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Minireview

Modern therapies in atopic dermatitis: biologics and small molecule drugs

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Summary

Atopic dermatitis (AD) is a frequent, chronic remittent skin disease. The pathophysiology of AD has been increasingly understood within the last years, which may help to identify different endotypes suitable for defined therapies in the future. A patient-oriented therapy considers phenotypical features in addition to genetic and biological markers. The most recent developments in biologics and small-molecule drugs for AD treatment are presented in this article. These molecules, if approved, could change the perspectives for future therapies.

Dupilumab is the first approved biologic for the treatment of moderate to severe atopic dermatitis in adolescence and adulthood and has led to a significant improvement in the treatment of this chronic disease. In the present article we present real-life data on the efficacy of dupilumab in adult dermatitis patients. We also discuss other data relevant to the use of dupilumab, and address open questions important for the standard care of atopic dermatitis patients.

Introduction

Together with psoriasis vulgaris, atopic dermatitis is one of the most common chronic inflammatory skin diseases. Children are more often affected (5–20 % of all children worldwide), while the prevalence in adults is estimated at 7–10 % [1, 2]. In recent years, the pathophysiology of atopic dermatitis has been increasingly better understood. Currently, it is assumed that two major mechanisms promote the chronic inflammation of the skin. First, a genetically determined impairment of the barrier function of the skin triggered by mutations in barrier and structural proteins, respectively [2], results in increased penetration of the skin by irritants, allergens, and microbes [3]. In addition, there is a genetically determined immunological disbalance characterized by an enhanced TH2 response accompanied by production of inflammatory cytokines, in particular IL-4 and IL-13 [3]. These cytokines support the development of a polyvalent type 1 sensitization [4] and promote barrier impairment. In recent years, additional cytokines have been identified that play an important role in the pathophysiology of chronic inflammation of the skin. These include IL-31, TSLP, IL-17 cytokines (A and C) and IL-22 [4, 5]. In concert, these mediators orchestrate chronic inflammation in the skin. In addition, they may have a negative effect on the expression of barrier proteins [5] (Figure 1, Table 1).

State of the art

According to the guidelines on treatment of atopic dermatitis, the only systemic medical therapies available for moderate to severe forms of the disease are cyclosporin and, since 2017, dupilumab, an antibody against the IL-4/IL-13 receptor [6, 7]. Given that both efficacy and tolerability of dupilumab are assessed as being very good, treatment options with the antibody has improved the care of patients with moderate to severe atopic dermatitis [8]. Compared to treatment with cyclosporin, for example, no regular lab controls are required during therapy. Nevertheless, numerous practice-oriented questions have arisen since the approval of dupilumab in adults, with respect to efficacy under everyday conditions, adherence of patients under non-trial conditions, tolerability during long-term use, and efficacy in other dermatological diseases.

