Use of biologicals in allergic and type-2 inflammatory diseases during the current COVID-19 pandemic

Ludger Klimek\textsuperscript{A,G,H,1}, Oliver Pfarr\textsuperscript{B,G,H,2}, Margitta Worm\textsuperscript{B,H,3}, Thomas Eiwegger\textsuperscript{H,4,5,6}, Jan Hagemann\textsuperscript{A,7}, Markus Oliert\textsuperscript{E,H,8,9}, Eva Untersmy\textsuperscript{H,10}, Karin Hoffmann-Sommergruber\textsuperscript{H,10}, Alessandra Vultaggio\textsuperscript{H,11}, Ioana Agache\textsuperscript{H,12}, Sevim Bavbek\textsuperscript{H,13}, Apostolos Bossios\textsuperscript{H,14,15}, Ingrid Casper\textsuperscript{A,1,16,17}, Susan Chan\textsuperscript{H,18}, Alexia Chatzipetrou\textsuperscript{H,19}, Christian Vogelberg\textsuperscript{G,20}, Davide Firini\textsuperscript{H,21}, Paula Kauppi\textsuperscript{H,22}, Antonios Kolios\textsuperscript{H,16,23}, Akash Kothari\textsuperscript{H,4}, Andrea Matusch\textsuperscript{H,11}, Oscar Palomares\textsuperscript{H,24}, Zsolt Szépfalusi\textsuperscript{D,25}, Wolfgang Pohj\textsuperscript{L,26}, Wolfram Hötzennecker\textsuperscript{L,27}, Alexander R. Rosenkranz\textsuperscript{D,28}, Karl-Christian Bergmann\textsuperscript{A,B,3}, Thomas Bieber\textsuperscript{G,29}, Roland Buti\textsuperscript{B,F,30}, Jeroen Buters\textsuperscript{G,31}, Ulf Darsow\textsuperscript{G,32}, Thomas Keil\textsuperscript{G,33}, Jörg Kleine-Tebbe\textsuperscript{A,34}, Susanne Lau\textsuperscript{B,H,35}, Marcus Maure\textsuperscript{G,H,36}, hans Merk\textsuperscript{A,36}, Ralph Mösberg\textsuperscript{B,37,38,39}, Joachim Saloga\textsuperscript{B,40,41}, Petra Staubach\textsuperscript{A,40}, Uta Jappe\textsuperscript{A,B,H,41}, Klaus F. Rabe\textsuperscript{G,42,43}, Claudia Vogelmeier\textsuperscript{G,44}, Tilo Biedermann\textsuperscript{B,H,32,45}, Kirsten Jung\textsuperscript{A,46}, Wolfgang Schlenger\textsuperscript{A,47}, Johannes Ring\textsuperscript{A,B,48,49}, Adam Chaker\textsuperscript{A,H,50,51}, Wolfgang Wehmann\textsuperscript{A,52}, Sven Becker\textsuperscript{A,53,54}, Laura Freulsperger\textsuperscript{A,7,55}, Norbert Mülleneisen\textsuperscript{A,56}, Katja Nemati\textsuperscript{A,55}, Wolfgang Czech\textsuperscript{A,56}, Holger Wrede\textsuperscript{A,57}, Randolf Breher\textsuperscript{A,58}, Thomas Fuchs\textsuperscript{A,59}, Peter-Valentin Tomazic\textsuperscript{H,60}, Werner Aberer\textsuperscript{O,61}, Antje-Henriette Fink-Wagner\textsuperscript{D,62}, Fritz Horak\textsuperscript{D,F,63}, Stefan Wöhrl\textsuperscript{D,64}, Verena Niederberger-Leppin\textsuperscript{G,65}, Isabella Pali-Schöll\textsuperscript{H,66,67}, Wolfgang Pohj\textsuperscript{G,68}, Regina Roller-Wimsberger\textsuperscript{G,69}, Otto Sprange\textsuperscript{G,70}, Rudolf Valenta\textsuperscript{G,71,94,95,96}, Mübecell Akdis\textsuperscript{H,72}, Paolo M. Matricardi\textsuperscript{A,73}, François Sperti\textsuperscript{A,74}, Nicolai Khaltaev\textsuperscript{75}, Jean-Pierre Michel\textsuperscript{76}, Larent Nicod\textsuperscript{77}, Peter Schmid-Grendelmeier\textsuperscript{78}, Marco Idzko\textsuperscript{G,79}, Eckard Hamelmann\textsuperscript{B,80}, Thiio Jakob\textsuperscript{B,81}, Thomas Werfel\textsuperscript{B,82}, Martin Wagenmann\textsuperscript{B,83}, Christian Taube\textsuperscript{B,84}, Erik Jensen-Jarolim\textsuperscript{D,H,10,66}, Stephanie Korn\textsuperscript{A,30}, Francois Hentges\textsuperscript{E,85}, Jürgen Schwarze\textsuperscript{H,86}, Liam O’ Mahony\textsuperscript{H,87}, Edward F. Knol\textsuperscript{H,88}, Stefano del Giacco\textsuperscript{H,89}, Tomás Chivato Pérez\textsuperscript{19,20}, Jean Bouquet\textsuperscript{G,91,92,93,10,95,97}, Anna Bedbrook\textsuperscript{G,91}, Torsten Zuberbier\textsuperscript{G,H,3,10,11}, Cezmi Akdis\textsuperscript{H,72}, and Marek Jutel\textsuperscript{H,96,97}

\textsuperscript{1-98}Affiliation details see list at the end of the article.

Abstract. Background: Since the beginning of the COVID-19 pandemic, the treatment of patients with allergic and atopy-associated diseases has faced major challenges. Recommendations for "social distancing" and the fear of patients becoming infected during a visit to a medical facility have led to a drastic decrease in personal doctor-patient contacts. This affects both acute care and treatment of the chronically ill. The immune response after SARS-CoV-2 infection is so far only insufficiently understood and could be altered in a favorable or unfavorable way by therapy with monoclonal antibodies. There is currently no evidence for an increased risk of a severe COVID-19...
course in allergic patients. Many patients are under ongoing therapy with biologicals that inhibit type 2 immune responses via various mechanisms. There is uncertainty about possible immunological interactions and potential risks of these biologicals in the case of an infection with SARS-CoV-2.

**Materials and methods:** A selective literature search was carried out in PubMed, Livivo, and the internet to cover the past 10 years (May 2010 – April 2020). Additionally, the current German-language publications were analyzed. Based on these data, the present position paper provides recommendations for the biological treatment of patients with allergic and atopy-associated diseases during the COVID-19 pandemic. **Results:** In order to maintain in-office consultation services, a safe treatment environment must be created that is adapted to the pandemic situation. To date, there is a lack of reliable study data on the care for patients with complex respiratory, atopic, and allergic diseases in times of an imminent infection risk from SARS-CoV-2. Type-2-dominant immune reactions, as they are frequently seen in allergic patients, could influence various phases of COVID-19, e.g., by slowing down the immune reactions. Theoretically, this could have an unfavorable effect in the early phase of a SARS-CoV-2 infection, but also a positive effect during a cytokine storm in the later phase of severe courses. However, since there is currently no evidence for this, all data from patients treated with a biological directed against type 2 immune reactions who develop COVID-19 should be collected in registries, and their disease courses documented in order to be able to provide experience-based instructions in the future. **Conclusion:** The use of biologicals for the treatment of bronchial asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, and spontaneous urticaria should be continued as usual in patients without suspected infection or proven SARS-CoV-2 infection. If available, it is recommended to prefer a formulation for self-application and to offer telemedical monitoring. Treatment should aim at the best possible control of difficult-to-control allergic and atopic diseases using adequate rescue and add-on therapy and should avoid the need for systemic glucocorticosteroids. If SARS-CoV-2 infection is proven or reasonably suspected, the therapy should be determined by weighing the benefits and risks individually for the patient in question, and the patient should be involved in the decision-making. It should be kept in mind that the potential effects of biologicals on the immune response in COVID-19 are currently not known. Telemedical offers are particularly desirable for the acute consultation needs of suitable patients.

### Introduction

The clinical symptoms of infection with the novel coronavirus (severe acute respiratory coronavirus 2; SARS-CoV-2) became known as the “coronavirus disease 2019 (COVID-19)” on February 11, 2020 [1]. The International Committee on Taxonomy of Viruses (ICTV) called this novel human pathogenic virus SARS-CoV-2 [1]. The global spread of the SARS-CoV-2 pandemic and patients with severe COVID-19 courses pose a major challenge to healthcare systems worldwide.

