Cytokines of the IL-17 family in psoriasis

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metex® PEN 7,5 mg / 10 mg / 12,5 mg / 15 mg / 17,5 mg / 20 mg / 22,5 mg / 25 mg/ 27,5 mg / 30 mg Injektionslösung im Fertigpen. *Wirkstoff:* Methotrexat-Dinatrium. **Zusammensetzung:** 1 Fertigpen mit 0,15 ml/ 0,20 ml/ 0,25 ml/ 0,30 ml/ 0,35 ml / 0,40 ml/ 0,45 ml/ 0,50 ml/ 0,55 ml/ 0,60 ml Lösung enthält 7,5 mg/ 10 mg/ 12,5 mg/ 15 mg/ 17,5 mg/ 20 mg/ 22,5 mg/ 25 mg/ 27,5 mg/ 30 mg Methotrexat. *Sonstige Bestandteile:* Natriumchlorid, Natriumhydroxid-Lösung 5%, Salzsäure 0,37%, Wasser für Injektionszwecke. **Anwendungsgebiete:** Aktive rheumatoide Arthritis bei erwachsenen Patienten; polyarthritische Formen von schwerer aktiver juveniler idiopathischer Arthritis (JIA), wenn das Ansprechen auf nicht-steroidale Antirheumatika (NSAR) nicht ausreichend war; mittelschwere bis schwere Psoriasis vulgaris bei erwachsenen Patienten, die für systemische Therapieformen in Frage kommen, sowie schwere Psoriasis arthropathica bei Erwachsenen; leichter bis mittelschwerer Morbus Crohn, entweder allein oder in Kombination mit Kortikosteroiden bei Erwachsenen, die auf Thiopurine nicht ansprechen oder diese nicht vertragen. **Gegenanzeigen:** Überempfindlichkeit gegen Methotrexat oder einen der sonstigen Bestandteile; schwere Leberfunktionsstörungen; Alkoholabusus; schwere Nierenfunktionsstörungen (Kreatinin-Clearance unter 30ml/min); vorbestehende Blutbildveränderungen wie Knochenmarkshypoplasie, Leukopenie, Thrombozytopenie oder signifikante Anämie; schwere, akute oder chronische Infektionen wie Tuberkulose, HIV oder andere Immundefizienzsyndrome; Ulzera der Mundhöhle und bekannte Ulzera des Magen-Darm-Traktes; Schwangerschaft, Stillzeit; gleichzeitige Impfung mit Lebendimpfstoffen. **Warnhinweis:**. metex PEN (Methotrexat) darf zur Behandlung von rheumatoider Arthritis, juveniler idiopathischer Arthritis, Psoriasis, Psoriasis arthropathica und Morbus Crohn nur einmal wöchentlich angewendet werden. Eine fehlerhafte Dosierung von metex PEN kann zu schwerwiegenden, einschließlich tödlich verlaufenden Nebenwirkungen, führen. **Nebenwirkungen:** Wichtigste Nebenwirkungen sind Beeinträchtigung des hämatopoetischen Systems und Erkrankungen des Gastrointestinaltrakts. Auftreten und Schweregrad hängen von Dosierung und Häufigkeit der Anwendung ab. Da es auch bei niedrigerer Dosierung zu schwerwiegenden Nebenwirkungen kommen kann, ist eine regelmäßige Überwachung durch den Arzt in kurzen zeitlichen Abständen unerlässlich. *Infektionen: Gelegentlich:* Pharyngitis. *Selten:* Infektionen einschließl. Reaktivierung inaktiver chronischer Infektionen, Sepsis, Konjunktivitis. *Neubildungen: Sehr selten:* Lymphom. *Blut und Lymphsystem: Häufig:* Leukozytopenie, Anämie, Thrombozytopenie. *Gelegentlich:* Panzytopenie. *Sehr selten:* Agranulozytose, schwere Verläufe von Knochenmarkdepression, lymphoproliferative Erkrankungen. Eosinophilie *(Häufigkeit nicht bekannt). Immunsystem: Selten:* Allergische Reaktionen, anaphylaktischer Schock, Hypogammaglobulinämie. *Stoffwechsel- Ernährung: Gelegentlich:* Manifestation eines Diabetes mellitus. *Psychiatrisch: Gelegentlich:* Depressionen, Verwirrtheit. *Selten:* Stimmungsschwankungen. *Nervensystem: