Daily, Once-Weekly, or No Asthma Controller Therapy At All: The Annoying Issue with Disease Remission in Clinical Asthma Trials

One of the main challenges in the management of patients with asthma is the variability of associated symptoms and airflow limitation over time. Graduation of different severities of the disease still refers to treatment intensity of a regularly applied controller mediation and the related treatment efficacy (1, 2). However, the stepwise treatment approach is not a one-way street and includes regular reassessment of symptoms, exacerbations, side-effects, lung function, and patient satisfaction, consequently encouraging physicians to "step down" to find the lowest possible treatment intensity appropriate to achieve asthma control (1).

Four new monoclonal antibodies have recently been introduced as add-on therapies for patients that have uncontrolled asthma under high-dose inhaled corticosteroid (ICS) therapy together with a second controller medication, usually a long-acting β_2-agonist (LABA) (3). Carefully administered to the right selection of patients, these drugs demonstrate a reduction in annualized exacerbation frequency and the need for continuous oral steroids (3–5). In patients clinically benefiting from such antibody therapies, reports that would clearly support disease-modifying potentials of these medications are missing, and it may still be too early for studies that would support the safe discontinuation of an applied antibody therapy after a certain period of successful add-on treatment.

Escalation on the one hand and deescalation or discontinuation of asthma treatment on the other not only address questions of disease severity but also the concept of disease remission. In pediatric asthma care, this concept is widely accepted, and responsible physicians are trained to carefully reevaluate their patients with respect to the general presence or absence of asthma symptoms and whether diagnostic asthma criteria are still met (6). With regard to puberty in particular, boys are likely to lose their symptoms and go into a phase of disease remission, whereas girls tend to experience new-onset disease during this period (Figure 1) (6). In adult patient care, reevaluation of diagnostic criteria is less common. In a carefully conducted study by Aaron and colleagues (7), investigators tried to reestablish asthma diagnosis in a population-based sample of ~17,000 Canadian households and finally included a sample of 613 participants with asthma that had been physician diagnosed within the previous 5 years. Among the 410 participants in whom the diagnosis could eventually be confirmed, only 86 patients (22.5%) demonstrated guideline-concordant reversibility of airflow limitation at the first study visit; others subsequently had their ICS/LABA controller medication tapered and finally discontinued and were challenged with methacholine up to five times in the upcoming 12 months to at least once meet lung function diagnostic criteria for asthma. Among those 203 participants that repeatedly did not fulfill diagnostic criteria for asthma within the study period, a considerably large proportion of 16% was found to have documented evidence of variable airflow limitation or bronchial hyperresponsiveness within the previous 5 years.

In this issue of the *Journal*, Psallidas and colleagues (pp. 296–306) present a study for which they, first of all, have to be congratulated (8). Their study design was high risk and strived for nothing less than a paradigm shift in asthma treatment. Although the efficacy results for the investigated inhaled TLR9 (Toll-like receptor 9) agonist AZD1419 have to be considered negative, the general conclusions of the study are noteworthy and may help to better understand asthma care delivery and asthma clinal trial design—and they therefore might be kept in mind in a sense of "fail early, fail fast, but always fail forward."

TLR9 recognizes the CpG DNA oligonucleotide motifs typical of bacterial and viral DNA, and its activation leads to production of type I IFN and induction of type 1 (T1)-associated immune responses (9). Investigators of the present study hypothesized that a once-weekly inhaled application of the TLR9 agonist AZD1419 in patients with features indicative of T2 airway inflammation might experience a "rebalancing" of their T2/T1-associated immune responses toward environmental allergens, which they assumed to translate into an effective asthma treatment. Patients were preselected according to the presence of blood eosinophilia (>250/μl prior to inclusion and >150/μl at the screening visit) and were otherwise thought to have stable, persistent asthma that was treated with mostly moderate doses of ICS together with LABA. The most striking—and risky—feature of the study design was the updosing of the study drug in the first 12 weeks of the trial and subsequent tapering of *1*) LABA and *2*) ICS, followed by 40 weeks of observation, thereby striving to replace the daily inhaled ICS/LABA controller therapy for a weekly inhaled TLR9 agonist monotherapy. Consequently, the primary endpoint was chosen to be the time to loss of asthma control as defined by symptoms, exacerbations, lung function, or physician assessment. Investigators assumed that at Week 52, only 20% of asthmatics in the placebo group, which goes along with a total absence of any controller medication for more than 40 weeks, remained controlled, whereas at least 60% in the treatment arm of the study were supposed to have controlled asthma. Although the performance of AZD1419 clearly remained below the expectations with respect to asthma control, a surprising proportion of 40% of patients in the placebo arm did not experience any signs of uncontrolled asthma and might be considered to be in a (temporary) state of "disease

