Roads to remission: evolving treatment concepts in type 2 inflammatory diseases

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Summary

Non-communicable diseases (NCDs) characterised by type 2 inflammation, including asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyps, atopic dermatitis, food allergies and eosinophilic esophagitis, are increasing in prevalence worldwide. Currently, there is a major paradigm shift in the management of these diseases, towards the concept of disease modification and the treatment goal remission, regardless of severity and age. Remission as a treatment goal in chronic inflammatory NCDs was first introduced in rheumatoid arthritis, and then adopted in other non-type 2 inflammatory diseases. Among diseases with type 2 Inflammation, this concept is novel and currently most advanced in asthma. This new paradigm has been developed based on a better understanding of the pathophysiology of type 2 inflammation and the advent of highly effective drugs selectively interfering with type 2 pathways. Here, we review the evolution of the new remission concepts in type 2 inflammatory diseases and discuss associated challenges and future research needs.

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Introduction

The ambitious goal of achieving remission in chronic non-communicable diseases (NCDs) is currently gaining attention in diseases associated with type 2 inflammation, due to the availability of drugs selectively and effectively interfering with this inflammatory pathway.[1] Treatment with highly effective, anti-inflammatory drugs targeting key signatures of type 2 inflammation can fundamentally change the course of type 2 diseases. This novel approach drives a paradigm shift in type 2 inflammatory diseases: from symptom control (with short-acting, non-specific drugs) to disease modification and remission (with long-acting, highly specific drugs).[2] This strategy includes the prevention or even a reversal

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of tissue remodeling,[3] such as the resolution of epidermal hyperplasia in atopic dermatitis[4] or of nasal polyps in chronic rhinosinusitis.[5] Here, we review the evolution of the new concepts of remission in type 2 inflammatory diseases and discuss associated challenges and future research needs.

The spectrum of type 2 diseases comprises allergic and non-allergic phenotypes (Fig. 1): some diseases have a predominantly allergic (such as allergic asthma, allergic rhinitis, atopic dermatitis and food allergies), others a predominantly non-allergic phenotype (such as intrinsic asthma or chronic rhinosinusitis with nasal polyps).[1] Altered epithelial barriers (regulating immune responses against environmental triggers) play a fundamental role in the pathogenesis of these diseases.[6] An abnormal secretion of epithelial mediators such as Interleukin-(IL)-33, IL-25 or Thymic stromal lymphopoietin (TSLP) in response to external stimuli (such as viruses, allergens or pollutants) attracts and activates several types of immune cells, including dendritic cells, T cells, B cells, and type 2 innate lymphoid cells (ILC2).[6] There are two main pathways of type 2 inflammation: one pathway is driven by the adaptive immune system (following allergen uptake, dendritic cells stimulate allergen-specific type 2 T-helper cells which in turn orchestrate allergic inflammation), the other pathway is driven by the innate immune system (e.g. orchestrated by ILC2 which are activated in response to epithelial cytokines).[1] Both pathways are characterised by an increased secretion of type 2 cytokines (such as IL-4, IL-5 and IL-13) and a typical accumulation of eosinophils[7] (Fig. 1). In addition, type 2 T-helper cells can stimulate the synthesis of allergen-specific IgE, whereas ILC2 can promote polyclonal Immunoglobulin E (IgE) production.[8,9] Of note, both type 2 pathways can also be activated simultaneously.[10] Chronic type 2 inflammation drives organ-specific pathologies, resulting in typical clinical symptoms such as wheezing (in patients with asthma) or itching (in patients with atopic dermatitis).[1]

Remission concepts: rheumatoid arthritis as the pioneer and role model

The concept of disease remission is well-established in many non-type 2 chronic inflammatory NCDs such as rheumatoid arthritis (RA),[11] vasculitis,[12] inflammatory bowel diseases[13] or connective tissue diseases.[14] Since the 1980s, RA is the pioneer and role model for remission concepts in chronic inflammatory NCDs. Therefore, we start with a short overview of the history of RA remission concepts. RA, the most common inflammatory rheumatic disease worldwide, is characterised by inflammation of the synovial lining (synovitis) of diarthrodial joints, tendon sheaths and bursae, manifesting clinically as swelling (excess synovial fluid), pain and stiffness.[11] Remodeling of synovial tissue causes cartilage thinning and progressive bone defects, reflected by hallmark radiographic features: joint space narrowing and bone erosions.[11] Disease activity in RA is measured using combined scores, encompassing pain