The coronavirus that caused the severe acute respiratory syndrome (SARS-CoV) in 2002/2003 has approximately an 80% nucleotide sequence identity with SARS-CoV-2 [1]. SARS-CoV-2 is a beta coronavirus of the subgenus Sarbecovirus, subfamily Orthocoronavirinae, and the 7th member of the Coronaviridae family that can infect humans. It can be isolated from human samples obtained from respiratory secretions, nasal and pharyngeal swabs and isolated on cell cultures [1, 2, 3].

It is covered by a lipid membrane that can be disrupted by detergents and is different from the Middle East respiratory syndrome-related coronavirus (MERS-CoV), from SARS-CoV, and from the coronavirus responsible for the common cold (229E, OC43, NL63, and HKU1) [1].
The incubation period after an infection with SARS-CoV-2 can be of up to 14 days, during which the infected person can be asymptomatic but nevertheless transmit the virus.

In a high number of patients, the infection leads to symptoms of the upper and lower airways, and, less frequently, also of other organ systems (nervous system, gastrointestinal tract, kidneys, blood vessels). In the worst case scenario, multi-organ failure and respiratory failure can result, as has been described for other coronavirus infections (SARS-CoV-1, MERS-CoV) [4, 5, 6].

In more severe cases, infection with SARS-CoV-2 can lead to pneumonia, severe acute respiratory syndrome, renal failure, and death [4, 7, 8, 9, 10]. Higher age and comorbidities such as chronic airway diseases (particularly COPD), diabetes mellitus, cardiovascular diseases, obesity, and immune deficiency of various origins have been described as risk factors of a severe course [4, 7, 8, 9]. The need for intensive care treatment and invasive ventilation is associated with high mortality.

We will present clinical and immunological aspects that have to be considered with regard to the COVID-19 pandemic in patients treated with biological therapy against IgE and mediators of type 2 inflammation (Table 1).

### Immune response in SARS-CoV-2 and other coronavirus infections

The characteristics of the immune response after infection with SARS-CoV-2 are still insufficiently understood. While various forms of the course of COVID-19 and the infection with the virus have been described, it is still unclear which immunological background influences the course of the disease. This is also true for the role of the innate...
and adaptive immune system with regard to SARS-CoV-2 infection. While natural killer (NK) cells traditionally play an important role in the early phase of viral infections, CD8+ T helper cells come into action in the subsequent phase [11]. Early antibody secretion and production in the mucosa-associated lymphatic tissue initially include antigen-specific IgM, IgA, and, later, IgG antibodies, and are essential for immune response [12, 13, 14]. Macrophages are activated and secrete inflammatory cytokines, with type 1 interferons (type 1 IFN) playing the most prominent role. In infections with other coronaviruses (e.g., SARS-CoV-1), type 1 IFN is responsible for the adequate initiation of the immune reaction, and patients with delayed or insufficient IFN production have a more severe disease course [6].

The activation of apoptosis or pyroptosis in epithelial cells serves as an antiviral defense, but excessive immune reactions can also contribute to local tissue damage through synergistic effects [15]. An excessive production of pro-inflammatory cytokines has already been observed in SARS-CoV-1, MERS-CoV, and recently also in SARS-CoV-2 infections, and has been described as a cytokine storm [4, 5]. Natural IgM, and probably also mannose-binding lectin (MBL), are believed to be the first line of defense against SARS-CoV-2 [16]. These antibodies and MBL recognize glycans and are abundant in children and young adults. However, they decrease dramatically with age and are over 50 times lower at the age of ≥ 60 than at the age of 20 – 30 years [16]. As they are part of the innate immunity, they are the only antibodies able to recognize SARS-CoV-2 before the adaptive immune response is initiated [16]. If the virus enters the lungs early enough, it can replicate in an unhindered manner, as no or only little resistance exists. The resulting inflammation with a massive activation of local mediators (complement and coagulation cascades interleukin-6 (IL-6), cytokine storm) can cause damages that lead to complications or, in some cases, even to death [16].

Extensive damage to the lungs leads to rapid clinical deterioration and usually to the need for intensive care treatment, which can be observed typically 7 – 14 days after infection. The risk of kidney, liver, and/or other organ damage as well as of consumption coagulopathy is significantly increased. Affected patients usually have highly increased interleukin (IL)-1 β, IL-6, IL-8, and TNF-α levels (Figure 1) [18]. The therapeutic blockade of one or more of these cytokines has been discussed as a potential future therapy option for severely affected patients in whom IL-6 can be massively increased [19]. IL-6 plays a central role in the cytokine storm, and tocilizumab has already been used as a biological with anti-IL-6 effects in COVID-19 [20, 21].

Approved indications for anti-IL-6 or anti-IL-6R antibodies (such as tocilizumab, sarilumab) currently include, for example, rheumatoid arthritis, juvenile rheumatoid arthritis, and Castleman disease. The immune reactions of type 1 and type 3 described here are contained by other cytokines, such as IL-10 and TGF- β, and type 2 inflammation could possibly counteract the cytokine storm. Increased levels of eosinophilic granulocytes, as one of the key cells of type 2 inflammation, have been ascribed a protective effect in severe viral infections, although the mechanism of action has not yet been identified [22]. On the other hand, low blood eosinophil counts could simply reflect the severity of the infection. The interaction of SARS-CoV-2 with its receptor on the cells of the respiratory system, the membrane-bound angiotensin-converting enzyme 2 (ACE2), which is responsible for the entry of the virus into the host cell, is far better investigated [17].

Therefore, the reduced expression of ACE2 in the airway epithelial cells of patients with allergic asthma is being discussed as a potentially protective factor against SARS-CoV-2 infection [23]. It can be assumed that only the interaction of the individual cytokine responses leads to an adequate and effective immune response in coronavirus infections. However, imbalances between type 1, type 2, and type 3 reactions might have a significant negative or positive impact on the course of the viral infection (Figure 1).
Figure 1. Sequence of immunological events in SARS-CoV-2 infection: If SARS-CoV-2 infects cells via the surface receptors ACE2 and TMPRSS2, this leads to active replication and release of the virus, the cells decay through pyroptosis. DAMPs are released that are recognized by neighboring epithelia, endothelia, and alveolar macrophages and trigger the release of pro-inflammatory cytokines such as IL-6, IP-10, MIP1α, MIP1β, and MCP1. This attracts monocytes, macrophages, and T cells, which, when IFN-γ is added, activate another inflammatory, self-reinforcing cascade. In defective immune responses (left), this can lead to accumulation of immune cells and overproduction of pro-inflammatory cytokines, which then damage the lung and may lead to a cytokine storm with multi-organ failure. Additionally, non-neutralizing antibodies produced by B cells may enhance the infection and lead to further organ damage. In a healthy immune response (right), the initial inflammation attracts virus-specific T cells to the infection site where they can eliminate the infected cells before the virus spreads further. Neutralizing antibodies selectively block the virus, alveolar macrophages recognize and phagocytize affected cells and neutralized viruses. Altogether, these processes clear the viral infection with minimal damage of respiratory tissue and lead to recovery. Reproduced from Tay et al. [65]. ACE2 = angiotensin-converting enzyme 2; ADE = antibody-dependent enhancement; DAMP = damage-associated molecular pattern; G-CSF = granulocyte colony-stimulating factor; IFN = interferon; IL = interleukin; MIP1α = macrophage inflammatory protein 1α; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF = tumor necrosis factor.
Experiences with COVID-19 in diseases involving type 2 inflammation

So far, there is insufficient evidence to indicate which risk factors cause a severe course of COVID-19. A history of lung disease has been considered a potential risk factor for developing COVID-19 and possibly also for a severe course. Bronchial asthma, which is the most important allergic indication for biologicals targeting IgE and type 2 inflammation, is possibly one of these diseases. However, since many patients with pulmonary disease also have other comorbidities, some of the suspected factors could turn out to be confounders once further studies are carried out. Thus, it remains unclear whether patients with type-2-associated bronchial asthma without any other possible risk factors should be considered high risk for a severe COVID-19 course. The currently available data rather contradict this. There is only limited data on COVID-19 in connection with a type-2-associated disease, and its prognostic value is very limited. The currently available studies do not indicate an increased risk for patients with allergies, asthma, or other atopy-associated diseases (Table 2) [8, 24, 25, 26, 27, 28, 29]. For example, in Wuhan and Italy, the percentage of seriously ill or deceased COVID-19 patients with known bronchial asthma was far below the prevalence of asthma in these places [18]. It also remains unclear why in many patients not only lymphopenia but also eosinopenia was detected at the time of admission [8]. Neither decreased nor increased eosinophil levels have so far been clearly associated with certain clinical courses of SARS-CoV-2 infection.