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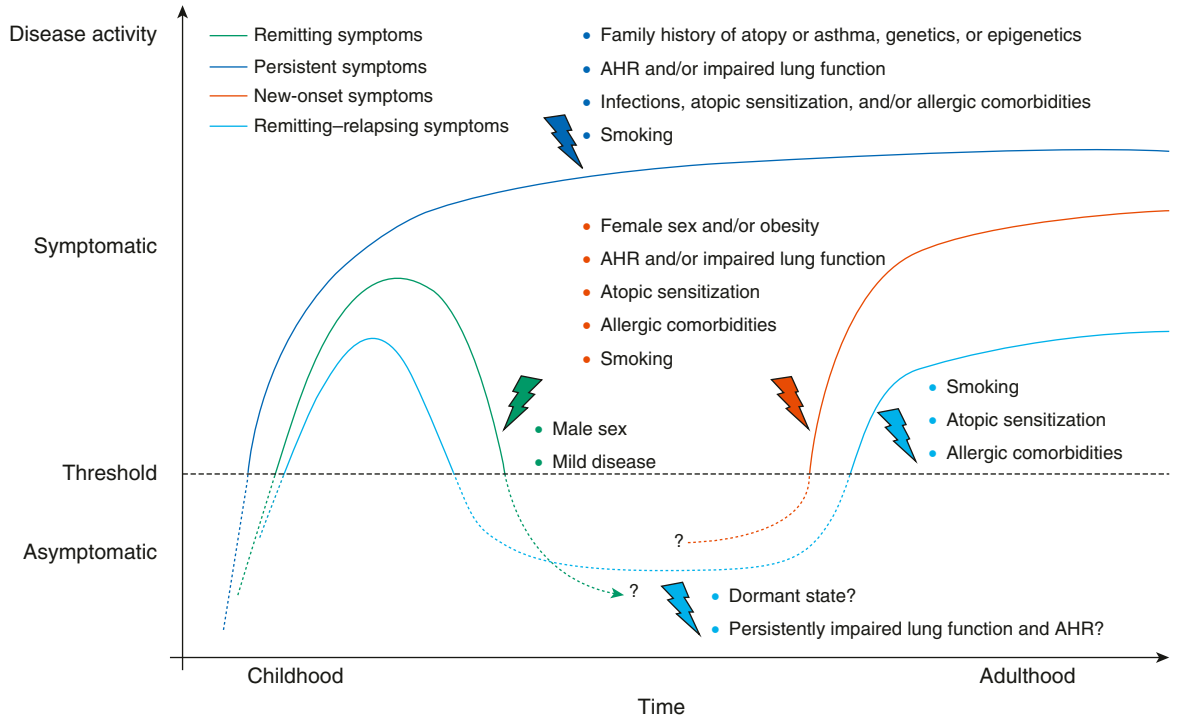

Figure 1. Longitudinal asthma cohort studies have identified genetic background, family history of asthma and atopy, infections early in life, allergic disease, and lung function as risk factors for persistent symptoms. In children and adolescents, male sex is one of the factors associated with remission of symptoms, while in adulthood female sex is associated with new-onset disease. The archetypical phenotype of persistent asthma that starts in childhood and is permanently present throughout life represents only a minority of patients with asthma. Reprinted with permission from Reference 6. AHR = airway hyperresponsiveness.

remission." In those subjects losing asthma control, the time point of time to loss of asthma control was preceded by increasing levels of fractional exhaled nitric oxide as early as 20 days in advance, potentially confirming previous studies using fractional exhaled nitric oxide to guide asthma therapy (10, 11).