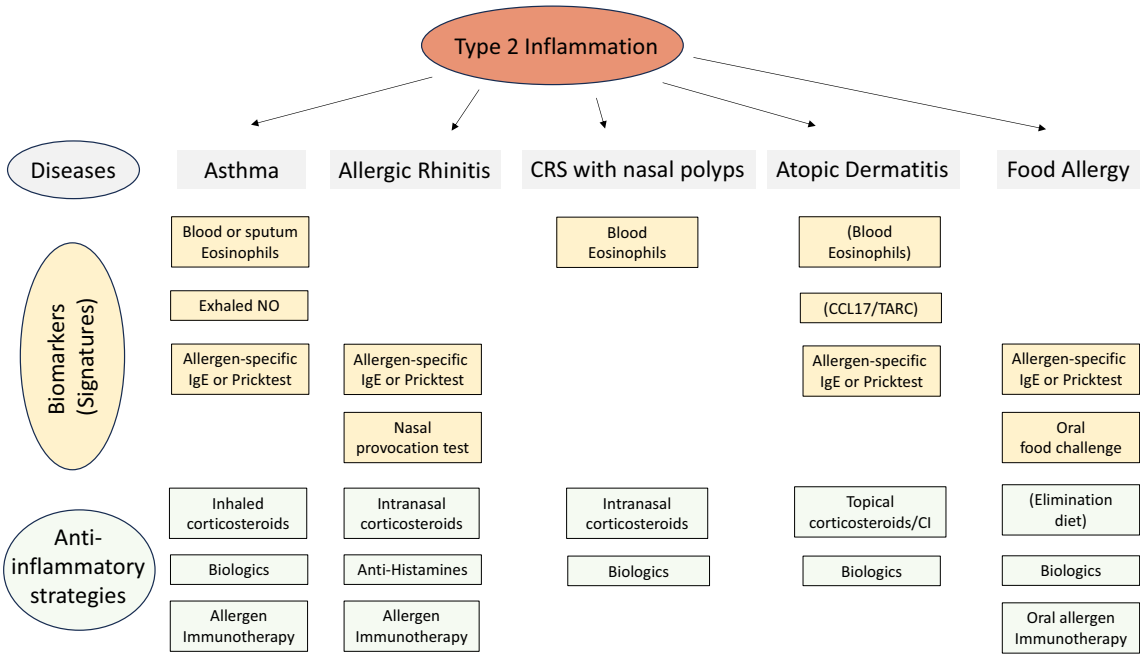

Fig. 1: Biomarkers and anti-inflammatory strategies in type 2 diseases. *Abbreviations denote*: Calcineurin inhibitor (CI), Chemokine ligand 17 (CCL17), Thymus and activation-regulated chemokine (TARC), Immunoglobulin E (IgE), Nitric oxide (NO).

(the leading symptom of active RA), inflammatory activity (measured by the number of swollen joints and systemic inflammatory variables, e.g. C-reactive protein, CRP, or erythrocyte sedimentation rate, ESR) and radiographic signs of joint damage.[15] The core set of disease activity measures defined by the American College of Rheumatology in the early 1990s[16] comprises tender and swollen joint counts, pain, physical function, the physician's global assessment of disease activity and an inflammatory measure. The commonly used disease activity score (DAS) referring to 28 joints (DAS28)[17] is calculated based on swollen and tender joint counts, ESR and the patient's global assessment of disease activity (DAS28-CRP score uses CRP instead of ESR[18]). Two simplified RA activity scores have been developed: the simplified disease activity index (SDAI)[19] and the even simpler clinical disease activity index (CDAI)[20] (Table 1). Concepts of RA control culminated in the concept of *tight control*,[24] where regular DAS28 assessments (every 4 weeks) guided pre-defined treatment escalations.

The concept of disease modification in RA and the term disease-modifying anti-rheumatic drugs (DMARDs) were introduced in the early 1980s[25] to distinguish drugs that inhibit progression of joint damage from purely symptomatic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs). At the same time, the concept of remission as a treatment goal in RA emerged, originally defined as the absence of clinical symptoms and signs of active arthritis (pain, swelling and long-lasting morning stiffness) and a normal ESR for at least two consecutive months.[26] Later on, the composite scores DAS28, SDAI and CDAI were utilised for defining remission and low and high disease activity in RA, using specific cut-off values (Table 1).[21,22] Current remission criteria are either Boolean-based (each of the variables tender joint count, swollen joint count, patient assessment of global disease activity and CRP must have a value of ≤1) or Index-based (e.g. SDAI and CDAI).[27] Treatment strategies aiming at remission include the concept of DMARD treatment *as early as possible* in order to prevent joint damage.[28] Based on these achievements as well as the availability of highly-effective biologics, a group of experts advocated a treat to target ("T2T") approach.[29] The experts defined abrogation of inflammation as the most important goal and remission as the primary treatment target and recommended the regular use of validated composite scores (such as DAS28 and SDAI) to guide treatment. The T2T approach was facilitated by the improved use of methotrexate (e.g. higher doses) as well as by the advent of biologic (bDMARDs) and targeted synthetic (tsDMARDs) drugs which provided significantly higher remission rates when combined with methotrexate.[30] However, it became clear that a substantial proportion of patients with RA cannot reach the ambitious goal of remission. Therefore, low disease activity (LDA) (Table 1) was established as an alternative treatment goal in RA. Dose reductions of DMARDs during follow-up (e.g. by extending treatment intervals by 50% every 3 months) were shown to be possible in a substantial proportion of patients with remission on treatment.[31] Importantly, while currently no biomarkers allow to predict therapeutic responses to DMARDs, early clinical response (within the first 3 months[32]) does and is part of the T2T strategy (significant improvement within 3 months and target achievement within 6 months).

