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Dupilumab Use in Atopic Conditions and Its Side Effects

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Abstract
Purpose of Review During the last years, dupilumab, a fully human monoclonal antibody directed against the IL-4 receptor α subunit has been investigated in several clinical trials with respect to efficacy, tolerability, and safety in different atopic diseases such as atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis. The aim of this review is to summarize this study data with focus on efficacy and safety.
Recent Findings In atopic dermatitis, three original publications (in total six phase 1, 2, and 3 studies) report consistently about a till today not known high grade of efficacy reducing disease activity. Significant improvement of disease burden has been also seen in two publications on asthma (two phase 2 trials) as well as on chronic sinusitis with nasal polyposis (phase 2 trial). Remarkable is the safety profile with only moderately increased rates for mild or moderate nasopharyngitis and injection site reactions (erythema). Organ toxicities, an increased cardiovascular risk or other health risks have not been described so far. However, a moderate increase of the rate of conjunctivitis in trials on atopic dermatitis remains unclear.
Conclusion The reviewed studies on various atopic diseases have shown that dupilumab is an innovative, highly efficient, well-tolerated biological drug and has the potential to become the first biological cytokine-directed drug to be authorized for atopic diseases such as atopic dermatitis or asthma. The safety profile seems to be unique with an extremely good tolerability as detected so far.

Keywords Atopic dermatitis · Dupilumab · IL-4 receptor alpha subunit · Asthma bronchiale · Chronic sinusitis · Nasal polyposis · Side effects

Introduction

Atopic dermatitis is a chronic inflammatory skin disorder showing high prevalence rates, both in adults (2–10%) and children (15–30%) [1, 2]. It is characterized by an impaired skin barrier function, recurrent bacterial and viral superinfections, severe pruritus, and a type 2 inflammation [2]) which result in a significant impact on quality of life [3]. Atopic dermatitis is part of a spectrum of atopic diseases to which also asthma and allergic rhinoconjunctivitis are accounted where the above mentioned type 2 inflammation plays an important role [4, 5]. In addition, patients suffering from asthma are known to be often affected by sinonasal symptoms often based on chronic sinusitis and nasal polyposis [6]. Moreover, there is recent evidence that patients with atopic dermatitis are also of a higher risk to develop comorbidities such as cardiovascular and metabolic diseases known to be associated with chronic inflammatory conditions [7].

It is well known that in all mentioned atopic diseases, upregulation of the Th2 immune response plays an important role in disease development [8]. This includes upregulation of the cytokines IL-4 and IL-13 which both bind to the IL-4R α receptor subunit. IL-4 can even bind both to the type 1 receptor (consisting of IL-4 receptor α subunit and γ-chain) and to the type 2 receptor (consisting of IL-4 receptor α subunit and IL-13 receptor α 1 subunit), whereas IL-13 has only the capacity to bind to the type 2 receptor [9].

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Therapy of atopic dermatitis is based on the regular use of emollients to improve the epidermal skin barrier function, and in the case of exacerbations, the intermittent use of topical steroids, topical calcineurin inhibitors such as tacrolimus or pimecrolimus. For more severe cases, phototherapy or the use of systemic drugs such as systemic steroids (as pulse therapy) or immunosuppressants such as cyclosporine, which is even authorized in several countries such as Germany, is recommended [10]. The use of other immune modulating/immunosuppressive drugs such as methotrexate, azathioprine, or mycophenolatmofetil is off label though showing efficacy in clinical trials [11, 12]. However, treatment of AD is not satisfying because of multiple side effects of the mentioned therapies and due to recurrent exacerbations.

Asthma is today treated with inhaled glucocorticoids and long-acting beta2-agonists (LABAs), in addition on demand short-acting beta2-agonists (SABAs) [13]. However, the disease is not satisfyingly controlled in 10–20% of patients [14]. For patients with uncontrolled asthma with a causative perennial aeroallergen and an IgE level from 76 to 1500 IU/ml, the monoclonal IgE antibody omalizumab is available [15].

As in all atopic diseases, upregulation of the so-called type 2 inflammation plays a role: A therapeutic approach would be the blockade of such Th2 cytokine system. Dupilumab is a fully human monoclonal antibody which binds to the IL-4 receptor α subunit blocking the signaling of both IL-4 and IL-13, the key players of Th2 immune response [16••, 17]. Due to its potential mode of action against type 2 inflammatory diseases, dupilumab has been tested so far in several clinical trials in atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis.