Häufig:* Kopfschmerzen, Müdigkeit, Verschlafenheit. *Gelegentlich:* Schwindel. *Sehr selten:* Schmerzen, Muskelschwäche oder Parästhesie/ Hypoästhesie, Geschmacksveränderungen (metallischer Geschmack), Krampfanfälle, Meningismus, akute aseptische Meningitis, Lähmungen. Enzephalopathie/ Leukenzephalopathie *(Häufigkeit nicht bekannt). Augen: Selten:* Sehstörungen. *Sehr selten:* Sehverschlechterung, Retinopathie. *Herz: Selten:* Perikarditis, Perikarderguss, Perikardtamponade. *Gefäße: Selten:* Hypotonie, thromboembolische Ereignisse. *Atemwege, Brustraum, Mediastinum: Häufig:* Pneumonie, interstitielle Alveolitis, Pneumonitis, oft verbunden mit Eosinophilie. Symptome, die auf potenziell schwere Lungenschädigungen (interstitielle Pneumonitis) hinweisen: trockener Reizhusten, Kurzatmigkeit, Fieber. *Selten:* Lungenfibrose, Pneumocystis-jirovecii-Pneumonie, Kurzatmigkeit, Asthma bronchiale, Pleuraerguss. Epistaxis, pulmonale alveoläre Blutung *(Häufigkeit nicht bekannt). Gastrointestinaltrakt: Sehr häufig:* Stomatitis, Dyspepsie, Übelkeit, Appetitlosigkeit, abdominale Schmerzen. *Häufig:* Ulzerationen der Mundschleimhaut, Diarrhö. *Gelegentlich:* Ulzerationen und Blutungen des Magen-Darm-Traktes, Enteritis, Erbrechen, Pankreatitis. *Selten:* Gingivitis. *Sehr selten:* Hämatemesis, Hämatorrhö, toxisches Megakolon. *Leber, Galle: Sehr häufig:* Abnorme Leberfunktionswerte (AST, ASAT, alkalische Phosphatase und Bilirubin erhöht). *Gelegentlich:* Leberzirrhose, Leberfibrose, Leberverfettung, Verminderung von Serumalbumin. *Selten:* Akute Hepatitis. *Sehr selten:* Leberversagen. *Haut, Unterhaut: Häufig:* Exantheme, Erythem, Pruritus. *Gelegentlich:* Photosensibilität, Haarausfall, Zunahme von Rheumaknoten, Hautulzera, Herpes Zoster, Vaskulitis, herpetiforme Hauteruptionen, Urtikaria. *Selten:* Verstärkte Pigmentierung, Akne, Petechien, Ekchymose, allergische Vaskulitis. *Sehr selten:* Stevens-Johnson-Syndrom, toxische epidermale Nekrolyse (Lyell-Syndrom), verstärkte Pigmentierung der Nägel, akute Paronychie, Furunkulose, Teleangiektasie. Exfoliation der Haut/ exfoliative Dermatitis *(Häufigkeit nicht bekannt). Skelettmuskulatur, Bindegewebe, Knochen: Gelegentlich:* Arthralgie, Myalgie, Osteoporose. *Selten:* Stressfraktur. Osteonekrose des Kiefers, sekundär zu lymphoproliferativen Erkrankungen *(Häufigkeit nicht bekannt). Niere, Harnwege: Gelegentlich:* Entzündungen und Ulzerationen der Harnblase, Nierenfunktionsstörungen, Miktionsstörungen. *Selten:* Niereninsuffizienz, Oligurie, Anurie, Elektrolytstörungen. Proteinurie *(Häufigkeit nicht bekannt). Geschlechtsorgane, Brustdrüse: Gelegentlich:* Entzündungen und Ulzerationen der Vagina. *Sehr selten:* Libidoverlust, Impotenz, Gynäkomastie, Oligospermie, Menstruationsstörungen, vaginaler Ausfluss. *Allgemein, Verabreichungsort: Selten:* Fieber, Wundheilungsstörungen. Asthenie. Nekrose an der Injektionsstelle, Ödem *(Häufigkeit nicht bekannt).* Subkutane Anwendung von MTX ist lokal gut verträglich; nur leichte örtliche Hautreaktionen wie Brennen, Erythem, Schwellung, Verfärbung, Pruritus, starker Juckreiz, Schmerzen, die im Laufe der Behandlung abnehmen. *Verschreibungspflichtig.* **medac GmbH**, Theaterstr. 6, 22880 Wedel, Deutschland. **Stand** Juli 2020