Asthma

Asthma, one of the most prevalent chronic NCDs affecting more than 300 million people globally,[33] is

Disease state	DAS28-Score	SDAI-Score	CDAI-Score
Moderate or high disease activity	> 3.2	> 11	> 10
Low disease activity (LDA)	2.6 - 3.2	3.3 - 11	2.8 - 10
Remission	< 2.6	< 3.3	< 2.8

Table 1: Thresholds defining high and low disease activity and remission in rheumatoid arthritis, in the disease activity score referring to 28 joints (DAS28), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI).[21–23]

associated with chronic inflammation, hyperresponsiveness and variable obstruction of the airways, resulting in symptoms such as dyspnea, wheezing, chest tightness and/or persistent coughing. Both allergic (often starting during childhood or adolescence: early-onset asthma) and non-allergic, intrinsic (often starting in adulthood: adult-onset asthma) phenotypes are typically characterised by type 2 inflammation. Other inflammatory patterns can be present in patients with asthma,[34] however, an absence of type 2 inflammation in a steroid-naïve patient with asthma is very rare in clinical practice.[35] Type 2 biomarker expression (blood eosinophils, exhaled nitric oxide) is higher in adult-onset than in early-onset asthma, especially in patients with severe disease[36]: this is one possible explanation for the observation that severe asthma (requiring treatment with biologics) is more prevalent among patients with symptom onset after the age of 40 years (10%) than among patients with early-onset disease (3%).[37]

Disease control

Over more than 100 years, asthma management had been aiming at symptom control, e.g. using various short-acting bronchodilators.[2] In line with this concept, the *Global Initiative for Asthma* (GINA) announced asthma control as the goal of asthma treatment, and defined 3 forms of control (controlled, partly controlled and uncontrolled asthma).[38] Two validated questionnaires are used to measure asthma control, the Asthma Control Questionnaire (ACQ[39]: primarily used in clinical studies) and the Asthma Control Test (ACT[40]: primarily used in clinical practice), focussing on short time periods (ACQ: 1 week, ACT: 4 weeks).[41] GINA definitions of asthma control use 4 symptom categories (daytime symptoms, nocturnal symptoms, need for rescue treatment, limitations of activities: within the last month)[42] (Table 2). The concept implies that one drug is added to another using a standard step-up scheme until asthma control is achieved ("treat-to-failure" approach): phenotyping is *not mandatory*.[44] The approach was validated in studies such as the GOAL (Gaining Optimal Asthma Control) study (2004): increasing doses of inhaled and oral corticosteroids and long-acting beta-agonists according to a standard protocol led to controlled asthma in a substantial proportion of the patients.[45] It was generally accepted that increasing amounts of drugs are associated with substantial adverse effects, especially in severe asthma where side-effect prone drugs such as systemic corticosteroids were tolerated as a means to reach asthma control.

Disease-modification and remission

The advances in the understanding of the underlying pathophysiology of asthma, especially on the nature of type 2 inflammatory signatures, resulted in the development of highly effective disease-modifying anti-asthmatic drugs (DMAADs), including inhaled corticosteroids (either alone or in combination with long-acting bronchodilators), allergen immunotherapy (either as sublingual or subcutaneous immunotherapy), and biologics.[2] DMAADs are not only characterised by remarkable efficacy and safety, but also collateral efficacy (beneficial effects on comorbidities).[46] The concept of disease modification is closely linked to the concept of asthma remission,[2] which has recently (2023) been adopted in several national guidelines as the general treatment asthma goal.[44] The term asthma remission includes a long-term vision (criteria must be fulfilled for at least one year) and encompasses 3 subtypes: spontaneous remission (e.g. during adolescence), remission off treatment (e.g. after allergen immunotherapy) and remission on treatment (e.g. during treatment with inhaled corticosteroids or biologics). Instead of a standard step-up treatment scheme (treat-to-failure concept), there are 2 phases using an individually tailored treat-to-target concept: induction and maintenance of asthma remission (Fig. 2).[44] Phenotyping is *essential* to identify the right DMAAD for the right patient at the right time.[44] Guidelines agree on 3 central elements in the definition of *clinical remission* ("3-component definition"): very mild or no asthma symptoms (good asthma control), no exacerbations and no use of systemic steroids for asthma treatment (Table 2).[44] There is an ongoing discussion whether stable or normal lung should be added as a fourth criterion ("4-component definition").[47] A recent meta-analysis showed that current remission definitions vary substantially between studies[48]: therefore, a globally standardised definition of asthma remission is needed, both for the comparability of clinical studies and for use in daily clinical routine.[47] Remission is achievable even in severe asthma[49–51]: on average, clinical remission is found in 38% (3-component definitions) or 30% (4-component definitions) of the patients with severe asthma treated with biologics.[48] The fact that not all patients with severe asthma achieve remission does not necessarily reflect an absence of type 2 inflammation in these patients, but rather the presence of factors reducing clinical treatment responses (e.g. biologic treatment not precisely tailored to the phenotype of the patient[52]; relevant comorbidities such as obesity or depression[48]; irreversible airway remodeling due to uncontrolled inflammation and/or cigarette smoke exposure over several decades[3]).