Clinical Efficacy

Efficacy in Atopic Dermatitis

The first publication about the use of dupilumab in atopic dermatitis reported about the results of two phase 1 studies and two phase 2 studies [16••]. Among these four trials, the largest study was a phase 2 placebo-controlled monotherapy study with dupilumab 300 mg per week s.c. treating patients with moderate to severe atopic dermatitis for 12 weeks showing that 85% of patients in the dupilumab group in comparison to 35% the patients in the placebo group (1:1 randomization, dupilumab n = 55, placebo n = 54) had at least a 50% reduction of the Eczema Area and Severity Index, EASI (EASI-50, p = o.oo1). The EASI is widely accepted to be a reliable tool to measure the disease activity by involving erythema, infiltration, excoriation, and lichenification in relationship to the area being affected [18]. These results could be confirmed in a later dose ranging phase 2b study including 379 patients with moderate to severe atopic dermatitis receiving 1 or more doses of the study drug [19, 20] showing a reduction in the EASI by 73.7% in the highest dosage group (300 mg once weekly) after 16 weeks of treatment. The second highest dose group (300 mg every 2 weeks) reached an EASI reduction by 68.2%. In comparison to that, the reduction in the placebo group was only 18.1% at week 16. In addition to this clinical efficacy data, results from analyses regarding patient reported outcomes (PROs) including quality of life, pruritus, sleep quality, anxiety, and depression measurements have been published recently [21]. Encouraged by these phase 1 and phase 2 clinical trial results, several phase 3 trials were initiated, and the results of two phase 3 trials on moderate to severe atopic dermatitis patients have just been published [22••]. The same study design was chosen with the intention of showing a replication of results. Therefore, 671 and 708 patients were included in each of the clinical trials treating moderate to severe atopic dermatitis patients. Dose groups were dupilumab 300 mg once weekly, 300 mg every 2 weeks or placebo (1:1:1) for a 16-week period (afterwards all patients had the possibility to be transferred into a long-term study with dupilumab 300 mg per week). After 16 weeks, there was a significant superiority in EASI reduction in both dupilumab dosing groups, but no difference among these groups (first study showing reduction by 72.3% with 300 mg/week and 72.0% with 300 mg every 2 weeks, the placebo group showed 37.6% EASI reduction). The second trial showed an EASI reduction in the once weekly group of 67.1%, in the every 2 weeks group of 69.1%, and in the placebo group of 30.9%. The percentage of patients achieving an EASI-75 (that means a reduction of the EASI of at least 75%) was reached by 52 and 44% of the patients in the highest dose group in comparison to 15 and 12% in the placebo treatment arm (dupilumab every 2 weeks 51 and 44%). It is remarkable that as early as after 1 week of treatment, significant differences in EASI and also pruritus, which is the most important symptom patients are suffering from, have been measured in all of the mentioned trials. Other endpoints such as significant improvement of symptoms of anxiety and depression and quality of life improvement could be confirmed in both phase 3 trials as well.

Efficacy in Asthma

Efficacy data also exists for another atopic disease, asthma bronchiale. In 2013, a phase 2a study was published [23]. One hundred four patients suffering from moderate to severe asthma were included (inclusion criteria were a blood eosinophil count of at least 300 cells per microliter or sputum eosinophil level of at least 3% and clinical symptoms not sufficiently controlled in spite of use of medium to high-dosed inhaled glucocorticoids in addition to LABAs). Randomization was 1:1 in comparison to placebo treatment while dupilumab (200 mg) was administered for a 12-week period subcutaneously. After 4 weeks of treatment with dupilumab versus placebo, LABAs were discontinued, and from weeks 4 to 9, the dose of the inhaled glucocorticoids (fluticasone) was tapered till a protocol-defined asthma

exacerbation occurred. The study results showed a significantly better outcome of the dupilumab treated patients. Asthma exacerbation occurred in only three patients receiving dupilumab (6%), but in 23 patients receiving placebo (44%), $p < 0.001$. Patients on dupilumab treatment also showed a significantly prolonged time interval till the occurrence of an asthma exacerbation. Many other secondary endpoints, such as nocturnal awakenings, lung function values such as FEV1, or other asthma scores such as SNOT-22 also improved significantly. Another phase 2b study on dupilumab efficacy and safety in adults with uncontrolled persistent asthma showed similar results [24]. In this trial, 769 patients were treated with either dupilumab (611 patients) in various dose regimens (200 or 300 mg every 2 or every 4 weeks) or placebo (158 patients) for a 24-week period. The included patients had to be on treatment with medium to high-dose-inhaled corticosteroids plus LABAs and were, by protocol in need of an additional treatment due to insufficient disease control. Except of the lowest dose group (200 mg every 4 weeks), all dose levels showed a significantly superiority to placebo treatment with respect to the various endpoints (primary endpoint FEV1 improvement, secondary endpoints were severe asthma exacerbation rate, time to severe asthma exacerbation, various asthma scores such as ACQ-5 score, Asthma Quality of Life Questionnaire (AQLQ), and number of inhalations of SABAs per day for symptom relief). The results were independent from the eosinophil count at baseline (< or ≥300 eosinophils/μl).