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Cytokines of the IL-17 family in psoriasis

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Summary

Various immune cells and their messenger substances influence the development of psoriasis. Cytokines of the IL-17 family are of particular importance. In addition to IL-17A, which plays a central role in the pathogenesis of psoriasis, other subtypes of the IL-17 family also have a proinflammatory effect. This review provides an up-to-date overview of the immunopathogenesis of psoriasis with regard to the six IL-17 subtypes, in particular their physiological and pathogenic properties, as well as their significance for psoriasis therapy.

Introduction

Psoriasis can affect individuals of any age and often causes significant physical and psychological constraints [1]. Typical comorbid diseases of psoriasis are the metabolic syndrome, cardiovascular diseases, and psychological diseases [2]. The WHO describes psoriasis as one of the five serious non-infectious diseases that require special treatment and research [1]. Effective treatments that are specifically aimed at the pathogenesis of psoriasis have been developed in recent years and are included in the psoriasis guidelines [3–6].

In the past, Th17 cells of the adaptive immune system and the IL-23/IL-17 axis were the main focus of psoriasis research. According to new research, however, the relationships that occur in the immunopathogenesis of psoriasis are much more complex. Studies have shown that various cell types of the innate immune system, including myeloid cells such as neutrophilic granulocytes, macrophages and mast cells, can produce IL-17A and IL-23 and can interact with cells of the adaptive immune response (such as Th17 and IL-17) that produce $CD8^+$ T lymphocytes. Besides IL-17A, the other IL-17 cytokines are also important, as is determination of how they induce inflammation in psoriasis [7–10].

Cytokines of the IL-17 family in the immunopathogenesis of psoriasis

The IL-17 family has six subtypes: IL-17A, IL-17B, IL-17C, IL-17 D, IL-17E (also known as IL-25) and IL-17F. The