Unmet needs and future research

There is currently no globally accepted definition of clinical asthma remission, especially the role of additional lung function criteria (4-component definition) and the precise thresholds for good asthma control in the context of remission are debated.[47] In addition, factors associated with achieving remission (such as a shorter disease duration, high type 2 markers or presence of nasal polyps)[53] and barriers hampering remission (such as late therapeutic interventions, smoke

	Asthma	Allergic Rhinits (AR)	CRS with nasal polyps	Atopic Dermatitis (AD)	Food Allergy
Symptom control	*GINA criteria for controlled asthma (for 1 month):* - no daytime symptoms - no noctural symptoms - no rescue medication use - no limitations of activities (*at least 3 must be fulfilled*)	*Visual analogue scales (VAS) (0-10 points):* - controlled AR (< 2) - partly controlled AR (2-5) - uncontrolled AR (> 5) *Other control scores:* CARAT, ARCT, RCAT	*EPOS/EUFOREA Control criteria (for 1 month):* - „patient reported control" - Absence of clinically relevant symptoms (*all must be fulfilled*)	*Eczema Activity and Severity Index (EASI, 0-72 points):* > 21 points = severe disease *SCORing Atopic Dermatitis (SCORAD, 0-103 points):* > 50 points = severe disease *Other control scores:* ADCT, RECAP	Allergen-specific threshold doses for clinical reactions after allergen ingestion (specific cut-offs defined by regulatory authorities)
Clinical remission	*Guidelines agree on 3 remission criteria (for a minimum of 1 year):* - Minimal or no asthma symptoms - No exacerbations - No systemic steroids for asthma treatment (*all must be fulfilled*)	*Proposed remission criteria (for a minimum of 1 year):* - Minimal or no symptoms (VAS < 2) - No exacerbations - No systemic steroids for AR treatment (*all must be fulfilled*)	*EPOS/EUFOREA remission criteria (for a minimum of 1 year):* - No CRS symptoms - Absence of signs of active disease (endoscopy) - No need for surgery - No systemic steroids for CRS treatment (*all must be fulfilled*)	*Proposed remission criteria (for a minimum of 1 year):* - Absence of AD skin signs - No itch - Undisturbed sleep - No systemic steroids for AD treatment (*all must be fulfilled*)	*Proposed remission criteria (for a minimum of 1 year):* - Ability to consume the allergen ad libitum - No need to check food ingredients - No need for an adrenalin autoinjector (*all must be fulfilled*)
Unmet needs	- Globally accepted definition of clinical remission - Clinical remission score - Role of lung function and/or type 2 biomarkers as remission criteria - Maintenance of remission: drug management	- Consensus on a definition of clinical remission - Consensus on symptom scores and related cut-offs - Role of biomarkers and endoscopic findings in remission definitions	- Validation of clinical remission criteria - Maintenance of remission: drug management - Endotyping of CRSwNP - New treatment options for CRS without nasal polyps	- Consensus on a definition of clinical remission - Treat-to-target approach with disease activity cut-offs - Prevention of atopic march by early disease modification - Elucidation of mechanisms of reverse remodeling	- Consensus on a definition of clinical remission - Consensus on protective allergen doses - New treatment options to reach remission on and off treatment

Remission definitions are independent from the current treatment status of the patients. *Abbreviations denote*: Atopic dermatitis control test (ADCT), Allergic Rhinitis Control Test (ARCT), Control of Allergic Rhinitis and Asthma Test (CARAT), Chronic rhinosinusitis (CRS), Chronic rhinosinusitis with nasal polyps (CRSwNP), European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS), European Forum for Research and Education in Allergy (EUFOREA), Global initiative for asthma (GINA), Recap of atopic eczema questionnaire (RECAP), Rhinitis Control Assessment Test (RCAT). Cut-off value for SCORAD according to.[43]

Table 2: **Measures of symptom control, concepts of clinical remission and unmet needs in type 2 inflammatory diseases.**

exposure or obesity)[52] need to be identified. Indeed, not all patients with asthma can achieve remission: therefore, the alternative goal of LDA in asthma (Fig. 2) will have to be defined. Furthermore, the usefulness and definition of *biological asthma remission* (e.g. defined as clinical remission plus low type 2 markers and absence of airway pathology) needs to be explored in future studies.[47] Finally, optimal maintenance treatment strategies in patients with remission during biologic treatment (e.g. reduction of inhaled therapies[54] or extensions of treatment intervals[55]) need to be identified in prospective studies.

Allergic rhinitis

Allergic rhinitis (AR) with or without allergic conjunctivitis is a common NCD (median prevalence: 18.1% among adults[56]) characterised by type 2 inflammation of the lining of the nose (associated with IgE-mediated allergic immune responses) and typical symptoms (anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose).[57] AR is classified according to symptom duration (intermittent and persistent AR), and symptom severity and the impact on health related quality of life (mild or moderate/severe AR).[57]

Disease control

Several tests have been developed to characterise symptom control in AR, e.g. the Control of Allergic Rhinitis and Asthma Test (CARAT[58]), the Rhinitis Control Assessment Test (RCAT[59]) or the Allergic Rhinitis Control Test (ARCT[60]). However, these tests were mainly evaluated in non-interventional trials and need to be validated in prospective interventional trials.[61] Visual analogue scales (VAS) are often used in clinical practice and recommended in guidelines, and have been found to correlate with symptoms and quality of life and to detect changes of symptoms and quality of life with high sensitivity[62] (Table 2). Based on VAS measurements, validated mobile Health (mHealth) apps developed threshold cut-offs for defining controlled versus partially/uncontrolled AR and for monitoring of effects of therapeutic interventions.[63]