Marketing approval of biologicals in type 2 inflammation in Germany, Austria, Luxembourg, and Switzerland

In recent years, several biologicals have been approved in Europe that block IgE antibodies or the interleukins IL-4, IL-5, and IL-13, which are relevant in type 2 inflammation, or their receptors [30, 31, 32, 33, 34, 35, 36, 37, 38, 39].

Omalizumab has been approved for the treatment of severe allergic bronchial asthma in adults and in children older than 6 years with proven sensitization against a perennial airborne allergen and reduced lung function. Another indication is antihistamine-resistant chronic spontaneous urticaria in adults and in adolescents older than 12 years. Mepolizumab, benralizumab, and reslizumab are

| Study/Reference | Population |
|-----------------|------------|
| Dong et al. [26] (Wuhan, China) | Case series of 11 patients with COVID-19, 3 of them with a history of allergic disease (1 allergic rhinitis, 1 atopic dermatitis, 1 urticaria) |
| Bhatragu et al. [25] (Seattle, WA, USA) | Report of 3 patients taking oral glucocorticosteroids because of breathing difficulties due to COVID-19 and known asthma who were hospitalized 1 week later with acute respiratory insufficiency |
| Wang et al. [27] (Wuhan, China) | 2 of 69 studied patients had asthma |
| Zhang et al. [8] (Wuhan, China) | Study of 140 patients of whom 2 had chronic urticaria, 1 had asthma, and 10 had unclear adverse drug reactions |
| Grasselli et al. [29] (Lombardy, Italy) | Study including 1,591, of whom 205 had a history of: bronchial asthma, anemia, inflammatory bowel disease, chronic respiratory insufficiency, endocrine disorders, chronic pancreatitis, diseases of the connective and supporting tissue, organ transplantation, epilepsy, neurological disease (reported as “other” in the study) |
| Dreher et al. [28] (Aachen, Germany) | Result: COVID-19 patients with a history of respiratory disease develop ARDS more frequently (58 vs. 42%; 14 vs. 11 patients; of these, 4 vs. 2 patients with asthma; n = 50) |

ARDS = acute respiratory distress syndrome.
IL-5 or IL-5 receptor blockers, available for adults and, partially, also for children.

Dupilumab has been approved for the treatment of: (i) atopic dermatitis in adolescents older than 12 years, (ii) severe type-2-dominant asthma in adults and (iii) chronic rhinosinusitis with nasal polyps (CRSwNP) in adults.

Table 2 shows the situation of approval in Germany, Austria, Luxembourg, and Switzerland. Self-administration by the patient is listed separately as it significantly facilitates care for suitable patients during the SARS-CoV-2 pandemic.

**Type 2 inflammation blocking and viral infections**

Viral infections of the upper and lower airways have been associated with the development and exacerbation of allergic disease [40, 41, 42]. Infection and the persistence of virus particles in the mucosa could inhibit the efficacy of the local innate immune system and promote type 2 inflammation. The blocking of type 2 inflammation by therapeutic antibodies against IgE, IL-5, or the IL-5 or IL-4/IL-13 receptors has so far not been suspected to increase the risk of viral infections. However, IL-4 has a dual role in viral infections due to two different haplotypes in the IL-4 gene. It can promote infections with the Herpes virus and the norovirus [43] as well as with the Ebola virus, which is related to the coronavirus [44]. On the other hand, IL-4 can also inhibit viral infections by promoting innate immunity [45, 46, 47].

Thus, more evidence from clinical observations is necessary to be able to provide clear recommendations with regard to COVID-19. Table 4 gives an overview of the frequency of viral infections occurring as adverse events in trials on these monoclonal antibodies. There have been reports on the lower incidence of viral infections under anti-IgE treatment with omalizumab, since this therapy may increase the functionality and the production of IFN-α by plasmacytoid dendritic cells (pDC). This leads to an enhanced antiviral defense and to an reduction of virus-induced asthma exacerbations [40, 48]. Also, for type 2 blockade with anti-IL-5 antibodies (mepolizumab, reslizumab) or anti-IL-5 receptor antibodies (benralizumab), the risk of respiratory viral infections in the active-agent study groups was equal to or lower than the risk in the placebo groups (Table 4).

**Type 2 inflammation blocking in SARS-CoV-2 infections**

It has not yet been clarified whether the blockade of type 2 inflammation or of IgE influences the risk of developing COVID-19 or its course. In the case of a cytokine storm, possible negative effects induced by blocking the type 2 immune response situation are conceivable; but these effects require further investigation. The first reports show that the disease course is not worse in COVID-19...
patients with eosinophilic diseases under biological therapy [24, 49]. However, further study results should be awaited, especially considering the fact that SARS-CoV-2 changes rapidly due to mutations [50].

Meta-analyses by Agache et al. [51, 52, 53] have shown a slightly increased rate (low to medium risk of association) of adverse events when anti-IL-5/5R, anti-IL-4/13R, and anti-IgE are used in severe asthma, in-

| Agent                  | Indication                                   | Interval/dosage                                      | Study (n)                  | Adverse events biological/placebo (n/group) |
|------------------------|----------------------------------------------|-----------------------------------------------------|----------------------------|---------------------------------------------|
| Benralizumab (anti-IL-5R) | Severe, uncontrolled asthma                  | Q4W + placebo, Q4W + Q4W, Q8W + placebo, Q8W + Q8W | Busse et al. (n = 1,576*) | VURTI 15 – 16%/14 – 15%** (1,030/546)       |
|                        |                                              |                                                     |                            | URTI 6%/7 – 8%                              |
|                        |                                              |                                                     |                            | Pnx < 1 – 1%                                |
| Dupilumab (anti-IL-4Ra) | Atopic dermatitis                            | Various (QW, Q2W, Q4W, Q8W, placebo)                | Worm et al. (n = 422)      | URTI 5.7 – 8.3/7.3                          |
|                        |                                              |                                                     |                            | IFZ 0 – 5.7/1.2                             |
|                        |                                              |                                                     |                            | HSV1 1.8 – 6/3.7                            |
|                        |                                              |                                                     |                            | VURTI 0 – 1/2/3.7                           |
|                        | 200 (adolescents)/300 mg Q2W, 300 mg Q4W, placebo | Simpson et al. (n = 250)                        |                            | URTI 7.2 – 12.2/17.6                        |
|                        |                                              |                                                     |                            | HSV 1.2 – 4/8/3.5                           |
|                        | 300 mg QW/Q2W, placebo                       | Simson et al. (n = 1,379)                           |                            | URTI 3 – 5/2                                |
|                        |                                              |                                                     |                            | HSV 0 – 3/1                                 |
|                        |                                              |                                                     |                            | HSV1 2 – 4/2                                |
|                        |                                              |                                                     |                            | HSV2 1/1                                    |
|                        |                                              |                                                     |                            | VZV 0 – 1/1                                 |
|                        |                                              |                                                     |                            |                                              |
|                        | 300 mg QW/Q2W, placebo                       | Blauvelt et al. (n = 740)                           |                            | URTI 10 – 14/10                             |
|                        |                                              |                                                     |                            | IFZ 3 – 4/5                                 |
|                        |                                              |                                                     |                            | HSV 2 – 3/1                                 |
|                        |                                              |                                                     |                            | HSV 4 – 5/3                                 |
|                        | 300 mg Q2W (open label)                      | Faiz et al. (n = 241)                               |                            | URTI 1.2                                    |
|                        |                                              |                                                     |                            | HSV < 2.4                                   |
|                        | 300 mg Q2W                                   | Deleuran et al. (n = 1,491)                         |                            | VURTI 2.5                                   |
|                        |                                              |                                                     |                            | IFZ 2.1                                     |
|                        |                                              |                                                     |                            | HSV1 4.3                                    |
| CRSwNP                 | 300 mg Q2W, placebo                          | Bachert et al. (n = 276)                            |                            | URTI 5.4 – 6.7/12.7                         |
|                        | Moderate to severe, uncontrolled asthma      | 200/300 mg Q2W, placebo                            | Castro et al. (n = 1,897)  | VURTI 18.2/19.6                             |
|                        |                                              |                                                     |                            | URTI 11.6/13.6                              |
|                        |                                              |                                                     |                            | IFZ 5.9/8.0                                 |
|                        | 300 mg Q2W, placebo                          | Rabe et al. (n = 210)                               |                            | VURTI 9/18                                  |
|                        | 300 mg Q2W                                   | Deleuran et al. (n = 1,491)                         |                            | IFZ 3/6                                     |
| Mepolizumab (anti-IL-5) | Severe eosinophilic asthma                   | 75 mg IV Q4W/100 mg SC Q4W                          | Ortega et al. (n = 576)    | IFZ 5/3 (191/191), 3/3 (194/191) VURTI 1/1/0 |
|                        |                                              |                                                     |                            | HSV1 < 1 all                                |
|                        |                                              |                                                     |                            | HSV2 < 1/0/1                                |
|                        |                                              |                                                     |                            | VZV < 1/0/1                                 |
|                        |                                              |                                                     |                            |                                              |
|                        | 100 mg Q4W                                   | Chupp et al. (n = 551)                              |                            | IFZ 3/1 (273/278)                            |
|                        |                                              |                                                     |                            | HSV 1 < 1/0                                 |
|                        |                                              |                                                     |                            | VZV < 1/1                                   |
|                        | 100 mg SC Q4W                                | Bel et al. (n = 135)                                |                            | IFZ 4/2 (69/66)                              |
|                        | 100 mg SC Q4W                                | Bel et al. (n = 135)                                |                            | VURTI 1/2                                   |
|                        | 100 mg SC Q4W                                | Bel et al. (n = 135)                                |                            | VZV 0/2                                    |
| Reslizumab (anti-IL-5)  | Severe eosinophilic asthma                   | 3 mg/kg IV Q4W                                     | Virchow et al. (n = 1,758) | URTI 9/9 (1,028/730)                         |
|                        |                                              |                                                     |                            | IFZ 3/5                                    |
| Omalizumab (anti-IgE)   | Severe allergic asthma                       | Q2W/Q4W                                             | Esquivel et al. (n = 327)  | Rhinovir 3.3/3.4 (243/84)                     |