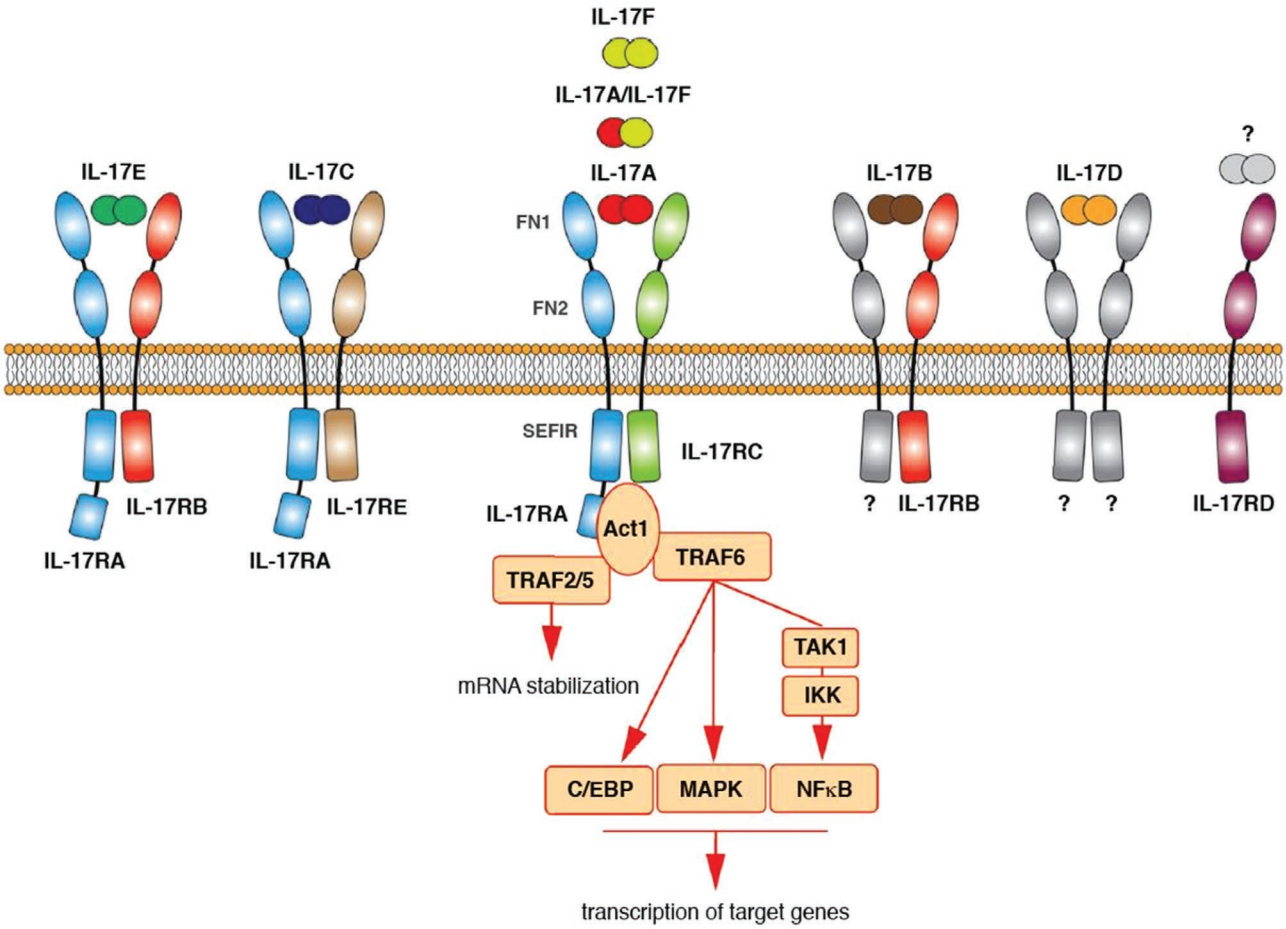

Figure 1 IL-17 family: ligands and receptors. Illustration of the different IL-17 cytokines and their receptors. The intracellular signaling cascade is shown here with an example of the activation of the IL-17A receptor (modified after [2]).

subtypes IL-17A and IL-17F have the highest homology (55 %) and are most often expressed together (co-expression). The sequences of IL-17B, IL-17D, and IL-17C overlap with IL-17A by about 23 % to 29 %, but the overlap with IL17-E is only 16 % [2]. IL-17 subtypes produce organ-specific pro- or anti-inflammatory responses via a total of six receptors [9] (Figure 1). Table 1 shows the IL-17 subtypes, their receptors, producing cells and effects on other cells, as well as their associations with various diseases [2].

IL-17A

IL-17A plays a central role in the pathogenesis of psoriasis. This was shown in several studies with the successful use of inhibiting antibodies [11]. It acts on non-hematopoietic cells, particularly epithelial cells, and plays an essential role in the immune response in neighboring organs. In the skin, IL-17A leads to increased proliferation and changed differentiation of keratinocytes, and induces antimicrobial peptides and chemokines. IL-17A also has a role in other inflammatory diseases. Elevated IL-17A concentrations have been measured in patients with multiple sclerosis (MS), rheumatoid arthritis and acute coronary syndrome that correlated with parameters of systemic inflammation [2, 7].

IL-17F

IL-17F and IL-17A are coded at the same gene locus (6p12) and are regulated in a similar way. IL-17F can create heterodimers together with IL-17A. In psoriasis patients, IL-17F can be found in plaques at higher levels than in unaffected parts of the skin.

Studies have shown synergistic effects of IL-17F and IL-17A: unlike the inhibition of IL-17A alone, simultaneous inhibition of both cytokines leads to a significant increase in downregulation of inflammatory mediators in skin and joint fibroblasts [2, 12]. IL-17F and IL-17A perform similar functions in bacterial or fungal infections [2, 13, 14].

Table 1 Overview of IL-17 subtypes with associated receptors, producing cells, effects on other cells as well as associations with diseases.