Efficacy of dupilumab under everyday conditions

Standardized data collection under real-life conditions is required to assess whether efficacy and tolerability of a drug in daily life are comparable to the results observed in controlled trials. A recently published article from Spain with data on
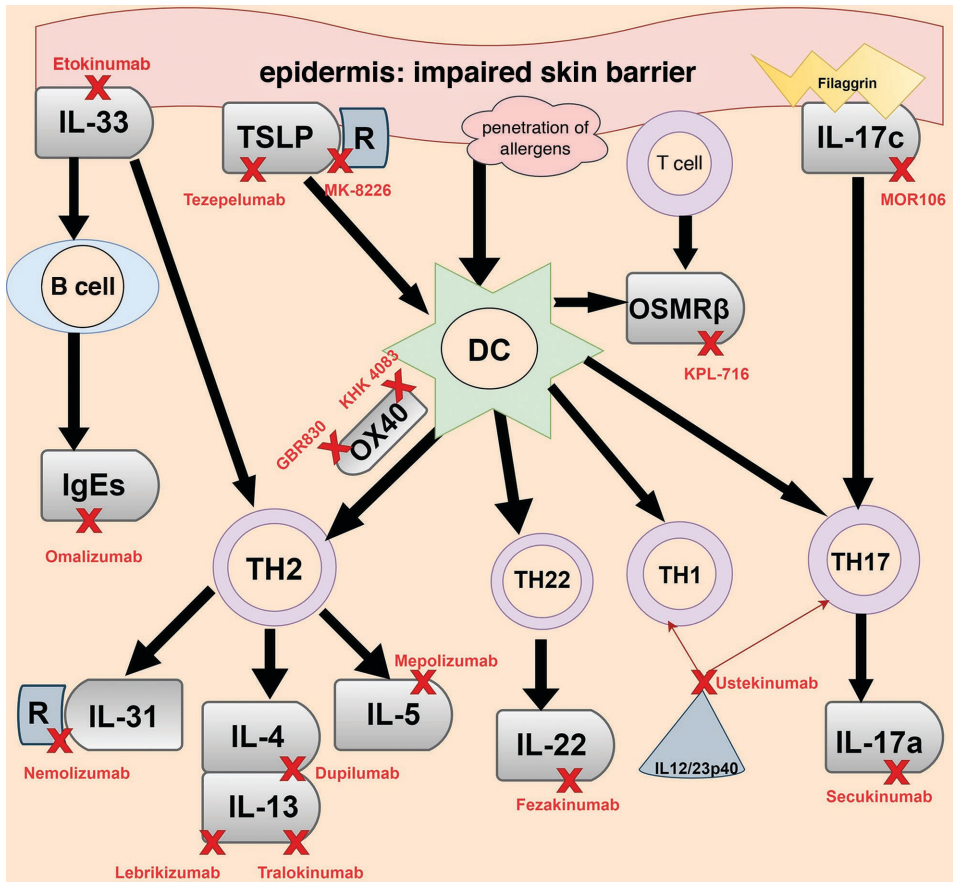
Figure 1 Therapeutic targets for biologics in atopic dermatitis (modified according to [5]).
Abbr.: R, receptor; DC, dendritic cells; TSLP, *thymic stromal lymphopoietin*; OSMRβ, oncostatin M receptor subunit β.

Table 1 Cytokines: mode of action in atopic dermatitis.

Cytokines	Main producers	Function
IL-33	Keratinocytes	Promotes TH2 cytokine response. Induces expression of IL-5 and IL-13, enhances eosinophils and immunoglobulins.
IL-25 or IL-17E	Keratinocytes	Promotes TH2 cytokine response. TSLP-activated dendritic cells promote TH2 polarization and IL-25 transmits this signal to the TH2 cells.
TSLP	Keratinocytes	Promotes TH2 cytokine response. Acts on T cell differentiation by activating dendritic cells.
IL-4	TH2 cells	TH2 cell differentiation, IgE production, and eosinophilia. Promotes epidermal inflammation, acanthosis, and fibrosis. Reduces AMP production.
IL-5	TH2 cells	Promotes eosinophilia.
IL-13	TH2 cells	Promotes epidermal inflammation and fibrosis. Reduces AMP production.
IL-31	TH2 cells, mast cells	Promotes pruritus and inflammation.
IL-17 (group of several homologous proteins)	TH1, TH2, TH17, and ILC cells	Triggers production of IL-4 in TH2 cells. Promotes differentiation of B cells to IgE-producing plasma cells. Promotes production of IL-8, TNFα, TSLP, CCL17, CXCL10, and antimicrobial peptides.
OX40	TH2 and CD8+ cells	Development and maintenance of TH2 response.
Modified according to [29–32].		
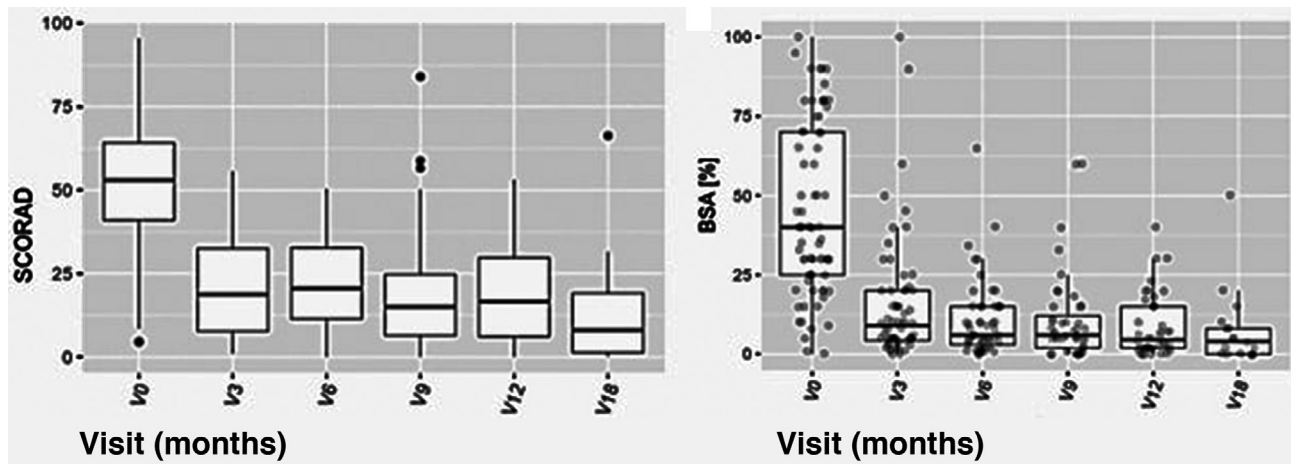
Figure 2 Real-life data of patients treated with Dupilumab (n = 104) at the Charité hospital in Berlin. This cohort includes 60 male (57.7%) and 44 female (42.3%) patients. The mean age at the beginning of therapy was 47.5 years for male and 44.9 years for female patients. The mean value of the SCORAD at the start of therapy was 51.7 for male and 48.7 for female patients. The mean value of the affected body surface area (BSA) at the beginning of the therapy was 26.5% in the male and 25.3% in the female patients. *Abbr.:* SCORAD, *SCORing atopic dermatitis*; BSA, affected body surface area.