*Multi-step design. Total number of all three sub-studies; **patients first received placebo, then active drug. Due to large differences in group sizes percentages are given. Pnx = pneumonia; CRSwNP = chronic rhinosinusitis with nasal polyps; HSV = herpes simplex virus; IFZ = influenza; (V)URTI = (viral) upper respiratory tract infections; VZV = varicella zoster virus.
Biologicals in allergic and type 2 inflammatory diseases during the current COVID-19 pandemic dependently of COVID-19. Thus, there is no clear recommendation regarding the decision-making to continue or temporarily interrupt a biological therapy during an infection with SARS-CoV-2. Treatment interruption could entail the risk of suboptimal control of the allergic disease or, in the case of exacerbations, the need for systemic glucocorticosteroids, for which an increased risk of a possibly more severe COVID-19 course has been described [54].

Recommendations for the management of allergic/atopy-associated diseases under anti-type-2 therapy during the COVID-19 pandemic (Table 1)

To ensure an appropriate, high-quality, and accurate care for patients on anti-type-2 treatment with underlying atopic-eosinophilic or allergic disease, antibody therapy should be continued and remain unchanged during the ongoing pandemic when there is no evidence of SARS-CoV-2 infection. To cope with the current shortfalls in hospitals and the more difficult hygiene conditions, telephone or telemedical follow-up should be considered in suitable patients when technical and medical requirements allow for it. For this purpose, comprehensive patient training with regard to documentation of the disease activity and, where applicable, to self-administration of the medication is desirable. This is facilitated by the partial availability of user-friendly pen systems for self-application.

In general, in countries with low infection numbers and a consequent relaxation of COVID-19-associated restrictions, there is no contraindication for starting biological therapy in patients without evidence of a current SARS-CoV-2 infection.

According to the current state of knowledge, biological therapy for the indications discussed here can be continued in mild to moderate cases of SARS-CoV2 infection/COVID-19 disease, if an individual consideration of risks and benefits supports this decision.

The risks and benefits have to be assessed by a specialist, and it is recommended to inform the patient about the fact that only limited data are available.

In severe courses of COVID-19, prolongation of the dosing interval or treatment interruption should be considered. When doing so, the risk of the potential requirement of treatment with systemic glucocorticoids should also be taken into account. In a quarantine situation, a telemedical approach might be feasible, in particular with the aim of continuing or expanding the basic therapy with topical steroids, inhaled bronchodilators, antihistamines, etc. in accordance with the relevant guideline recommendations [36, 37, 54, 55, 56, 57, 58].

If hospitalization due to the exacerbation of asthma- or type-2-associated diseases becomes necessary, current guidelines on diagnosis and treatment must be followed. Sinus surgery for CRSwNP should, if possible, be delayed in patients with suspected or confirmed COVID-19 disease.

In the case of urgently indicated systemic therapy for severe atopic dermatitis, consideration should be given to therapy with either biologicals, classic immunosuppressants, or systemic glucocorticosteroids, although systemic glucocorticosteroids are not recommended due to their broad immunosuppressive effect (see above). For cyclosporin A (CyA) as an approved therapeutic option for atopic dermatitis, in vitro studies have suggested antiviral effects [60]. T-cell-directed immunosuppression performed after organ transplantation (CyA, tacrolimus) is being discussed as a possible protective factor against serious clinical complications of SAS-CoV-2 infection [61], as well as the use of CyA in COVID-19 [62, 63]. However, reliable clinical data have not yet been published. Possible metabolic interactions between CyA and lopinavir/ritonavir (CYP3 inhibitors) have to be taken into account. Severe COVID-19 courses have been reported in two patients with atopic dermatitis treated with dupilumab [64].

Conclusion

The currently available data suggest that the risk of developing a severe course of COVID-19 is probably not increased in patients with allergies and atopy-associated diseases. However, there is a lack of study
results including subgroup analyses on seriously ill atopy patients and their treatment. The effects of IgE or type 2 inflammation blocking on SARS-CoV-2 infection have not yet been clarified.

In cases of a mild to moderate COVID-19 course, we advise to continue biological therapy for the indications mentioned here, if the patient-based assessment of the benefits and risks supports this approach and if the patient agrees after adequate information about the limited availability of data.

In severe courses of COVID-19, prolongation of the dosing interval or treatment interruption should be considered for the indications discussed here. This assessment should be patient-based and should consider the risk of the possible requirement of systemic glucocorticosteroids.

In all other patients, in whom neither a suspected nor a proven SARS-CoV-2 infection is present, the use of biologicals for the treatment of bronchial asthma, atopic dermatitis, CRSwNP, and spontaneous urticaria can be unchanged or can be re-started in the current SARS-CoV-2 pandemic.

The use of telemedicine for treatment support and patient education is recommended and can facilitate the continuation of biological administration by self-injection.

**Conflict of interest**

E. Untersmayr, I. Agache, S. Bavbek, I. Casper, S. Chan, A. Chatzipetrou, W. Pohl, T. Bieber, T. Keil, J. Kleine-Tebbe, J. Saloga, P. Staubach, U. Rabe, C. Vogelmeier, K. Jung, J. Ring, W. Wehrmann, S. Becker, L. Freudelsperger, K. Nemat, H. Wrede, T. Fuchs, V. Niederberger-Leppin, W. Pohl, R. Roller-Wimsberger, P.M. Matricardi, F. Spertini, N. Khaltava, L. Nicod, M. Izdeko, E. Hamelmann, T. Jakob, C. Taube, L. O’Mahony, S. del Giacco, T. Zuberbier, C. Akdis, M. Jutel, T. Eiwegger, K.-C. Bergmann, M. Akdis, O. Spranger, N. Mülleneisen, A.-H. Fink-Wagner, K.F. Rabe, W. Czech, S. Wöhrl, J. Buters, F. Horak, W. Schleuter, I. Pali-Schöll, A. Mattucci, A. Vultaggio, Z. Szepfalus, C. Vogelberg, T. Werfel, U. Jappe, J.-P. Michel, P. Kauppi, A. Chaker, E.F. Knol, T. Chivato Pérez, K. Hoffmann-Sommergruber, A.R. Rosenkranz, W. Hötzenecner, M. Ollert, A. Kothari, W. Ab-

er, A. Kolios, D. Firimu, P.-V. Tomazic, E. Jensen-Jarolim, F. Hentges, and A. Bedbrook state that no conflicts of interest exist.