Disease modification and remission

The concept of disease modification in AR is currently mainly discussed in the context of allergen immunotherapy (AIT).[64] Most authors relate the term disease modification to persistent ("carry-over") immunological effects after AIT cessation.[65,66] There is currently no accepted definition of clinical remission in AR. However, definitions of clinical remission in AR should

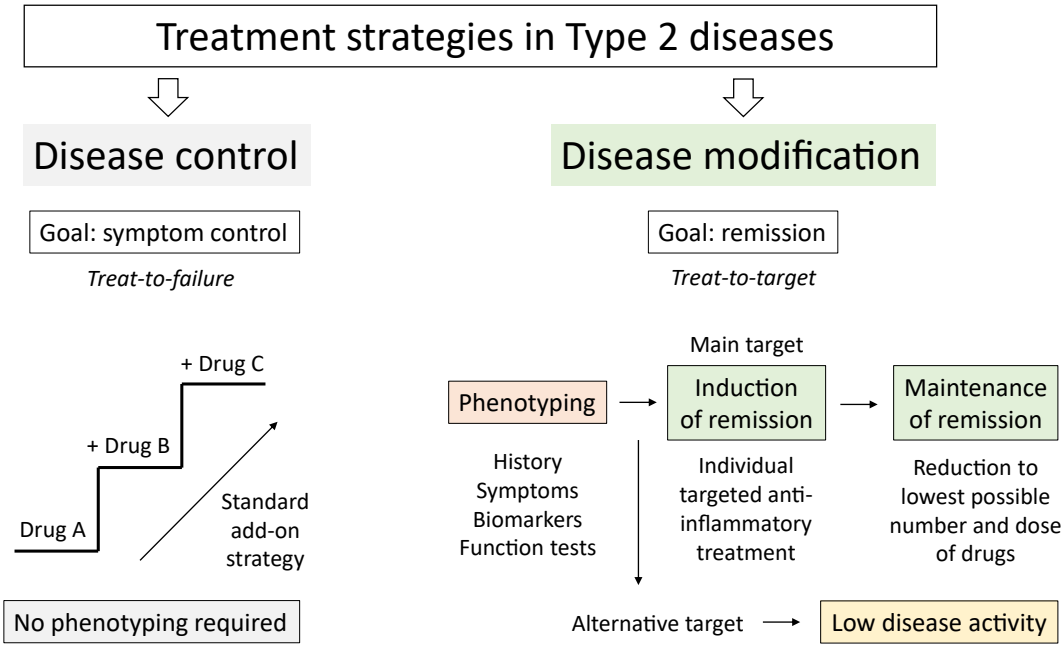

Fig. 2: Treatment strategies in type 2 inflammatory diseases: disease control versus disease modification.

contain patient-related outcome measures (over a period of at least 12 months). In order to define the effects of AIT on AR, the European Medicines Agency (EMA) has proposed 4 categories for use in clinical trials: (1) persistent symptoms during AIT, (2) sustained efficacy during the course of AIT, (3) carry-over efficacy after cessation of AIT and (4) the cure of allergies.[67] In analogy to remission concepts in other diseases, EMA category 2 is comparable with the concept of "remission on treatment" and EMA categories 3 and 4 with the concept of "remission off treatment".[67] We propose a remission definition with 3 components (all must be fulfilled for a period of at least 1 year): (1) minimal or no symptoms (VAS <2), (2) no exacerbations, (3) no need for systemic steroids for AR treatment (Table 2).

Unmet needs and future research

A consensus on the definition of clinical remission and LDA in AR is needed and should be validated in future clinical trials. Consented cut-offs of AR symptom measures will be a prerequisite for this definition. Of note, changes in biomarkers have not been found to correlate well with changes in AR symptoms following AIT[68]: therefore, the role of biomarkers in AR remission definitions needs to be further explored. Finally, research efforts on the role of endoscopic and/or histologic findings for remission concepts are needed in AR.

Chronic rhinosinusitis with nasal polyps

Around 1–2% of adults have chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP). This subgroup of CRS differs from the more common CRS without nasal polyps (CRSsNP) by the presence of polyps (which are determined endoscopically). Although type 2 inflammation is present in most patients with CRSwNP, there is no association with allergies.[69] CRSwNP is often associated with adult-onset eosinophilic asthma, and sometimes with NSAID-exacerbated airway disease (N-ERD) and/or eosinophilic granulomatosis with polyangiitis (EGPA).[69] Typical symptoms of CRSwNP are nasal obstruction, reduction in (or even loss of) sense of smell, nasal discharge, and sleep disturbances.[69] Disease burden of CRSwNP is high, given the major impairment in quality of life and high recurrence rates despite surgical treatment.[70]