70 patients treated with dupilumab showed good efficacy regarding both skin condition and pruritus [9]. In this cohort, the skin condition improved by 60–70 % after six months of treatment. We obtained similar data in patients treated with dupilumab at the Department of Dermatology at the Charité in Berlin (n = 104). After three months of therapy, 32 % of the patients achieved a SCORAD (*Scoring atopic dermatitis*) of 75 and 67 % achieved SCORAD50. Even after six months of therapy, the SCORAD continued to improve by more than 60 %. In addition, the affected body surface area (BSA) was significantly reduced (from 42.17 % to 9.9 %) (Figure 2). As illustrated in Figure 2, both reduction of the affected body surface area and stabilization of SCORAD was observed in these patients with a therapy duration of up to 18 months. Additional details on this cohort can be found in the figure legend.

The first published data from the German TREAT registry also showed a reduction of EASI (*Eczema Area and Severity Index*) and *objective* SCORAD (oSCORAD) after three and six months of dupilumab therapy [10]. (oSCORAD mean percentage reduction to 54.7 % after three months, and EASI mean reduction to 74.2 % after three months of therapy.)

So far, there are no published data on the adherence of patients to dupilumab therapy. Based on our own experience from special consultations, more than 90 % of the patients adhere to the therapy. In the present case, adherence is defined as patients regularly coming to the clinic for scheduled visits within a year and therapy being performed according to the physician's instructions.

Skin infections on dupilumab therapy

Infections of the skin are a common problem in atopic dermatitis, especially in moderately to severely affected patients. Analysis of pooled data from patients treated with dupilumab demonstrated no increased risk of skin infections on long-term therapy with dupilumab [11]. Interestingly, the relative risk of skin infections was reduced especially in patients receiving supplementary anti-inflammatory treatment with corticosteroids in addition to the systemic dupilumab therapy [11].

Efficacy of dupilumab in other atopic and dermatological diseases

In respect to other atopic diseases, good efficacy of dupilumab has been shown in treatment of allergic asthma, especially in patients with peripheral eosinophilia and increased fractional exhaled nitric oxide (NO) [12]. Dupilumab was approved for allergic asthma at a dosage of 200 mg every 14 days in June 2019 and for the therapy of chronic sinusitis with nasal polyposis in November 2019 [13]. This has opened another, much needed therapeutic option for patients with particularly severe, recurrent sinusitis with nasal polyps [14]. Currently, dupilumab trials are being conducted in the USA for treatment of eosinophilic esophagitis and food allergy. In addition, the efficacy of the antibody is being evaluated for diseases outside of the atopic spectrum. There are, for example, trials underway

on the treatment of chronic obstructive pulmonary disease (COPD) in the USA.

Only individual case reports are available on the use of dupilumab for the treatment of other dermatological diseases. Besides a recently described case of improved alopecia areata [15], there are also case reports claiming development of the condition during dupilumab therapy. In a few isolated cases, patients with severe atopic dermatitis and simultaneous malignant disease have been treated with dupilumab [16]. Future long-term data are required for a final safety assessment of this treatment form in this patient group.