R. Mösges received personal fees and/or grants from Allergopharma, Allergy Therapeutics, Bencard, Leti, Lofarma, Stallergenes, Optima, Friulchem, Hexal, Klosterfrau, FAES, Meda, Novartis, UCB, BitopAG, Hulka, Ursapharm, Menarini, Mundipharma, Pohl-Boskamp, Immunotek, Hikma, Sandoz, Lek, Cassella, SanofiGenzyme, Engelhard, SmartPeakFlow, and Strathos outside the submitted work.

M. Maurer received grants/research support and/or personal, consultancy, or speaker fees from Amgen, Allakos, Celldex, CSL Behring, FAES, Genentech, Lilly, Merkelle Recordati, Moxie, Novartis, Roche, Sanofi, Takeda, MSD, UCB, and Uriach outside the submitted work.

P. Schmid-Grendelmeier received speaker and personal fees from AstraZeneca, GSK, Novartis Pharma, and Sanofi–Genzyme outside the submitted work.

M. Worm received personal and/or consultancy fees from ALK-Abelló Arzneimittel GmbH, Mylan Deutschland GmbH, Leo Pharma GmbH, Sanofi-Aventis Deutschland GmbH, Regeneron Pharmaceuticals, DBV Technologies SA, Stallergenes GmbH, HAL Allergie GmbH, Allergopharma GmbH & Co.KG, Bencard Allergie GmbH, Aimmune Therapeutics UK Limited, Actelion Pharmaceuticals Deutschland GmbH, Novartis AG, Biotest AG, AbbVie Deutschland GmbH & Co. KG, and Lilly Deutschland GmbH outside the submitted work.

O. Pfaar received personal fees and/or grants from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL Allergy Holding BV/HAL Allergie GmbH, Bencard Allergie GmbH/Allergietherapeutika, Lofarma, Biomay, Circassia, ASIT Biotech Tools SA, Laboratorios LETI/LETI Pharma, MEDA Pharma/MYLAN, Anergis SA, Mobile Chamber Experts (einem GA2LEN-Partner), Indoor Biotechnologies, Glaxo Smith Kline, Astellas Pharma Global, EUFORICA, ROX-ALL, NOVARTIS, SANOFI AVENTIS, Med Update Europe GmbH, streamedup! outside the submitted work.

H. Merk reports grants and/or personal fees from Meda, Stallergenes, Sanofi, Bayer, BMS, J & J outside the submitted work.
S. Lau is a member of the Advisory Board of Sanofi Aventis.

S. Korn received speaker and personal adviser’s fees from AstraZeneca, GSK, Novartis, and Sanofi outside the submitted work.

U. Darsow was a lecturer, principal investigator, and consultant for ALK Abello, Bencard, and Novartis Pharma outside the submitted work.

O. Palomares received research grants and/or personal fees from AstraZeneca, Biotech Tools, Genentech, Circassia, Fabre, Pohl Boskamp, Stallergenes, ThermoFischer, Biotech Tools, Genentech, Circassia. Fabre, Pohl Boskamp, Stallergenes, Thermo-Oto-Rhino-Laryngologischer Verein, Pierre Dr. Pfleger, HAL, Leti, Merck, Novartis, Information und Organisation mbH, GSK, and TEVA outside the submitted work.

T. Biedermann was a consultant to or received personal lecture fees or research grants from ALK-Abelló, Celgene-BMS, Lilly Deutschland GmbH, Mylan, Novartis, Phadia-Thermo Fisher, Sanofi-Genzyme, Regeneron.

R. Valenta received research grants from Viravaxx, Vienna, Austria, and from HVD Life Sciences, Vienna, Austria, and acts as a consultant for Viravaxx.

R. Buhl received personal lecture and/or consultant fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Novartis, Roche, Sanofi, and TEVA as well as research support for Universitätsmedizin Mainz from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche outside the submitted work.

R. Brehler received personal fees for lectures and/or consultancy and/or clinical studies from ALK, Allergopharma, Almirall, Astra Zeneca, Bencard, Gesellschaft zur Förderung der Dermatologischen Forschung und Fortbildung e.V., Gesellschaft für Information und Organisation mbH, GSK, Dr. Pfleger, HAL, Leti, Merck, Novartis, Oto-Rhino-Laryngologischer Verein, Pierre Fabre, Pohl Boskamp, Stallergenes, ThermoFischer, Biotech Tools, Genentech, Circassia.

A. Bossios reports personal consultant and/or lecture fees from Novartis, AstraZeneca, GSK, and TEVA outside the submitted work.

J. Bouquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, KYomed-Innov, and Purina outside the submitted work.

J. Schwarze received personal fees from MYLAN, F2F events; support from industry for educational activities of the Scottish Allergy and Respiratory Academy as well as the Children and Young People’s Allergy Network Scotland outside the submitted work; support from industry for EAACI; J. Schwarze is EAACI Secretary General 2019 – 2021.

J. Hagemann received speaker fees from Novartis Pharma.

M. Wagenmann received personal consultant and/or speaker fees from ALK-Abelló, Allergopharma, AstraZeneca, Bencard-Allergie, Genzyme, HAL-Allergie, Infectopharm, LETI Pharma, MEDA Pharma, Novartis, Sanofi Aventis, Stallergenes, Teva.

L. Klimek reports grants and/or personal fees from Allergopharma, MEDA/Mylan, HAL Allergie, ALK-Abelló, LETI Pharma, Stallergenes, Quintiles, Sanofi, ASIT Biotech, Lofarma, Allergy Therapeutics, AstraZeneca, Bencard-Allergie, Genzyme, HAL-Allergie, Immunologie, HNO-BV GPA, EAACI.

References

[1] Coronavirusidae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020; 5: 536-544. CrossRef PubMed

[2] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JT, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020; 382: 1199-1207. CrossRef PubMed

[3] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu J, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382: 1708-1720. CrossRef PubMed

[4] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395: 497-506. CrossRef PubMed

[5] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology.
[6] Xu X, Gao X. Immunological responses against SARS-coronavirus infection in humans. Cell Mol Immunol. 2004; 1: 119-122. PubMed

[7] Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. J Med Virol. 2020; 92: 418-423. CrossRef PubMed

[8] Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020. Epub ahead of print. PubMed

[9] Zhou F, Yu T, Duan R, Fan G, Liu Y, Liu X, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-1062. CrossRef PubMed

[10] WHO. World Health Organization. www.who.int. 2020.

[11] Aoshi T, Small C, Kiyohara K, Akira S, Ishii KJ. Innate and adaptive immune responses to viral infection and vaccination. Curr Opin Virol. 2011; 1: 226-232. CrossRef PubMed

[12] Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, Perlman S. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe. 2016; 19: 181-193. CrossRef PubMed

[13] Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, Jia X, Nicholson S, Catton M, Cowie B, Tong SYC, Levin SR, Kedzierska K. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med. 2020; 26: 453-455. CrossRef PubMed

[14] Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang Q, Xu S, Zhu H, Xu Y, Jin Q, Sharma L, Wang L, Wang J. Profiling early humoral response to diagnosis novel coronavirus disease (COVID-19). Clin Infect Dis. 2020. Epub ahead of print. CrossRef PubMed

[15] To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, Yip CC, Cui JP, Chan JM, Chik TS, Lau DP, Choi CY, Chen LL, Chan WM, Chan KH, Ip JD, Ng AC, Poon RW, Lau CT, Cheng VC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020; 20: 556-575. CrossRef PubMed

[16] Matricardi PM, Dal Negro RW, Nissim R. The first, holistic immunological model of COVID-19: implications for prevention, diagnosis, and public health measures. Pediatr Allergy Immunol. 2020. Epub ahead of print. PubMed

[17] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181: 271-280.e8. CrossRef PubMed

[18] Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, Ren H, Liu X, Xie J, Xie M, Zhao J, Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020. Epub ahead of print. PubMed

[19] Lagunas-Rangel FA, Chávez-Valencia V. High IL-6/IFN-γ ratio could be associated with severe disease in COVID-19 patients. J Med Virol. 2020. Epub ahead of print. CrossRef PubMed

[20] Arnaldez FI, O’Day SJ, Drake CG, Fox BA, Fu B, Urba WJ, Montesarchio V, Weber JS, Wei H, Wigginton JM, Ascieto Pd. The society for immunotherapy of cancer perspective on regulation of interleukin-6 signaling in COVID-19-related systemic inflammatory response. J Immunother Cancer. 2020; 8: e000930. CrossRef PubMed