IL-17 subtype	Receptor(s)	Producing cells	Effect on other cells	Associations with diseases
IL-17A	– IL-17-RA – IL-17-RC	– Th17 cells – γδ-T cells – ILC3 cells – Neutrophil granulocytes – Mast cells	– Proinflammatory effect on epithelial cells – IL-17F in synergy with IL-17A	– Psoriasis – Atopic eczema – Multiple sclerosis – Rheumatoid arthritis – Psoriatic arthritis – Chronic inflammatory intestinal diseases – Inflammation with acute coronary syndrome
IL-17B	– IL-17-RB?	– Neutrophil granulocytes – B-lymphocytes, neurons	– Increase of TNF-α production by fibroblasts – Associated with a poor prognosis in breast and stomach cancer	– Rheumatoid arthritis
IL-17C	– IL-17-RA – IL-17-RE	– Primarily epithelial cells – Rarely immune cells	– Autocrine stimulation of epithelial cells – Proinflammatory effect on epithelial cells via the expression of cytokines, chemokines, and antimicrobial peptides. – Synergistic effect with TNF	– Psoriasis – Atopic eczema – Rheumatoid arthritis – Chronic inflammatory intestinal diseases
IL-17D	– ? – ?	– Weak expression in lymphocytes and monocytes – Expression in skeletal muscle, brain, fat tissue, heart, lung, pancreas	– Modulation of cytokine production by endothelial cells, release of proinflammatory cytokines such as IL-6, IL-8 and GM-CSF	– Rheumatoid arthritis
IL-17E (also known as IL-25)	– IL-17-RA – IL-17-RB	– Epithelial and endothelial cells – T cells – Macrophages – Myeloid cells type 2 – Dendritic cells – Eosinophil granulocytes – ILC2 cells	– Induces the loss of cellular barrier function – Modulation of proinflammatory cytokines such as IL-8, CCL-5 and GM-CSF – Reduced IL-17E expression in chronic inflammatory intestinal diseases	– Psoriasis – Atopic eczema – Allergic contact dermatitis – Bronchial asthma – Rheumatoid arthritis – Chronic inflammatory intestinal diseases
IL-17F	– IL-17-RA – IL-17-RC	– Th17 cells – γδ-T cells – ILC3 cells	– Synergistic effect with IL-17A – Proinflammatory effect on epithelial cells	– Psoriasis – Atopic eczema – Multiple sclerosis – Rheumatoid arthritis – Psoriatic arthritis – Chronic inflammatory intestinal diseases

IL-17B

The function of IL-17B in psoriasis is largely unknown, and only weak expression has been described in psoriasis lesions [2]. IL-17B is not produced by activated T lymphocytes, but it has been found in neutrophil granulocytes, B-cells, neurons, stroma cells and colorectal epithelial cells.

Synovial and pannus tissue in patients with rheumatoid arthritis (RA) has shown increased expression of IL-17B. IL-17B amplifies the effects of TNF-α in fibroblasts. This could be important for the immunogenesis of RA [15].

IL-17D

IL-17D is expressed in many cells and organs, but only weakly in immune cells such as lymphocytes and monocytes. IL-17D *in vitro* induced the production of IL-6, IL-8 and GM-CSF in endothelial cells. An inhibitory effect on the hematopoiesis of myeloid precursor cells was also detected [16]. Other studies have shown an association of IL-17D with viral and oncological diseases, particularly via recruitment of natural killer cells (NK cells). However, current data on IL-17D during tumor development are contradictory [17]. A deficiency in IL-17D led to a higher vulnerability to viruses in animal models.

IL-17C

IL-17C is not produced by T lymphocyte cells, but primarily by epithelial cells such as keratinocytes. A high concentration of IL-17C has been measured in human psoriasis plaques [18]. It can act as an autocrine stimulant for epithelial inflammation, particularly in combination with TNF-α. Overexpression of IL-17C in keratinocytes leads to psoriasiform dermatitis in mice [19]. IL-17C also leads to increased growth of sensory nerves. It was shown in a mouse model of herpes simplex infections of the skin that IL-17C can induce neuronal growth in a way similar to that of NGF (nerve growth factor) [18, 20, 21]. It has also been reported that depletion of IL-17C in mouse models of psoriasis and atopic dermatitis significantly reduces the inflammatory reaction. IL-17C therefore acts independently of T cells as an epithelial stimulant of immune reactions [19].