Approval of dupilumab in adolescents

Recently, dupilumab was also approved for the treatment of adolescents from the age of twelve. For a weight of > 60 kg, treatment is performed at the adult dosage, and for a weight of < 60 kg at a dosage of 200 mg every two weeks after a loading dose of 400 mg [17].

Other biologics for the treatment of atopic dermatitis

Other cytokine inhibitors and cytokine receptor antagonists currently in clinical development for the treatment of atopic dermatitis are presented in Table 2. These include antibodies against IL-13, IL-31, OX40, TSLP and TSLP receptor, IL-33, IL-22, as well as IL-17 (Table 1).

Furthest advanced is the development of tralokinumab, an antibody directed against IL-13 that blocks the IL-13 signaling pathway. The phase IIb trial recently published by Wollenberg et al. revealed a significant reduction in the EASI in patients with moderate to severe atopic dermatitis. Response rates of up to 70 % for EASI50 and up to 40 % for EASI75 have been achieved [18]. Comparably positive results have been shown for another antibody against IL-13 (lebrikizumab), which has been studied in a phase III trial since November 2019 [19]. Based on the low rate of side effects with respect to eye symptoms, this antibody may show better tolerability, though additional studies are required. Dermatologists may expect approval within the next 1–2 years.

Interference with IL-31 is another very interesting approach for dermatology. After a promising first phase II trial with the antibody nemolizumab, an inhibitor of the interleukin 31 receptor, these results were recently confirmed in another phase II trial [20]. Again, a dose-dependent effect of the antibody against the IL-31 receptor on the severity of atopic eczema and especially of pruritus was demonstrated. It should be mentioned that a certain severity level of pruritus was required as inclusion criterion for this trial. Furthermore, the data showed the earliest observed response after eight

Table 2 Cytokine inhibitors and cytokine receptor antagonists.

Name	Target	Phase
Dupilumab	IL-4/IL-13	Approved for adults and adolescents
Lebrikizumab	IL-13	II completed
Tralokinumab	IL-13	III active, recruitment completed
Nemolizumab	IL-31RA	II in recruitment
KPL-716	OSMRβ	II for prurigo nodularis
GBR830	OX40	II in recruitment
KHK4083	OX40	II active, recruitment completed
Tezepelumab	TSLP	II in recruitment
MK-8226	TSLPR	II terminated by sponsor
Etokimab (ANB020)	IL-33	II in recruitment
Fezakinumab	IL-22	II completed
Ustekinumab	IL-12/23p40	II completed
Secukinumab	IL-17A	II in recruitment
MOR 106	IL-17C	II
Omalizumab	IgE	IV completed
Mepolizumab	IL-5	II terminated prematurely

Table was created with data from www.clinicaltrial.gov and was modifies according to Li et al. [5].

weeks, with a better response after 16 weeks [20]. In accordance with the positive results of the trial with respect to pruritus, a significant improvement in sleep was also observed. For this purpose, electronic clocks were used to record nocturnal movement during sleep. In conclusion, the data from clinical trials demonstrate that nemolizumab is especially effective against pruritus [20]. Accordingly, diseases of the spectrum of prurigo may be of interest for treatment with this antibody in the future.