[21] Cunningham, K, Kimber I, Baskett DA, MacFauldon JP. Why judiciously timed anti-IL-6 therapy may be of benefit in severe COVID-19 infection. Autoimmun Rev. 2020. Epub ahead of print. CrossRef PubMed

[22] Sabogal Piñeros YS, Bal SM, Dijkhuis A, Majoor CJ, Dierdorf BS, Dekker T, Hoefsmit EP, Bonta PJ, Picavet D, van der Weij MN, Koenderman L, Sterk PJ, Ravanneit L, Luther R. Eosinophilic capture viruses, a capacity that is defective in asthma. Allergy. 2019; 74: 1898-1909. CrossRef PubMed

[23] Jackson DJ, Busse WW, Bacharier LB, Kattan M, O’Connor GT, Wood RA, Visnes CM, Durham SR, Larson D, Exnault S, Ober C, Gergen PJ, Becker P, Togias A, Gern JE, Altman MC. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. J Allergy Clin Immunol. 2020. Epub ahead of print. PubMed

[24] Lindley AW, Schwartz JT, Rodenbeck MG. Eosinophil responses during COVID-19 infections and coronavirus vaccination. J Allergy Clin Immunol. 2020. Epub ahead of print. PubMed

[25] Bhatraj PK, Ghassemi BH, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Warfel MM, Evans L, Kritek P, West TE, Luk S, Gerbino A, Dale CR, Goldman JD, O’Mahony S, Mikacenic C. Covid-19 in critically ill patients in the Seattle region – case series. N Engl J Med. 2020; 382: 2012-2022. CrossRef PubMed

[26] Dong X, Cao YY, Lu XX, Zhang JJ, Du H, Yan YQ, Akdis CA, Gao YD. Eleven faces of coronavirus disease 2019. Allergy. 2020. Epub ahead of print. CrossRef PubMed

[27] Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020. Epub ahead of print. CrossRef PubMed

[28] Drehne M, Kersten A, Bickenbach J, Balfonz P, Hartmann B, Cornilissen C, Daher A, Söhr R, Kléines M, Lemmen SW, Brokkan M, Müller T, Müller-Wieland D, Marx G, Marx N. The characteristics of 50 hospitalized COVID-19 Patients with and without ARDS. Dtsch Arztebl Int. 2020; 117: 271-278. CrossRef

[29] Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020; 323: 1574-1581. PubMed

[30] Agache I, Akdis CA. Precision medicine and phenotypes, endotypes, genotypes, regiotypes, and theratypies of allergic diseases. J Clin Invest. 2019; 130: 1493-1503. CrossRef PubMed

[31] Boyman O, Kaege C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A, Eiwegger T, Firrura D, Harr T, Knarr B, Meyer A, Rumana O, Schmidt-Werner C, Simon HU, Steiner-UC, Vullaggio A, Akdis CA, Sportini F. EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders.
Biologicals in allergic and type 2 inflammatory diseases during the current COVID-19 pandemic

[32] Breiteneder H, Diamant Z, Eiweger T, Fokkens WJ, Traidl-Hoffmann C, Nauze K, O’Hehir RE, O’Meara P, Pizarro O, Tüll MJ, Wang Y, Zhang L, Ackis CA. Future research trends in understanding the mechanisms underlying allergic diseases for improved patient care. Allergy. 2019; 74: 2293-2311. CrossRef PubMed

[33] Palomares O, Untersmayr E, Gutermuth J, Agache I, Ajeanova S, Bavbek S, Chau S, Jutel M, Quince S, Schmidt-Grendelmeier P, Schmidt-Weber C, Torres MJ, Eiweger T. Biologicals in allergic diseases and asthma: Toward personalized medicine and precision health: highlights of the 3rd EAACI Master Class on Biologicals, San Lorenzo de El Escorial, Madrid, 2019. Allergy. 2020; 75: 936-940. CrossRef PubMed

[34] Pfüller B, Yepes-Nuñez JJ, Agache I, Ackis DA, Alsalamah M, Bavbek S, Bossios A, Boyman O, Chaker A, Chan S, Chatzipetrou A, du Toit G, Jutel M, Kauppi P, Kolios A, Li C, Matteucci A, Marson A, Bendien S, Palomares O, et al. Biologicals in atopic disease in pregnancy: an EAACI position paper. Allergy. 2020. Epub ahead of print. CrossRef PubMed

[35] Eyerich S, Metz M, Bossios A, Eyerich K. New biological treatments for asthma and skin allergies. Allergy. 2020; 75: 546-560. CrossRef PubMed

[36] Zuberbier T, Abeler W, Asero R, Abdul Latif AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindels-Jensen C, Brzoza Z, Buene Bedrikov R, Canonica GW, Church MK, Craig T, Danielycheva IV, Dressler C, Ensinca LF, Giménez-Arnau A, Godke K, Gonçalo M, Gruttan C, et al. Endorsed by the following societies: AAAAI, AAD, AAITO, ACAAI, AD, APAACI, ASBAS, ASCIA, BADA, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGA, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GALEN, IAACI, IADVL, JDA, NVA, MSAS, OGDW, PSA, RAACI, SACB, SDF, SGAI, SGDV, SIAUC, SIDeMAST, SPDW, TSD, UNBB, UNEV and WAO. The EAACI/GA2LEN/EV SO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018; 73: 1393-1414. CrossRef PubMed

[37] Fokkens WJ, Lund V, Bachert C, Mullol J, Björner L, Bouzaqet J, Canonica GW, Deneyrier L, Desrosiers M, Diamant Z, Hun J, Heffler E, Hopkins C, Jankovski R, Joos G, Knoll A, Lee J, Lee SE, Marién G, Pugno B, et al. EUFEROA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019; 74: 2312-2319. CrossRef PubMed

[38] Jonstam K, Swanston BN, Mannent LP, Cardell LO, Tian N, Wang Y, Zhang D, Fan C, Holtpaepols G, Hamilton JD, Grabber A, Graham NMH, Pirozzi G, Bachert C. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy. 2019; 74: 743-752. CrossRef PubMed

[39] Hassani M, Koenderman L. Immunological and hematological effects of IL-5(R)-targeted therapy: An overview. Allergy. 2018; 73: 1979-1988. CrossRef PubMed

[40] Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Lin AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SE, Calatroni A, Togias A, Thompson KM, Szefler SJ, Sorkness CA. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011; 364: 1005-1015. CrossRef PubMed

[41] Edwards MR, Strong K, Cameron A, Walton RP, Jackson DJ, Johnston SL. Viral infections in allergy and immunology: how allergic inflammation influences viral infections and illness. J Allergy Clin Immunol. 2017; 140: 909-920. CrossRef PubMed

[42] Jartti T, Smits HI, Bonnelykke K, Bircan O, Elefants V, Konradsen JR, Maggina P, Makrinioti H, Stoholm J, Hedlin G, Papadopoulos N, Ruzeczynski M, Ryzaj K, Schaub B, Schwarze J, Skvank C, Steinberg-Hammar K, Felezko W. EAACI Task Force on Clinical Practice Recommendations on Preschool Wheeze. Bronchiolitis needs a revisit: Distinguishing between virus entities and their treatments. Allergy. 2019; 74: 40-52. CrossRef PubMed

[43] Maitzels RM, William CG. How helminths go viral: Cellular signals during helminth infections can skew the immune response to favor viral spreading. Science. 2014; 345: 517-518. CrossRef PubMed

[44] Rogers KJ, Brunton B, Mallinger L, Bohan D, Sevick KM, Chen J, Ruggio N, Maury W. IL-4/IL-13 polarization of macrophages enhances Ebola virus glycoprotein-dependent infection. PLoS Negl Trop Dis. 2019; 13: e0007819. CrossRef PubMed

[45] Lee A, Park SP, Park CH, Kang BH, Park SH, Ha SJ, Jung KC. IL-4 induced innate CD8+ T Cells Control Persistent Viral Infection. PLoS Pathog. 2015; 11: e1005193. CrossRef PubMed

[46] Lin S-J, Shu P-Y, Chang C, Ng A-K, Hu C-P. IL-4 suppresses the expression and the replication of hepatitis B virus in the hepatocellular carcinoma cell line Hep3B. The Journal of Immunology. 2003; 170: 4708-4716. CrossRef PubMed