So, did AZD1419 fail as a drug? First, a proportion of 40% of patients currently not requiring any asthma medication in the placebo group might be too large to detect any differences and indicates that disease remission in asthma might be an issue that is larger than expected and potentially interferes with clinical trial design. Second, the patients studied were 57 years old on average, with an average age of asthma diagnosis at 43 years. There were slightly more females (55% AZD1419 vs. 58% placebo) in the study, and most patients were overweight. All these factors combined might resemble a distinct asthma phenotype (i.e., female, obese, late onset) that has been identified in several cluster analyses (12, 13). Therefore, the negative results of this study might not readily be transferable to other asthma phenotypes such as the "classic" childhood-onset, atopic phenotype with one or more allergic comorbidities, in whom airway hyperresponsiveness to airborne particles might be the driving pathological feature. Maybe physicians taking take of children with asthma might reconsider the potentials of TLR9 agonists in their respective setting. For physicians taking care of adult patients with asthma, the study by Psallidas and colleagues has delivered many noteworthy insights with respect to disease remission and safe deescalation of established inhaled controller medications but no new drug. ■

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Invasive Pulmonary Aspergillosis Goes Viral Again?

In the last decade, influenza emerged as a risk factor for invasive pulmonary aspergillosis (IPA) in patients admitted to an ICU for respiratory failure (1, 2). A case definition for influenza-associated pulmonary aspergillosis (IAPA) was recently proposed by an expert panel (3). However, the diagnosis of IPA in critically ill patients remains challenging, and the current EORTC-MSG criteria were not validated in immunocompetent ICU patients. Given that the specificity of a positive *Aspergillus* culture of an upper airway sample is low, measurement of galactomannan (GM) in BAL has become an important diagnostic tool in ICU patients (4). The increased awareness and the high mortality of IAPA has generated worldwide concerns that IPA may also occur in critically ill patients with coronavirus disease (COVID-19). Recently, studies of COVID-19–associated pulmonary aspergillosis (CAPA) reported incidences in the range of 3–33% (5, 6).

In this issue of the *Journal*, Fekkar and colleagues (pp. 307–317) report on a retrospective study on the incidence of invasive pulmonary fungal infections in 145 mechanically ventilated patients with COVID-19 (54% on extracorporeal membrane oxygenation) admitted to a large ICU in a 1,850-bed tertiary care center in France (7). A probable or putative invasive pulmonary mold infection was diagnosed in seven patients (4.8%), and four died. The authors used stringent definitions and did not consider an isolated positive non–culture-based fungal diagnostic test or an isolated positive fungal culture with negative follow-up cultures to be proof of infection. This occurred in 25 patients (17.2%). Multivariate analysis found solid organ transplantation and use of corticosteroids to be risk factors for CAPA. The authors should be commended for the careful assessment of CAPA and for providing detailed clinical and microbiological information that helps in distinguishing infection from colonization or a false-positive test result. Yet, as in previous CAPA publications, there was no control group. This precludes definite conclusions on severe COVID-19 being an independent risk factor for IPA. A recent elegant study by Yusuf and colleagues compared the rate of any positive *Aspergillus* test (culture, GM, or PCR) in patients admitted to the ICU for influenza, pneumococcal pneumonia, or COVID-19 (8). A positive *Aspergillus* test on BAL was observed in 18.8% of the patients with influenza, 5.4% of the patients with COVID-19, and 4.6% of the patients with pneumococcal pneumonia. Together with the data provided by Fekkar and colleagues, this study suggests that COVID-19 may not pose a high risk for IPA.

Several possible reasons may explain why the incidence of CAPA varies across studies. First, various definitions were used with a heterogeneity of diagnostic criteria, including BAL and other respiratory samples, such as tracheal aspirates or nonbronchoscopic lavages. In contrast to the definition of IPA in classically immunocompromised patients, the definition of IPA in critically ill patients is associated with much more uncertainty. Second, during the first wave of the pandemic, physicians were reluctant to do aerosol-forming procedures including bronchoscopies in critically ill patients with COVID-19. This explains why GM testing on BAL was often unavailable. Third, the use of immune modulating therapies and, in particular, corticosteroids, known to be associated with an increased risk for IPA, varied substantially between centers. In the study by Fekkar and colleagues, only 17% of the patients received corticosteroid therapy, possibly leading to an underestimation of the CAPA incidence. Now that dexamethasone has become the standard of care for critically ill patients with COVID-19, data on IPA in patients with COVID-19 collected later into the pandemic will be required to take this into account (9).

IAPA has also been reported with variable incidences (1, 10). The time window between ICU admission and diagnosis of IAPA tends to be very short (median, 3 d), whereas CAPA seems to occur later during ICU stay (median, 8–10 d) (11). From a pathophysiological standpoint, severe influenza causes destruction of the respiratory epithelium and of the associated ciliary function necessary to brush out *Aspergillus* conidia, leading to extensive

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