IL-17E (also known as IL-25)

IL-17E induces proliferation of keratinocytes and is able to activate innate immune cells. In psoriasis, IL-17E is strongly expressed by keratinocytes and activates specific subtypes of macrophages (M2 or tissue macrophages). In psoriasis lesions, IL-17E expression correlates positively with the number of neutrophil granulocytes and negatively with the number of T lymphocytes. This is surprising, since IL-17E was seen for a long time as a cytokine with a role in the Th2 immune response. An animal model of allergic asthma showed that inhibition of IL-17E by a neutralizing antibody resulted in a significant reduction of bronchial hyperreactivity, serum IgE concentration and histological signs of inflammation [22]. Similarly, IL-17E is also strongly expressed in atopic eczema [23, 24].

Like IL-17C, IL-17E appears to amplify innate inflammatory processes in the skin, independently of the cells that contribute to the adaptive immune system [25].

Clinical aspects of IL-17 subtypes in psoriasis

Contrary to earlier notions of the pathogenesis of psoriasis, we now understand that there are other important inflammatory cycles apart from the IL-17A/IL-23 axis. On the one hand, the epithelial IL-17 cytokines IL-17C and IL-17E stimulate innate immune cells and the production of antimicrobial peptides. On the other hand, IL-17F leads to a pronounced increase of the IL-17A effects on epithelial cells. Animal experiments have shown the importance of these independent inflammatory cascades. For instance, the mouse model of psoriasis showed that when IL-17C is blocked, other immune mechanisms are stimulated that can allow the disease to persist [26].

This is a possible immunological explanation for the secondary loss of efficacy. Inhibition of a cytokine of the IL-17A/IL-23 axis could therefore modulate the inflammatory reaction and induce epithelial IL-17 cytokines such as IL-17C and IL-17E. However, there is currently no scientific evidence for this in humans.

Therapeutic consequences

Various biologics are currently approved for the treatment of psoriasis. Inhibition is focused on TNF-α, IL-12 (in combination with IL-23 inhibition) and the IL-17 subtypes IL-17A and IL-17F, or the subunit of the IL-17 receptor. The latter prevents an interaction of IL-17A, A/F, F, C, and E with the IL-17 receptor. Table 2 shows the biologics that are currently approved in the EU and that inhibit the effects of IL-17 subtypes or those of the IL-17A/IL-23 axis.

With regard to IL-17 subtypes and associated inflammatory cycles, it might be easier to stratify patients with psoriasis in the future. It is conceivable that some patients have a primarily adaptively driven psoriasis [7, 27] that responds very well to IL-23 or IL-17A inhibition. From an immunological perspective, these could be patients who have only recently started to suffer from the disease, since

Table 2 Overview of biologics directed against the IL-23/IL-17 axis in psoriasis therapy.