[47] Portales-Cervantes L, Crump OM, Duda S, Livieski CR, Gotovina J, Haidl ID, Marshall JS. IL-4 enhances interferon production by virus-infected human mast cells. J Allergy Clin Immunol. 2020. Epub ahead of print. CrossRef PubMed

[48] Teach SJ, Gill MA, Togias A, Sorkness CA, Arbjs SJr, Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Radeke JA, Kercsmar CM, Khurana Hershey GK, Gruchalla RS, Liu AH, Zoratti EM, Kattan M, Grindle KA, Gern JE, Russe WW, Szefler SJ. Pre-seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin Immunol. 2015; 136: 1476-1485. CrossRef PubMed

[49] Carugno A, Raponi F, Locatelli AG, et al. No evidence of increased risk for COVID-19 infection in patients treated with Dupilumab for atopic dermatitis in a high-epidemic area – Bergamo, Lombardy, Italy. Journal of the European Academy of Dermatology and Venereology. 2020. Epub ahead of print. CrossRef PubMed

[50] Karamloof F, König R. SARS-CoV-2 immunogenicity at the crossroads. Allergy. 2020. Epub ahead of print. CrossRef PubMed

[51] Agache I, Song Y, Rocha C, et al. Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma. Allergy. 2020; 75: 1058-1068. CrossRef PubMed

[52] Agache I, Rocha C, Beltran J, Song Y, Posso M, Sols I. Immunology. Pow allergy, immunology. 2020.
cacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: a systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. Allergy. 2020; 75: 1043-1057. CrossRef PubMed

[53] Agache I, Beltran J, Akis C, Akas M, Canelo-Ayar A, Canonica GW, Casale T, Chivate T, Corren J, Del Giacco S, Ewigegger T, Firina D, Gern JE, Hamelmann E, Hanania N, Mäkelä M, Hernández-Martín I, Nair P, O'Mahony L, Papadopoulos NG, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and resizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. Allergy. 2020; 75: 1023-1042. CrossRef PubMed

[54] Klimek L, Förster-Ruhmann U, Becker S, Chaker A, Huppertz T, Deitmer T, Olte H, Strieth S, Wrede H, Schlenert W, Löhler J, Wollenberg B, Beule AG, Rudack C, Bachert C, Dietz A; Autoren im Auftrag des Ärztetverbandes Deutscher Allergologen (AeDA), des Deutschen Berufsverbandes der HNO-Arzte (BVHNO) and der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNO-KHC). Stellungnahme zur Anwendung von Glukokortikosteroiden bei entzündlichen Erkrankungen der oberen Atemwege (u. a. allergische Rhinitis/chronische Rhinosinusitis) während der aktuellen COVID-19-Pandemie – Empfehlungen des Ärzteverbandes Deutscher Allergologen (AeDA), des Deutschen Berufsverbandes der HNO-Arzte (BVHNO) und der AGis Klinische Immunologie, Allergologie und Umweltmedizin und Rhinologie und Rhinochirurgie der Deutschen Gesellschaft für HNO-Heilkunde, Kopf- und Halschirurgie (DGHNO-KHC). Laryngorhinootologie. 2020; 99: 280-281. CrossRef PubMed

[55] Agache I, Lau S, Akis CA, Smolinska S, Bonini M, Cavikatar O, Flood B, Gajdanowicz S, Ishura K, Kalayci M, Mesegos R, Palomares O, Papadopoulos NG, Sokolovska M, Angier E, Fernandez-Rivas M, Pajno G, Pfärr O, Roberts GC, Ryan D, et al. EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma. Allergy. 2019; 74: 855-873. CrossRef PubMed

[56] Buhl R, Bals R, Baur X, Berdel D, Criée CP, Gappa M, Gillissen A, Greulich T, Haidl P, Hamelmann E, Kardos P, Korn K, Klimek L, Korn S, Lommatsch M, Magnussen H, Nicolai T, Nowak D, Pfärr O, Rabe KF, et al. [Guideline for the diagnosis and treatment of asthma – guideline of the German Respiratory Society and the German Atemwegsliga in Cooperation with the Paediatric Respiratory Society and the Austrian Society of Pneumology]. Pneumologie. 2017; 71:e3. PubMed

[57] Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akis CA, Alvaro-Lozano M, Beyer K, Bindseil-Jensen C, Burks W, Elshawa M, Eigenmann P, Knol E, Nadeau KC, Poulsen LK, van Rees R, Santos AF, du Toit G, Dhami S, Nurmatov U, Bolot Y, et al; EAACI Allergen Immunotherapy Guidelines Group. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy. 2018; 73: 799-815. CrossRef PubMed

[58] Roberts G, Pfärr O, Akis CA, Ansonogu IJ, Durham SR, Gerth van Wijk R, Halken S, Larenas-Linnemann D, Pawankar R, Pitsios C, Sheikh A, Worm M, Arasi S, Calderon MA, Cingi C, Dhami S, Fauguet J-L, Hamelmann E, Hellings P, Jacobsen L, et al. EAACI Guidelines on allergen immunotherapy: allergic rhinoconjunctivitis. Allergy. 2018; 73: 765-798.

[59] Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akis CA, Antolin-Amérgio D, Cichocka-Janosz E, Gawlik R, Jakob T, Kosnik M, Lange J, Mingomataj E, Mitsias DI, Olleri M, Oude Elberink JNG, Pfärr O, Pitsios C, Pravettoni V, Rieff E, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy. 2018; 73: 744-764. CrossRef PubMed

[60] de Wilde AH, Pugh U, Potshuma CC, Snijder EJ. Cyclophilins and cyclophilin inhibitors in nido-virus replication. Virology. 2018; 522: 46-55. CrossRef PubMed

[61] Romanelli A, Mascolo S. Immunosuppression drug-related and clinical manifestation of Coronavirus disease 2019: a therapeutic hypothesis. Am J Transplant. 2020. Epub ahead of print. CrossRef PubMed

[62] Rudnicka L, Goldust M, Głowacka P, Sikora M, Sar-Pomian M, Rakowska A, Samochocki Z, Olszewska M. Cyclosporine therapy during the COVID-19 pandemic is not a reason for concern. J Am Acad Dermatol. 2020. Epub ahead of print. CrossRef PubMed

[63] Tian L, Liu W, Sun L. [Role of cyclophilins A during coronavirus replication and the antiviral activities of its inhibitors]. Sheng Wu Gong Cheng Xue Bao. 2020; 36: 605-611. PubMed

[64] Ferrucci S, Romagnuolo M, Angileri L, Berti E, Tavecchio S. Safety of dupilumab in severe atopic dermatitis and infection of Covid-19: two case reports. Journal of the European Academy of Dermatology and Venereology. 2020. Epub ahead of print.

[65] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020; 20: 363-374. CrossRef PubMed

[66] Valaggio A, Agache I, Akis CA, Akis M, Babev S, Bossios A, Bousquet J, Boyman O, Chaker AM, Chan S, Chatzipetrou A, Feleszko W, Firina D, Janet M, Kauppi P, Klimek L, Kollós A, Kothari A, Kowalski ML, Mattucci A, Palomares O, Pfärr O, Rogala B, Untersmayer E, Ewigegger T. Considerations on biologicals for patients with allergic disease in times of the COVID-19 pandemic: an EAACI statement. Allergy. 2020 (epub ahead of print). CrossRef PubMed
Affiliation details