Disease control

Symptom control was the aim of CRSwNP treatment over decades, using intranasal and/or systemic corticosteroids and (often recurrent) endoscopic sinus surgery.[69] Symptoms (such as rhinorrhoea, sneezing, nasal obstruction, reduction in sense of smell, headache, postnasal drip, fatigue, facial pain and pressure) are assessed using VAS scores (scales from 0, indicating total absence of symptoms, to 10, indicating worst symptoms).[71] In addition, the Sino-Nasal Outcome Test (SNOT-22) is used in clinical practice, a validated 22-item questionnaire measuring disease-specific, health-related quality of life in patients with rhinosinusitis.[72] In 2021, the European Forum for Research and Education in Allergy (EUFOREA) defined *severe CRSwNP* as bilateral CRSwNP with a nasal polyp score of at least 4 of 8

points and persistent symptoms, including loss of smell and/or taste, nasal obstruction, secretion and/or post-nasal drip, and facial pain or pressure, with the need for add-on treatment to supplement intranasal corticosteroids.[73] *Uncontrolled CRSwNP* was defined as persistent or recurring CRSwNP despite long-term treatment with intranasal corticosteroids and having received at least 1 course of systemic corticosteroids in the preceding 2 years and/or previous sino-nasal surgery[73] (Table 2). A recent international consensus defined CRSwNP control as patient-reported disease control and the absence of clinically relevant sino-nasal symptoms (determined by VAS ≤5 cm for overall symptom severity, nasal obstruction, and loss of smell) within the last month.[5]

Disease modification and remission

Advances in the understanding of CRSwNP pathophysiology and the availability of biologics (since 2019) have paved the way for CRSwNP treatment without surgery and systemic steroids.[74] Currently, three highly-effective biologics (dupilumab, omalizumab, and mepolizumab) are approved for severe CRSwNP treatment.[75] These biologics have not only been incorporated in clinical guidelines,[74,76] but also stimulating discussions on disease modification and remission in CRSwNP. A recent consensus of international experts defined CRSwNP remission as the absence of symptoms, absence of endoscopic CRSwNP features and absence of a need for surgery or systemic corticosteroid treatment for a period of at least 12 months[5] (Table 2). This definition is independent from the current treatment status, thus encompassing remission on and off treatment.[5] Data from real-world-studies demonstrated that clinical remission can be achieved in a substantial proportion of patients with severe CRSwNP.[77]

Unmet needs and future research

The current definition of CRSwNP remission[5] needs to be prospectively validated in clinical trials and has to prove its applicability in clinical routine. In addition, the CRSwNP management during remission requires further studies: recent evidence suggests that extensions of treatment intervals are feasible in the majority of patients with on-treatment remission.[78] Because there are CRSwNP endotypes without type 2 inflammation,[79] characterisation of the patients before biologic treatment will gain attention. All currently available biologics approved for CRSwNP treatment target type 2 inflammation: therefore, new treatment options for CRSwNP without type 2 inflammation need to be developed.

Atopic dermatitis

Atopic dermatitis (AD), a chronic inflammatory NCD of the skin affecting up to 20% of the pediatric (highest incidence in the first 2 years of life) and up to 5% of the adult population is characterised by itch (the most disturbing symptom for many patients), dryness of the skin, and typical skin lesions (including lichenification).[80] The pathophysiology of AD is complex, involving skin barrier dysfunction, altered microbiome and immune dysregulation (including overexpression of type 2 cytokines and alarmins).[81] Several intrinsic and extrinsic factors (e.g. allergens, irritants, *Staphylococcus aureus* colonisation) can trigger the disease. There may be ethnic and age-specific differences in AD pathophysiology.[82] Type 2 comorbidities such as food allergy, allergic asthma and AR are most commonly observed in severe cases with early onset disease, poly-sensitisation and an atopic family history.[83]

Disease control

Symptom control, improvement in severity of skin lesions and improvement of quality of life have been the general treatment goals in AD for decades. The severity of AD symptoms is assessed by the 2 validated scores: the Eczema Activity and Severity Index (EASI), which describes the extent and morphologic features of affected skin lesions (a maximum of 72 points can be achieved, with higher scores indicating more severe disease),[84] and the SCORing Atopic Dermatitis (SCORAD) score (a maximum of 103 points can be achieved, with higher scores indicating more severe disease) which not only describes the severity and extent of the lesions, but also includes subjective symptoms (such as pruritus and sleep disturbances) and xerosis of non-lesional skin sites (Table 2). However, US regulators require measuring severity with the Investigator Global Assessment (IGA) which was recently improved by the addition of greater morphologic descriptors (referred to as the validated IGA, vIGA: a maximum of 4 points can be achieved, with higher scores indicating more severe disease).[85] The EASI and vIGA scores are primarily used in clinical trials, describing the proportion of patients achieving 50% (EASI-50), 75% (EASI-75) or 90% (EASI-90) improvements or the percentage of patients achieving a vIGA score of 0 or 1. Other assessment tools are the pruritus VAS (0–10) and the quality of life questionnaire DLQI (dermatology-life-quality-index, pediatric version: CDLQI). Although the atopic dermatitis control test (ADCT) or the recap of atopic eczema questionnaire (RECAP)[86] have been validated, they have just recently become more commonly employed in clinical practice.