In conclusion, dupilumab is the first effective and very well tolerated biologic available for treatment of moderate to severe atopic dermatitis. First real-life data show that study results can be confirmed in practice and that patients greatly benefit from the treatment. This is also reflected in a very good adherence. Furthermore, additional biologic agents are currently in clinical development. Here, the development of tralokinumab is most advanced. Moreover, nemolizumab, an antibody directed against IL-31, is another biologic of interest for dermatology. Finally, numerous additional biologics are
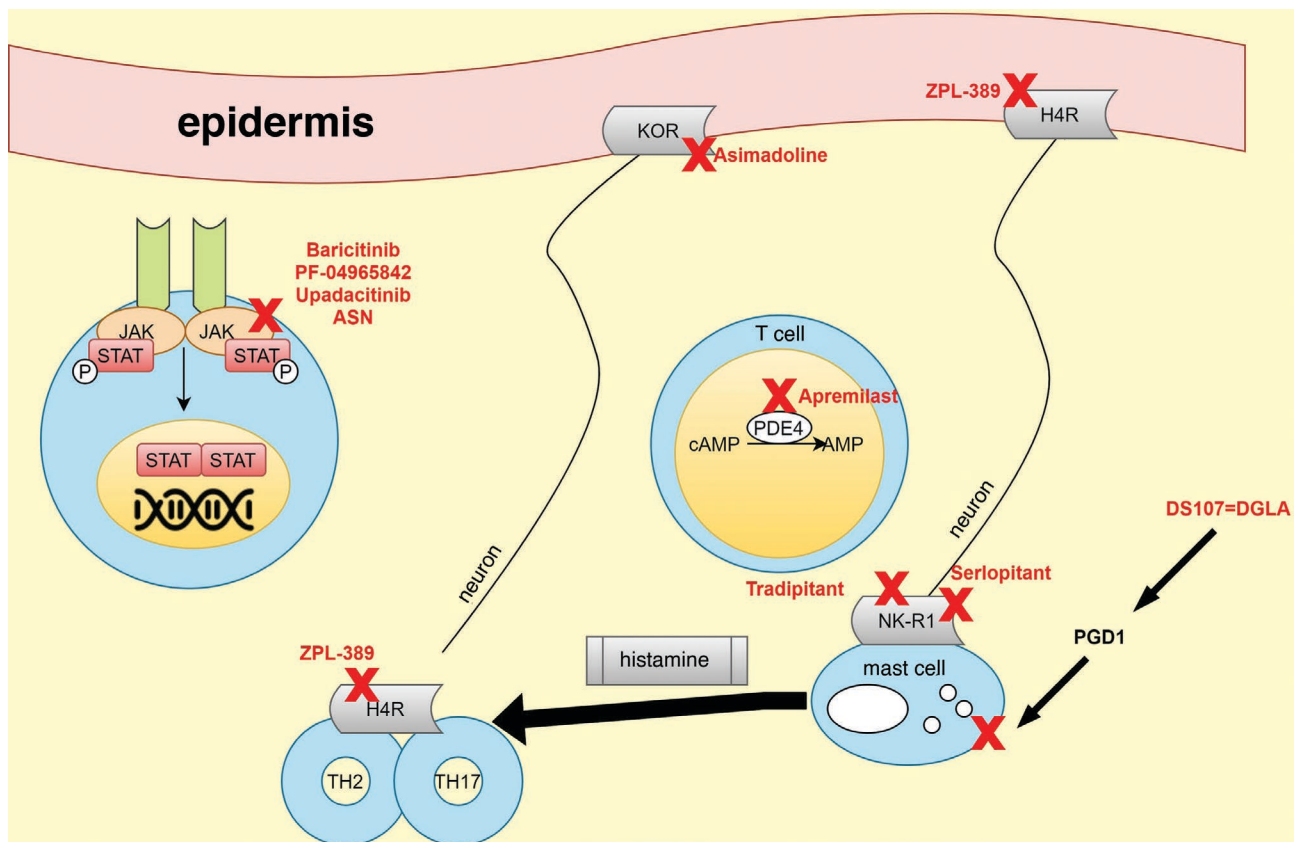
Figure 3 Small-molecule drugs for the treatment of atopic dermatitis (modified according to [5]). *Abbr.:* KOR, kappa opioid receptor; H4R, histamine H4 receptor; JAK, Janus kinase; STAT, signal transducers and activators of transcription; cAMP, cyclic adenosine monophosphate; PDE4, phosphodiesterase 4; NK-R1, neurokinin 1 receptor; PGD1, prostaglandin D1; DGLA, dihomo-gamma-linolenic acid.

currently under clinical investigation (for example, antibodies against OX40, IL-22, IL-17) and may expand the range of therapies for treatment of atopic dermatitis in the future.

Small-molecule drugs for the treatment of atopic dermatitis

Whereas antibody-based therapies usually target cytokines or their receptors, small molecules are used to interfere with intracellular signaling pathways. The largest group of these molecules are the Janus kinase (JAK) inhibitors. JAKs are intracellular enzymes mediating the signaling cascade from a cytokine receptor into the cell (Figure 3). To date, various JAK inhibitors with different binding capacities for individual subtypes of Janus kinases (JAK1–3) have been developed. The most advanced oral JAK inhibitors include baricitinib, PF01, and ASN (Table 3). Data from initial phase II clinical trials show an efficacy between 60 % and 82 % with respect

to EASI50, although different treatment periods and study protocols need to be taken into account [21].