1Zentrum für Rhinologie und Allergologie, Wiesbaden, 2HNO-Universitätsklinik Marburg, Sektion Rhinologie und Allergologie, Medizinische Fakultät Marburg, Philipps-Universität Marburg, 3Comprehensive Allergy Centre Charité, Klinik für Dermatologie, Venerologie und Allergologie, Charité – Universitätsmedizin Berlin, Germany, 4 Translational Medicine Program, Peter Gilgan Centre for Research and Learning, Hospital for Sick Children, Toronto, Ontario, Canada, 5Division of Immunology and Allergy, Food Allergy and Anaphylaxis Program, The Hospital for Sick Children, Toronto, Ontario, Canada, 6Department of Immunology, University of Toronto, Toronto, Ontario, Canada, 7Hals-, Nasen-, Ohrenklinik und Poliklinik, Universitätsmedizin Mainz, Germany 8Department of Infection and Immunity, Luxembourg Institute of Health (LIH), Esch-sur-Alzette, Luxemburg, 9Department of Dermatology and Allergy Center, Odense Research Center for Anaphylaxis, University of Southern Denmark, Odense, Denmark, 10Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medizinische Fakultät der Universität Wien, Vienna, Austria, 11Immunologia and Allergologie Unit, Careggi University Hospital, Florence, Italy, 12Transylvania University, Cluj Napoca, Romania, 13Ankara University, School of Medicine, Department of Chest Disease, Division of, Immunology and Allergy, Ankara, Turkey, 14Abteilung für Atemwegsmedizin und Allergie, Karolinska University Hospital, Huddinge and Abteilung für Medizin, Huddinge, Karolinska Institutet, Stockholm, Sweden, 15Zentrum für Allergieforschung, Karolinska Institutet, Stockholm, Sweden, 16Department of Immunology, University Hospital Zürich, Zürich, Switzerland, 17Faculty of Medicine, University of Zürich, Zürich, Switzerland, 18Guy’s and St. Thomas’ NHS Foundation Trust, Westminster Bridge Road, London, United Kingdom, King’s College London School of Life Course Sciences & School of Immunology & Microbial Sciences, King’s Health Partners, United Kingdom, 19Allergy Unit 2nd Department of Dermatology and Venereology, National University of Athens, Medical School, University General Hospital „ATTIKON“, Athen, Greece, 20Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Kinder- und Jugendmedizin, Fachbereich Kinderpneumologie/Allergologie, Dresden, Germany 21Department of Medical Sciences and Public Health, University of Cagliari, Monseratto, Italy, 22Abteilung für Allergie, Entzündungszentrum, Universitätsklinikum Hamburg, Hamburg, Germany 23Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA, 24Department of Biochemistry and Molecular Biology, Chemistry School, Complutense University of Madrid, Spain, 25Abteilung für Pädiatrische Pulmologie, Allergologie und Endokrinologie, Universitätsklinikum für Kinder- und Jugendheilkunde, Comprehensive Center for Pediatrics, Medizinische Universität Wien, Vienna, Austria, 26Abteilung für Atem- und Lungenerkrankungen, Krankenhaus Hietzing, Vienna, Austria, 27Abteilung für Dermatologie und Venerologie, Kepler Universitätssklinikum, Linz, Austria, 28Klinische Abteilung für Nephrologie, Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Graz, Austria, 29Klinik für Dermatologie und Allergologie, Universität Bonn, Bonn, 30Schwerpunkt Pneumologie, III. Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz, Mainz, 31Zentrum Allergie und Umwelt (ZAUM) Technische Universität und Helmholtz Zentrum München, 32Klinik und Poliklinik für Dermatologie und Allergologie der Technischen Universität München, 33Institut für Klinische Epidemiologie und Biometrie, Universität Würzburg, 34Allergie- und Asthma-Zentrum Westend, Berlin, 35Klinik für Pädiatrie m. S. Pneumologie, Immunologie und Intensivmedizin, Charité – Universitätsmedizin Berlin, 36Abteilung Dermatologie und Allergologie, RWTH Universität, Aachen, 37Medizinische Fakultät der Universität zu Köln, Cologne 38CRI – Clinical Research International Ltd., Hamburg, 39ClinCompetence Cologne GmbH, Köln, Cologne 40Hautklinik und Poliklinik, Universitätsmedizin Mainz, 41Forschungsgruppe Klinische und Molekulare Allergologie des Forschungszentrums Borstel, Airway Research Center North (ARCN), Mitglied des Deutschen Zentrums für Lungenforschung (DZL); Interdisziplinäre Allergie-Ambulanz, Medizinische Klinik III, Universität zu Lübeck, 42LungenClinic Grosshansdorf, Großhansdorf, 43Klinik für Allergologie, Johanniter-Krankenhaus im Fläming Treuenbrietzen GmbH, Treuenbrietzen, 44Klinik für Innere Medizin Schwerpunkt Pneumologie, Philipps-Universität Marburg, 45Einheit für Klinische Allergologie (EKA), Helmholtz Zentrum München, German Research Center for Environmental Health Gmbh, Neuherberg, 46Praxis für Dermatologie, Immunologie und Allergologie, Erfurt, 47Ärzteverband Deutscher Allergologen, Dreieich, 48Haut- und Laserzentrum an der Oper, München, Munich, 49Academia München, 50HNO-Klinik, Universitätsklinik TUM, München, 51ZAUM, Helmholtz Zentrum München, Munich 52Praxis für Dermatologie und Allergologie, Münster, 53Klinik für Hals-, Nasen- und Ohrenheilkunde, Universität Tübingen, 54Asthma und
Allergiezentrum Leverkusen, Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Carl Gustav Carus, Dresden; Praxis für Kinderpneumologie/Allergologie am Kinderzentrum Dresden (Kid), Dresden, Praxis und Klinik für Dermatologie/Allergologie am Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Hals-, Nasen- und Ohrenarzt, Nordrhein-Westfalen, Universitätsklinikum Münster, Klinik für Hautkrankheiten, Ambulanz für Allergologie, Berufsdermatologie und Umweltmedizin, Münster, Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum, Georg-August-Universität, Göttingen, Germany, Klinische Abteilung für allgemeine HNO, Medizinische Universität Graz, Austria, Universitätsklinikum für Dermatologie und Venerologie, Medizinische Universität Graz, Austria, Global Allergy and Airways Patient Platform GAAPP, Vienna, Austria, Allergiezentrum Wien West, Vienna, Austria, Praxis und Klinik für Dermatologie/Allergologie am Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Hals-, Nasen- und Ohrenarzt, Nordrhein-Westfalen, Universitätsklinikum Münster, Klinik für Hautkrankheiten, Ambulanz für Allergologie, Berufsdermatologie und Umweltmedizin, Münster, Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum, Georg-August-Universität, Göttingen, Germany, Klinische Abteilung für allgemeine HNO, Medizinische Universität Graz, Austria, Universitätsklinik für Dermatologie und Venerologie, Medizinische Universität Graz, Austria, Institut für Pathophysiologie und Allergieforschung, Medizinische Universität Wien, Abteilung für Atmungs- und Lungenkrankungen, Krankenhaus Hietzing, Vienna, Austria, Universitätsklinik für Innere Medizin, Medizinische Universität Graz, Austria, Österreichische Lungenunion, Vienna, Austria, Immunopathologie, Abteilung für Pathophysiologie und Allergieforschung, Zentrum für Pathophysiologie, Infektiologie und Immunologie, Medizinische Universität Wien, Austria, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland, Charité – Universitätsmedizin Berlin, Division of Allergy and Immunology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, GARD Chairman, Genf, Switzerland, Department of Rehabilitation and Geriatrics, University of Geneva, Genf, Switzerland, Clinic Cecil of Hirsländen Group of Lausanne; Centre Hôpitalier Universitaire du canton de Vaud Lausanne, Switzerland, Allergiestation, Dermatologische Klinik, Universitätsspital Zürich, Switzerland, Klinische Abteilung für Pneumologie, Universitätsklinik für Innere Medizin II, Medizinische Universität Wien, Austria, Kinderzentrum Bethel, Evangelisches Klinikum Bethel, Universitätsmedizin OWL der Universität Bielefeld, Klinik für Dermatologie und Allergologie, Universitätsklinikum Gießen, UKGM, Justus-Liebig-Universität, Gießen, Klinik für Dermatologie, Allergologie und Venerologie Medizinische Hochschule Hannover, HNO-Klinik, Universitätsklinikum Düsseldorf, Universitätsklinikum Essen (AöR), Germany, Service Immunologie-Allergologie Centre Hospitalier de Luxembourg, Luxemburg, Kinderleben und Gesundheit, Universität von Edinburgh, United Kingdom, Medicine and Microbiology, APC Microbiome Ireland, National University of Ireland, Cork, Ireland, Departments of Immunology, Dermatology and Allergology, University Medical Center Utrecht, the Netherlands, Universität degli Studi di Cagliari, Cagliari, Italy, University Foundation San Pablo CEU, Madrid, Spain, MACVIA-France, Fondation partenariale FMC VIA-LR, Montpellier, France, INSERM U 1168, VIMA: Ageing and chronic diseases Epidemiological and public health approaches, Villejuif, France, Université Versailles St-Quentin-en-Yvelines, UMR-S 1168, Montigny le Bretonneux, France, Euforea, Brussels, Belgium, Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, Germany, Department of Clinical Immunology, Wroclaw Medical University, Wroclaw, Poland, ALL-MED Medical Research Institute, Wroclaw, Poland, and Dermatologische Allergologie, Allergie-Centrum-Charité, Klinik für Dermatologie, Venerologie und Allergologie, Charité – Universitätsmedizin Berlin, Germany.