Disease modification and remission

The treatment landscape of AD has fundamentally changed over the last years.[4] Until 2017, broadly acting anti-inflammatory agents such as topical or oral corticosteroids, cyclosporine and topical immunomodulators (tacrolimus, pimecrolimus) were used in clinical practice, with their long-term use limited by side effects. The first biologic licensed for AD was dupilumab (targeting the type 2 cytokines IL-4 and IL-13), and is currently the

only biologic licensed for moderate-severe AD in preschool children (6 months–6 years). Dupilumab does not only substantially improve AD symptom scores,[87] but also rapidly normalises the skin microbiome,[88] improves the disrupted skin barrier,[89] strengthens virus-specific immune responses[90] and reduces allergen sensitisation.[91] Results of a meta-analysis of clinical trials in patients with AD of different age groups point to an overall reduction of specific IgE levels and symptoms related to atopy and allergy following dupilumab treatment.[91] These effects led to the hypothesis that early intervention with dupilumab may not only modify the course of AD but also interrupt the atopic march (development of co–or poly-morbidities): this has to be addressed in further studies. Spontaneous remission is common in AD, among patients with an early onset of AD, more than 40% are in remission by the age of 3 years.[92] However, there is currently neither an accepted definition for spontaneous remission nor an accepted definition for remission on treatment in AD, although there is an ongoing discussion whether a treat-to-target approach (analogous to RA) should also be used in AD.[93] We, therefore, propose a remission definition with 4 components (all must be fulfilled for a period of at least 1 year): (1) absence of AD skin signs, (2) no itch, (3) undisturbed sleep, (4) no need for systemic steroids for AD treatment (Table 2).

Unmet needs and future research

Given the profound disease-modifying effects of biologics in AD, a generally accepted definition of remission and LDA is urgently needed in AD,[4] as a prerequisite for treat-to-target approaches in AD. In addition, research is needed to elucidate whether early biologic treatment of AD can stop the atopic march (subsequent development of allergic asthma or allergic rhinitis) and poly-morbidity (such as concurrent anxiety, depression, infections, attention deficit hyperactivity disorder, osteopenia/osteoporosis), respectively. Finally, mechanisms of reverse remodeling in AD (e.g. resolution of skin abnormalities) during biologic treatment should be explored.

Food allergy

IgE-mediated food allergy (FA) poses a worldwide health problem. The prevalence of self- or parent-reported FA ranges between 7.6% in children[94] and 10.8% in adults,[95] however, the prevalence of proved FA (using double-blind, placebo-controlled oral food challenges) is much lower.[96] Following allergen ingestion, the spectrum of symptoms can range from tingling of the mouth to acute, systemic (possibly life-threatening) allergic reactions. Patients at risk are advised to strictly avoid the allergen and carry an adrenaline autoinjector. In addition to allergen avoidance, new treatment options such as oral AIT[97] or biologics[98] have recently been approved.

Search strategy and selection criteria

Data and reference articles for this viewpoint (published before Dec 1, 2024) were identified by searches of MEDLINE, PubMed, and references from articles, using the combination of one of the diseases examined ("asthma", "allergic rhinitis", "chronic rhinosinusitis with nasal polyps", "atopic dermatitis", "food allergy" or "eosinophilic esophagitis") and the term "remission" OR "disease modification" OR "control". Candidate studies (including brief reports and case reports) were reviewed and relevant articles about type 2 inflammatory diseases were selected based on titles and abstracts. These studies were obtained and read in full, and all relevant information extracted and collated.

Disease control

Ideal disease control in FA is the protection of patients from allergic reactions after accidentally ingesting the allergen, resulting in less severe and/or less frequent allergic reactions. Due to the relatively low number of accidental events,[99] trials using these events as a primary outcome would either require a huge number of participants or many years of follow-up. Therefore, regulatory authorities proposed a surrogate marker for disease control, i.e. the measurement of a state of "desensitisation" (increased threshold allergen dose for clinical reactions after food ingestion)[100](Table 2). However, "protective" threshold levels can be controversial, e.g. for trials on oral AIT for peanut allergy. In addition, these thresholds can be influenced by individual factors such as exercise or sleep deprivation.[101]

Disease modification and remission

There is currently no accepted definition of clinical remission for FA. We propose a remission definition with 3 patient-related components: (1) the ability to consume the allergen any time at any dose (ad libitum), (2) no need to check food ingredients and (3) no need for an adrenalin autoinjector (Table 2). Spontaneous remission would be close to the term "spontaneous tolerance", which relates to patients who outgrow FA without any treatment. (e.g. 89% of egg allergic and 30% of peanut allergic infants develop spontaneous tolerance by 6 years of age[102]). Despite the advent of oral AIT for peanut allergy[97] and the anti-IgE antibody omalizumab for multiple FA[98] in clinical practice, there is currently no evidence that remission on treatment can be achieved with these treatments: accidental reactions after allergen ingestion still occur.[98,103] Remission off treatment might resemble the concept of "sustained unresponsiveness" (persistent increase in allergen threshold) following oral AIT. Studies demonstrating "sustained unresponsiveness" following AIT did not show that patients can eat the allergen ad libitum or stop carrying their adrenalin autoinjector,[104] and revealed response

rates similar to patients with "spontaneous tolerance".[105] Oral AIT,[106] epicutaneous AIT[107] and sublingual AIT[108] in small children can be an efficacious approach. A window of opportunity in very young patients (<3 years of age) to achieve remission following AIT is anticipated.[106] More clinical studies with standardised allergen preparations and long-term follow-up are needed to prove this hypothesis.