Efficacy in Chronic Sinusitis and Nasal Polyposis

Since it is well known that chronic sinusitis is associated with an increased asthma prevalence [6], and nasal polyposis with chronic sinusitis is a Th2-driven, eosinophilic inflammation of the upper airways, a phase 2 study on efficacy and safety of dupilumab in patients with chronic sinusitis and nasal polyposis was designed [25]. Sixty patients were randomized to receive either dupilumab or placebo (1:1), 300 mg weekly (after a 600 mg loading dose) for 16 weeks in addition to mometasone furoate nasal spray on a stable dose during the treatment period. If asthma was known, the specific asthma therapy was continued (35 patients had comorbid asthma). The results showed that there was a significant decrease of the bilateral endoscopic nasal polyp score (primary endpoint) after 16 weeks of treatment in the dupilumab group in comparison to placebo. Other endpoints such as Lund-Mackay CT total score, morning peak nasal inspiratory flow, quality of life scores (SNOT-22), and the UPSIT score. In summary, patients with asthma responded better to dupilumab treatment than patients without asthma.

Safety

The above mentioned clinical trials on dupilumab in various indications all showed a unique safety profile of the IL-4 receptor α antibody. In atopic dermatitis, the first published 4 studies (two phase 1 and two phase 2 studies) [16••] showed in all studies a similar frequency of adverse events both in placebo and in dupilumab-treated groups. The majority of the adverse events was mild to moderate and transient. Nasopharyngitis and headache were described being the most common adverse events with a higher frequency in dupilumab treated patients than in those with placebo. With respect to the occurrence of serious adverse events (SAEs), the number of SAEs was always higher in the placebo in comparison to the dupilumab groups. In all of the four presented trials, 13 SAEs occurred in 9 of 80 patients in the placebo groups, but only two SAEs in two of 127 patients in the various dupilumab groups. Five patients of the placebo groups had to discontinue study treatment due to their SAE in comparison to only one patient in the dupilumab groups. The majority of the SAEs were either exacerbation of atopic dermatitis or skin infections. Regarding to skin infections, 17 skin infections in total occurred among the placebo treated patients in comparison to only six skin infections among the 127 dupilumab treated patients. In the 12-week phase 2 study, seven patients on placebo needed hospitalization for skin infections or exacerbation of atopic dermatitis in comparison to only one patient in the dupilumab group (reason: facial fracture). No opportunistic infections appeared or any death.

Also in the phase 2 study presented by Thaçi et al. [19], the majority of adverse events were mild or moderate. The most common treatment emergent adverse events were nasopharyngitis, exacerbation of atopic dermatitis, headache, and upper respiratory tract infect in the dupilumab group. Interestingly, more patients in the dupilumab group showed an episode of herpes viral infection than in the placebo group (8 versus 2%, respectively). These infections were all mild or moderate and located in the perioral area.

Seven percent of the dupilumab treated patients (22 of 318) reported about injection site reactions in comparison to 3% in the placebo group (2 of 61). These reactions were not clearly dose dependent with respect to the given dupilumab doses.

Treatment-emergent SAEs occurred in 7% (4 of 61) in the placebo group and in 4% (12 of 318 patients) in the dupilumab groups. The rate of serious dupilumab treatment-emergent adverse events of infection or respiratory disorders was low: three patients with serious infections (all on various dupilumab regimens), two patients with respiratory disorders (exacerbation of asthma, respiratory failure), and both patients on various dupilumab regimens.

The recent publication of two phase 3 trials on dupilumab in atopic dermatitis showed an adverse event incidence in the dupilumab treated groups and the placebo groups, in both trials on a similar level [22••]. SAEs and AEs leading to treatment discontinuation were rare. With respect to SAEs being assigned to more than two patients in any treatment group, there were only three patients on dupilumab, but eight patients

on placebo with serious exacerbation of atopic dermatitis. During the whole course of the studies 28–35% of the patients on dupilumab developed an infectious adverse event in comparison to 28–32% in the placebo groups. With respect to the mentioned infectious AEs, skin infections appeared in 8.1–11.1% of the placebo treated patients and in 5.7–6.4% of the dupilumab treated patients (mostly skin infections of bacterial origin). Non-skin infections appeared in 22.1–24.4% of placebo and in 24.6–30.7 of the dupilumab treated patients. In general, most common AEs were nasopharyngitis, upper respiratory tract infections, and conjunctivitis. In both phase 3 trials, there were similar numbers of herpes infections so that the results of the phase 2 study [19] could not be verified. Patients treated with dupilumab showed a higher incidence of injection site reactions as already seen in the other published studies on atopic dermatitis (most of these reactions were mild or moderate). However, the incidence of conjunctivitis either of allergic origin or unspecified cause, was higher in both dupilumab groups in comparison to placebo groups. That incidence remains however unclear.