The first results of two large, phase III trials with 624 and 625 patients, respectively, are now available for baricitinib [21] at dosages of 1, 2, and 4 mg/day compared to placebo with no permitted use of topical corticosteroids. These show an improvement in EASI of 59 % for the BREEZE-AD 1 trial and 55 % for BREEZE-AD 2 trial at a dosage of 4 mg/day. Compared to dupilumab, the side effect profile is broader. An increased incidence of infections, in particular with herpes virus, has been observed. A dose-finding study with upadacitinib produced comparable data. After 16 weeks of treatment at a dosage of 30 mg/day, a mean percentage improvement of EASI was observed in 74.4 % of the patients [22]. Also in this study, an increased number of infections were observed, but also elevated liver function values, blood count changes, and elevated CK values [23].

In conclusion, JAK inhibitors can effectively treat atopic dermatitis. Of particular interest is their rapid onset of effect.

Table 3 Small-molecule drugs for the treatment of atopic dermatitis.

	Name	Target	Phase	Status
oral	Baricitinib	JAK1/JAK2	III	In recruitment
	PF-04965842	JAK1	III	In recruitment
	Upadacitinib	JAK1	III	In recruitment
	ASN002	JAK/SYK	II	Completed
	Apremilast	PDE4	II	Completed
	Tradipitant	NK-1R	III	In recruitment
	Serlopitant	NK-1R	II	Completed
	ZPL-389	H4R	II	In recruitment
	Asimadoline	KOR	II	Completed
	DS107	DGLA	II	In recruitment
topical	Tofacitinib	JAK1/JAK2	II	Completed
	Delgocitinib	JAK1/JAK2/JAK3	II	In recruitment
	Ruxolitinib	JAK1/JAK2	III	In recruitment

Table 2 was created with data from www.clinicaltrial.gov and was modifies according to Li et al. (5).

The side effect profile demonstrates that infections are more common and that certain lab parameters are altered under therapy, necessitating more intensive patient monitoring. JAK inhibitors may, therefore, be particularly beneficial for short-term interval treatment of patients with atopic dermatitis. The side effect profile is dependent on substance and dosage (for example, changes in blood count) and may be improved by topical application.

Topical JAK inhibitors

As discussed above, systemic JAK inhibitors are associated with the risk of certain side effects. It seems therefore reasonable to verify whether these molecules may be suitable for topical treatment. Due to their small molecular size, JAK inhibitors can penetrate through the skin, thus enabling topical application. Substances currently in clinical trials include tofacitinib, delgocitinib, and ruxolitinib (Table 3). In general, patients with moderate to moderately severe atopic dermatitis have been treated, and initial study data shows a response rate of 70 % to 80 % after a mean treatment time of four weeks [24]. Initial clinical data on the treatment of children are also promising, demonstrating moderate to good clinical efficacy and good tolerability [25].

In a phase III trial and the open-label follow-up study, delgocitinib also demonstrated good tolerability and good efficacy in Japanese patients. During the treatment period of 28 weeks, reduction and maintenance of modified EASI

(mEASI)50 by 51.9 % and of mEASI75 by 26.4 % was observed [26]. These results confirm that topical JAK inhibitors are promising therapeutic candidates. The first results of the phase II trial for ruxolitinib have also been promising, in particular with respect to pruritus. A limitation of the study was that facial lesions were not treated because of the reference product (triamcinolone) [27].

The results mentioned above highlight the relevance of the anti-pruritic efficacy of this class of drugs, which may present a risk-reduced and well-tolerated option for anti-inflammatory local treatment in the future.

Outlook

The prospects of a patient severely affected with atopic dermatitis for example would be treatment with a biologic and a topical JAK inhibitor in the future. Future studies are required to characterize in detail the selection of specific substances for individual patients and the optimal duration of therapy. In addition to phenotypic features, a patient-oriented therapy also takes genetic and biological markers into account. This may then help to identify different endotypes that are optimally suited for defined therapeutic regimens. Long-term data from registries such as TREAT [28], allow for extended monitoring of safety and disease modification in patients treated with biologics or small-molecule drugs. Beyond that, there is a lack of data on how the treatment of patients achieving clinical remission should be adjusted in the long term.

Conflict of interest

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