Unmet needs and future research

An international consensus on the exact "protective dose" for disease control needs to be established. Real-world data on the frequency of accidental reactions on treatment will help to find such a consensus. Definitions of remission and LDA in FA are needed. Although none of the current available therapies reach the goal of remission, spontaneous remission does occur and future therapeutic options might be more effective in reaching remission on treatment. Therefore, the authors propose to further explore a new patient-centred definition of remission in FA (ability to consume the allergen ad libitum, no need to check food ingredients, no need for an adrenalin autoinjector).

Less common type 2 inflammatory diseases: eosinophilic esophagitis as an example

Remission concepts are currently gaining attention in less common type 2 inflammatory diseases, too. One example is eosinophilic esophagitis (EoE). Current estimates suggest that the prevalence of EoE is about 0.1% in general populations (with large variations across countries and age groups).[109,110] EoE is associated with type 2 inflammation (and often type 2 comorbidities), an impaired mucosal barrier (leading to tissue remodeling and progressive organ dysfunction) and symptoms such as vomiting, abdominal pain, feeding intolerance (younger patients) or heartburn, dysphagia and food impactions (adults).[111] Recent trials[112,113] have not only shown that a biologic (dupilumab) can be more effective than traditional options (e.g. food allergen avoidance, use of swallowed corticosteroids) in EoE, but have also introduced the concept of remission in EoE, which will be explored in future clinical trials.[114]

Outstanding questions

Despite recent progress regarding remission concepts in type 2 diseases, several important questions remain to be answered. *(1) Definitions and Scores:* There is an urgent need to develop consensus definitions of clinical remission in type 2 diseases (i.e. specific remission definitions for each disease). In addition, there is a need for easy-to-use, multidimensional scores (encompassing symptoms, organ function and inflammation) to quantify disease activity. *(2) Safety:* The safety of disease-modifying drugs needs to be further explored, including long-term safety (e.g. biologic treatment over decades[115]), safety in vulnerable populations (e.g. very young children,[116] pregnant women[117] or patients with immunodeficiencies[118]) and safety of combined treatments (e.g. dual biologic therapy[119]). *(3) Dosing:* Reductions of drug doses[54] or extensions of treatment intervals (spacing)[120] during remission will need to be investigated, in order to minimise adverse effects and treatment burden. *(4) Alternative Target:* Remission cannot be achieved in all patients with type 2 diseases: therefore, the alternative target of LDA needs to be defined in each disease. *(5) Mechanisms:* Clinical research will have to be combined with investigations of underlying mechanisms, aiming at the discovery of novel disease-modifying pathways and biomarkers. In this regard, the role of *biologic remission* concepts (e.g. clinical remission plus absence of inflammation) will require further research. *(6) Remodeling:* Structural improvements (even reverse remodeling) are part of the remission picture[3] and warrant further mechanistic elucidation (e.g. role of mesenchymal stem cells).

Conclusion

Remission as a treatment goal in chronic inflammatory NCDs was first introduced in RA, and then adopted in other non-type 2 inflammatory diseases. Among diseases with type 2 Inflammation, this concept is novel and currently most advanced in asthma.[44,47] Aiming at remission in type 2 inflammatory diseases offers many opportunities in the future. However, much more clinical and mechanistic insight has to be gained until this concept can be fully established.

Contributors

ML and HR wrote the initial draft of the manuscript. IHT and JSS wrote the initial draft of the paragraph on rheumatoid arthritis. ML, GGB, SL, EH and CT wrote the initial draft of the paragraph on asthma. JB and OP wrote the initial draft of the paragraph on allergic rhinitis. MWa, WJF and OP wrote the initial draft of the paragraph on chronic rhinosinusitis. LAB, SL, HO and TW wrote the initial draft of the paragraph on atopic dermatitis. KB, MWo and HAS wrote the initial draft of the paragraph on food allergies. HAS wrote the initial draft of the paragraph on eosinophilic esophagitis. All authors read and approved the final version of the manuscript.

Data sharing statement

This article does not contain shareable data.

Declaration of interests

ML reports grants for research or clinical trials, paid to his institution, from AstraZeneca, Deutsche Forschungsgemeinschaft (DFG), and GSK; and consulting fees, travel expenses, or honoraria for lectures from ALK, Allergopharma, Apontis, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GSK, HAL Allergy, Leti, Novartis, MSD, Sanofi, Stallergenes, Teva. KB reports on grants for research or clinical trials, paid to the institution from Aimmune therapeutics, Nestle, DBV technologies, Novartis, Hipp GmbH and consulting fees, travel expenses, or honoraria for lectures from ALK-Abello Arzneimittel GmbH, Allergopharma, Aimmune therapeutics, Allergy therapeutics, Danone Deutschland GmbH, DBV Technologies, Engelhard Arzneimittel, Novartis Pharma AG, Sanofi, ThermoFisher Scientific, Mylan Germany GmbH, German society of clinical chemistry and laboratory medicine, Stallergenes GmbH, German society of allergology and clinical immunology, German society of

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