In all published trials on dupilumab in atopic dermatitis, the laboratory results, vital signs, and the electrocardiographic assessments did not show any clinically remarkable differences among the various treatment groups or placebo except a transient increase of blood eosinophil count in the phase 3 trials (see below).

The first phase 2 trial on asthma with elevated eosinophil level [23] also reported about a similar rate of AEs among the dupilumab and the placebo treated patients. They were again mild to moderate. There were three SAEs in the placebo and one in the dupilumab group (no SAE related to study drug in the opinion of the investigators). No death occurred. With respect to AEs, three AEs led to study discontinuation in the placebo group (psoriasis, exacerbation of asthma, infection of the upper respiratory tract) as well as three AEs in the dupilumab group (deterioration of asthma symptoms, worsening of bipolar disorder, angioedema). The most common AEs were injection site reactions and nasopharyngitis (both more often in the dupilumab group) as well as upper respiratory tract infections (similar occurrence among both groups). The second publication on asthma [24] again showed similar treatment adverse event rates among dupilumab and placebo patients. These included headache and upper respiratory tract infections. Injection site reactions with erythema were more common among dupilumab than among placebo treated patients (13 versus 8%). These reactions only rarely led to discontinuation of trial participation (<1%). Among dupilumab treated patients, there was no increase of bacterial, opportunistic, or herpes viral infections. The occurrence of serious treatment-emergent AEs was similar among dupilumab and placebo patients (7 versus 6%). These results were similar among the subgroups of eosinophil blood count (< or ≥300 eosinophils/μl). That study as well as the two phase 3 trials on dupilumab in atopic dermatitis [22••] showed a transient increase of blood eosinophils beginning from week 4 until weeks 8 or 16 (no significant difference after week 16).

A clinical trial on chronic sinusitis and nasal polyps also showed a favorite safety profile of dupilumab with similar AE rates in both placebo and dupilumab treated patients. There were higher rates of mild and moderate nasopharyngitis in dupilumab patients and injection site reactions, but similar rates for headache and the most other adverse events among the two treatment groups. Four SAEs were detected in the placebo and two in the dupilumab groups. There were no SAEs considered by the investigators to be related to dupilumab.

Conclusion

- All presented clinical trials on atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis showed clear superiority with respect to efficacy of dupilumab in the treated diseases in comparison to placebo. These improvements did not show any trend to be weakened during the course of the various trials up to a maximum of 24 weeks. The drug discontinuation rates were amazingly low among all trials which is a sign for excellent tolerability of the study drug. This is underlined by the safety results which show unique results in comparison to various other immunomodulating drugs. The AE rates between serum and placebo group were always roughly the same with slightly higher ranges for nasopharyngitis and injection site reactions in the dupilumab treated patients. The occurrence of herpes viral infections was only described in one phase 2 trial [19] and could not be verified in two large phase 3 trials on atopic dermatitis [22••]. However, these two phase 3 trials showed an increase risk of conjunctivitis, both of allergic or unknown origin. That increase remains unclear and is at the moment under observation in ongoing phase 3 trials (NCT01949311). An explanation could be that the eye belongs to the so-called immune-privileged organs where the immunomodulating effect of dupilumab might not be seen because of lack of penetration of sufficient amounts of the antibody dupilumab into the eyes, especially to the cornea and anterior segment of the eye [26]. Therefore, the eyes, respectively, the conjunctiva could be the last refugium where the atopic inflammatory disease persists and might even become more intense. However, this has to be scientifically evaluated in the future.

With respect to laboratory value changes (organ toxicity, blood count influence), risk of infections, or ECG changes, dupilumab reveals to open a new era in comparison to the so far known systemic non-biological and biological drugs. There are no safety signals showing an increased risk for both serious infections, opportunistic infections, and parasitic infections

(although the Th2 immune system is downregulated), no signal for MACE (major adverse cardiac events) or cancerogenesis. Therefore, dupilumab has the potential to become the first biological drug for various atopic diseases such as atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis to be approved and to significantly increase the efficacy of treatment and quality of life with almost no impairment or increased health risks. With respect to the latest news, dupilumab is about to be released by the FDA for the treatment of atopic dermatitis during these days.

Compliance with Ethical Standards

Conflict of Interest T.A. Luger participated as investigators in multiple clinical trials on dupilumab sponsored by Regeneron.

A. Tsianakas participated as investigator in multiple clinical trials on dupilumab sponsored by Regeneron.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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