Substance	Inhibited cytokine	Indication	Dosage and Application	EMA approval status
Ustekinumab	IL-23 and IL-12	– Plaque psoriasis – Psoriatic arthritis – Crohn's disease – Ulcerative colitis	Initially 45 mg, 45 mg in week 4, then every 12 weeks; b.w. > 100 kg: initially 90 mg, 90 mg in week 4, then every 12 weeks. Children/adolescents: according to dosage table in week 0 and 4, then every 12 weeks. The patient can do the subcutaneous injection himself after proper training (FI last modified 09/2019).	Approved 01/2009, approval extended 09/2013
Secukinumab	IL-17A	– Plaque psoriasis – Psoriatic arthritis – Ankylosing spondylitis (Bechterew's disease)	Plaque psoriasis: 300 mg in week 0, 1, 2 and 3, 300 mg per month starting in week 4. In case of concomitant moderate to severe plaque psoriasis or insufficient response to anti-TNF-α: 300 mg at week 0,1,2,3 and 4, then monthly. In all other patients: 150 mg 0, 1, 2, 3 and 4, then monthly; dose may be increased to 300 mg. Patient can do the subcutaneous injection himself after proper training (FI last modified 10/2019).	Approved 01/2015
Ixekizumab	IL-17A	– Plaque psoriasis – Psoriatic arthritis	Plaque psoriasis: 160 mg in week 0, then 80 mg in week 2, 4, 6, 8, 10 and 12; then 80 mg every 4 weeks. Psoriatic arthritis: 160 mg in week 0, then 80 mg every 4 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 05/2018).	Approved 04/2016
Brodalumab	IL-17 receptor A and thus IL-17A, IL-17C, IL-17E, IL-17F and IL-17A/F Heterodimer	– Plaque psoriasis	210 mg in week 0, 1 and 2, then 210 mg every 2 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 09/2017).	Approved 07/2017
Guselkumab	IL-23	– Plaque psoriasis	100 mg in week 0, week 4, then every 8 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 11/2018).	Approved 11/2017
Tildrakizumab	IL-23	– Plaque psoriasis	100 mg in week 0 and 4, then every 12 weeks. For patients with particular characteristics (e.g. high disease burden, b.w. ≥ 90 kg), 200 mg could be more effective. Patient can do the subcutaneous injection himself after proper training (FI last modified 09/2018).	Approved 09/2018
Risankizumab	IL-23	– Plaque psoriasis	150 mg in week 0 and 4, then every 12 weeks. Patient can do the subcutaneous injection himself after proper training (FI last modified 07/2019).	Approved 04/2019
Bimekizumab	IL-17A and IL-17F	– Plaque psoriasis		Not yet approved, currently in Phase-III studies

Abbr.: b.w., body weight; FI, summary of product characteristics.

chronic development and activation of other inflammatory cascades (such as epithelial IL-17 cytokines) has not yet occurred. Patients with stable psoriasis vulgaris without significant inflammation could also fall into this category. However, other patients might profit from the inhibition of several IL-17 cytokines. It is conceivable that these are patients who have suffered from psoriasis longer, have eczematized forms or possibly more inflammatory forms, since for them, activation of additional IL-17 cytokines (and other mediators such as IL-36) might sustain disease activity [7, 27]. The stimulating effect of IL-17C on the growth of cutaneous nerves could also mean that patients with very itchy or inflammatory forms of psoriasis could benefit from the additional inhibition of IL-17C. Since IL-17E stimulates the inflammatory response of psoriasis on the one hand but also induces TH2 cytokines on the other hand, inhibition of IL-17E might positively affect accompanying allergic illnesses. Future studies must determine whether specific disease types can be defined and whether therapeutic decisions based on immunologic aspects can be made for selected psoriasis patients.

Conflict of interest

Felix Lauffer received honoraria for speaker and consulting activities from AbbVie, Leo Pharma, Lilly, Novartis, Roche and Sanofi. Kilian Eyrich received honoraria for speaker and consulting activities from AbbVie, Almirall, Bristol-Myers Squibb, Celgene, Hexal, Janssen, Lilly, Novartis, Sanofi and UCB. Wolf-Henning Boehncke received honoraria for speaker and consulting activities from AbbVie, Almirall, Celgene, Janssen, Leo Pharma, Lilly, Novartis and UCB as well as a research grant from Pfizer. Khusru Asadullah received honoraria for speaker and consulting activities from AbbVie, Almirall, Antabio, Bayer, Emeritipharma, Galderma, Janssen-Cilag, Leo Pharma, L'Oréal, Novartis, Pierre Fabre, Sanofi Genzyme and UCB. Stefan Beissert received honoraria from AbbVie, Actelion, Bristol-Myers Squibb, Galderma, GSK, Janssen-Cilag, MSD, Novartis and Roche Posay. Honoraria for serving on advisory boards: AbbVie, Actelion, Amgen, Celgene, Galderma, Janssen-Cilag, Leo Pharma, Lilly, Menlo Therapeutics, MSD, Novartis, Pfizer and UCB Pharma. Kamran Ghoreschi received honoraria for speaker and consulting activities from AbbVie, Almirall, Biogen IDEC, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Janssen-Cilag, LEO Pharma, Lilly, MSD, Novartis, Pfizer and Roche. Michael P. Schön received honoraria for speaker and consulting activities from AbbVie, Celgene, Janssen-Cilag, Leo Pharma, Lilly, Novartis and UCB.

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