverse areas of application was examined more closely by Prof. Bernhard Homey (atopic dermatitis; AD), Dr. Sebastian Reuter (bronchial asthma), and Dr. Mandy Cuevas (nasal polyps) at the symposium "New Biologics in Studies" organized by the DGAKI Junior Members in cooperation with the still young working group Biologics and New Pharmaceuticals of the DGAKI at the 14th German Allergy Congress in Hannover, Germany. In the following, the biologics currently being studied for these indications will be summarized based on the presentations.

Following the successful approval of the anti-IL-4 receptor antibody dupilumab for adults and children over 12 years of age with moderate to severe AD [113, 114], approval could soon be extended to children under 12 years of age, as a recently completed study by Cork et al. suggests [113].

Two other biologics are likely to become available soon for the treatment of moderate to severe AD, the anti-IL-13 antibody tralokinumab and the JAK inhibitor baricitinib. Phase 3 trials of both tralokinumab and baricitinib have reached their primary endpoints [115, 116], and the manufacturer of tralokinumab reports that a marketing authorization application has already been approved by the European Medicines Agency. As a result, tralokinumab will soon be available for the treatment of AD, and baricitinib may be next.

There are, however, other cytokine- or receptor-targeted biologics currently being evaluated in clinical trials, including the anti-IL-13 antibody lebrikizumab, whose phase 2 study results showed an early treatment response and a safe to acceptable risk profile [117]. Phase 3 studies are currently being conducted. In addition, IL-17 is also an interesting target in AD. The anti-IL-17a antibody secukinumab, which is already approved for psoriasis, is currently being evaluated in a phase 2 clinical trial for the treatment of AD. The anti-IL-22 antibody fezakinumab was also recently tested in a phase 2 study [118]. Response rates of patients with severe AD were better than those of patients with moderate AD. There was a significant superiority in response when compared to placebo with good tolerability [118, 119]. The monoclonal antibody nemolizumab is directed against IL-31RA. A phase 2 study over 52

weeks showed sustained efficacy and good tolerability [120]. Furthermore, the phase 2 study with the anti-IL-33 antibody etokimab has just been completed. Preliminary results made a promising impression [121]. However, it appears that the primary endpoint of the study could not be met.

After some biologics (omalizumab, ustekinumab, MOR106) failed in the indication AD, there are currently some promising candidates that could become available for the treatment of AD in addition to dupilumab in the next few years.

For many years, the use of biologics in nasal polyposis has been predominantly in patients with comorbidity to severe asthma or as off-label use. However, targeted registration studies are currently being conducted for various biologics in nasal polyposis [summarized in 122].

Patients with CRSwNP have a significant reduction in quality of life, sleep quality, and daily productivity due to nasal obstruction, anterior and posterior secretion, and associated facial pain and olfactory disorders. The established treatment options so far are drug therapy (steroid-containing nasal sprays) and surgical measures (surgical removal of polyps). However, the risk of recurrence is high, and therefore not every patient can be treated satisfactorily. In CRSwNP, besides the IgE-mediated allergic reaction, the importance of Th2 cells and their mediators in the development and maintenance of the disease is well known. For this reason, approaches of targeted therapy with biologicals that inhibit this signaling pathway have been increasingly pursued in recent years. Phase 3 studies with the anti-IgE antibody omalizumab, the anti-IL-5 antibodies mepolizumab and reslizumab, the anti-IL-5Rα antibody benralizumab and the anti-IL-4R antibody dupilumab show promising results [123].

With the European approval of dupilumab in autumn 2019 as an add-on therapy with intranasal glucocorticoids for the treatment of adults with severe CRSwNP, which cannot be adequately controlled by systemic glucocorticoids and/or surgery, a biological agent for the primary therapy of CRSwNP is available for the first time and is prescribable and reimbursable in Germany.

Recent years have brought significant progress in the treatment of bronchial asthma. In particular, the more precise definition of clinical phenotypes and immunological endotypes allows a more targeted therapy of patients [124]. Beneficiaries of this are the previously therapy-refractory severe asthmatics with eosinophilia, the so-called type 2 high asthma [125]. With the antibodies against IL-5 (mepolizumab, reslizumab), against IL-5R (benralizumab), and against the alpha subunit of IL-4R (dupilumab), four candidates have been launched on the market that focus on this endotype [14, 126].

Another promising approach is the suppression of alarmins, such as IL-33 and TSLP, which are messengers of epithelial cells at the beginning of the inflammation cascade. The inhibition of these immunomodulators could already reduce or prevent the inflammatory reaction in its development [127]. An antibody against IL-33 (etokimab) was shown to improve FEV1 levels and eosinophilia in blood in a phase 2 study. The TSLP-neutralizing antibody tezepelumab showed a significant improvement in annual exacerbations in a phase 2 study. Another interesting result of the TSLP study was that not only asthmatics with type 2-high benefited from the new therapy, but also those with type 2-low, for whom no biologicals were previously available [128, 129].

Asthmatics with this endotype often show a neutrophilic inflammatory response and respond less well to corticosteroids. Type 2-low asthma is much less well understood than type 2-high asthma, but we do know that Th1 and Th17 cells and their mediators orchestrate the neutrophil inflammatory response [130]. First biologics that specifically target this endotype by suppressing the IL-17 and TNF target structures did not achieve the desired effects [131, 132, 133]. Preliminary results on an antibody against CXCR2 (AZD5069) are more promising. CXCR2 is a receptor on neutrophils whose blockade prevents activation by IL-8. In initial studies, the antibody showed good safety and reduced neutrophil numbers, but could not show a significant effect on exacerbation rates [134, 135].

Overall, we now have targeted therapeutics for the different phenotypes of atopic diseases.

In view of the rapidly developing study situation for possible new marketing autho-

rizations, care must be taken with regard to the observation and documentation of side effects. For this purpose, the registration of patients treated with biologicals in registries is a methodically sound way. But also the research and development of suitable diagnostic methods for the registration of immunologically caused side effects or the registration of the "theratype", i.e., the differentiation of potential therapy responders from non-responders, is certainly of higher importance than commonly assumed so far.

Conflict of interest

CT, MRE, UJ, AG, HB, JP, KCB have no conflict of interest.

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