Review Article

Psoriasis as a Systemic Disease

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Summary

Background: Psoriasis was long regarded as an inflammatory disease limited to the skin. Data from dermatologic, rheumatologic and cardiologic research now show it to be a systemic disease, for which the term psoriatic disease is used.

Methods: This paper is based on a selective literature search with special attention to the findings of clinical trials and other current publications, as well as the recommendations of international guidelines.

Results: Immunologically mediated inflammation of the skin, arteries, bones, and joints is a central feature of psoriatic disease. Other diseases that are known to be associated with psoriatic disease include hypertension, metabolic syndrome, and depression. The main risk factor for the development of psoriatic disease is obesity, which also increases the likelihood of psoriatic arthritis. The main known trigger factors are stress, infection, and, less commonly, medication. Psoriatic disease is characterized by complex genetics and by a characteristic pattern of inflammation that involves elements of both innate and acquired immunity and, in particular, the cytokines interleukin 17 and 23. The inflammatory processes underlying psoriatic disease can now be targeted with modern biologic and other therapies.

Conclusion: In view of the complexity of psoriatic disease, structured management is now recommended so that physicians and patients can work together to determine the optimal treatment strategy.

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Psoriasis is a common, chronic, and incurable disease, affecting 2 out of every 100 people in Germany (1). It is characterized by sharply defined, red, raised plaques that are usually covered with scales. Frequently affected sites are the hairy scalp (79.9%), the extensor surfaces of the upper and lower limbs, the lumbosacral region, the genital area including the anal cleft (30.7%), and the nails (45.5%) (e1). In principle, however, any area of the skin can be affected. Itching of the lesions is common and very distressing (2).

Psoriasis is still widely thought of as being merely a skin disease. Yet people with psoriasis have long been known to suffer disproportionately from hypertension, dyslipidemia, metabolic syndrome/diabetes mellitus, and cardiovascular disease (e2). Large-scale studies have identified further comorbidities including Crohn's disease, depression, and metabolic fatty liver disease. One in five persons with psoriasis suffers from psoriatic arthritis (PsA) with involvement of musculoskeletal structures such as the entheses, the joints themselves, or the spine; in most such cases, rheumatoid factors or antibodies against cyclic citrullinated peptides cannot be detected. PsA was also previously classified as a comorbidity of psoriasis, rather than a component of psoriatic disease. The links between psoriasis and obesity and tobacco smoking were also recognized long ago.

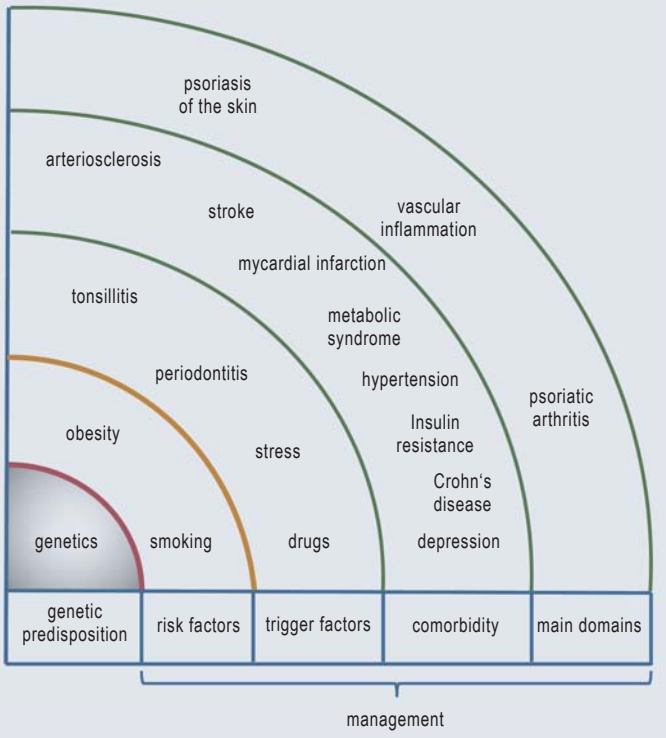
These and many other findings have led to a redefinition of psoriasis. It is no longer regarded as a disease of the skin, but rather as a systemic inflammatory disease, and is therefore called psoriatic disease.

The currently known elements of psoriatic disease are summarized in *Figure 1*. Psoriatic disease involves inflammation in at least three organ systems (domains): the skin, the blood vessels, and the bones and joints (3).

Common inflammatory signature

A particular signature of inflammation is common to all three domains of psoriatic disease *(Figure 2)*. The factors leading to the development of psoriasis are still unclear but are thought to include autoantigens and signals that particularly target the epidermal keratinocytes. Central to this process is the

Figure 1



Psoriatic dsease (modified from: [3])

activation of antigen-presenting dendritic cells to produce the cytokine interleukin (IL)-23 (4). IL-23 can activate T cells (CD4– and CD8-positive), which, in turn, release cytokines of the IL-17 family, the most important of which are IL-17A and IL-17F (5). Since Th17 immunity is physiologically required for the control of bacterial and mycotic infections, especially with Candida, stimulation with IL-17 cytokines represents a danger signal for keratinocytes. This leads to increased proliferation, impaired differentiation and the release of antimicrobial proteins (including β-defensin 2, LL-37) and chemokines (e.g., CXCL8, CCL20) in the epidermis. As a result, neutrophilic granulocytes are recruited; these form the typical Munro's microabscesses in the stratum corneum. Studies have shown that special T cell populations can form during immunological activation that are still present in the epidermis and dermis even after the skin lesions regress completely. These tissue-resident memory cells (Trm) (6) are thought to be at least partly responsible for new disease relapses (7). A current topic of study is whether a reduction in Trms through early, effective treatment can alter the natural, chronic course of the disease and the development of comorbidities. Regulatory T cells (Treg) play an important role in the inflammatory response in the skin and presumably elsewhere as well (8). Any decline in their number and/or activity promotes the inflammatory reaction.

The genetics underlying psoriatic disease is complex, and the presence of the currently known susceptibility genes does not adequately account for the development of the disease (9). A familial clustering of psoriatic disease and the findings of twin studies suggest an important genetic component. New concepts define psoriasis as an "MHC-1-opathy" (10) because of its association with HLA-C*06:02, similarly to ankylosing spondylitis (HLA-B*27) and Behçet's disease (HLA-B*51).

An almost identical inflammatory signature to that seen in the skin is also seen in the two other domains, i.e., the bones and joints and the blood vessels. These central cytokines are sensitive target structures for modern therapeutic agents that can be used with a highly beneficial effect *(Figure 2)*.

Vascular inflammation in psoriatic disease

Cardiological research, in particular, has shown that psoriatic disease causes arterial inflammation, especially in the coronary arteries, along with marked inflammation of the pericoronary adipose tissue, promoting the formation of so-called non-calcifying plaques on the endothelial cells (11). This vascular inflammation arises even in younger people with psoriasis and markedly elevates the risk of both myocardial infarction (3-fold) and stroke (1.6-fold) and lowers the life expectancy (12, e3, e4). There are common genetic features (13), but these play no more than a small role in vascular inflammation (e5). Cytokines of the IL-17 family, IL-6, and TNF are especially involved in the development of the initial non-calcifying arteriosclerotic plaques. Of particular interest is an open, experimental study that showed reduced inflammation of the pericoronary adipose tissue after treatment with IL-17 inhibitors, as well as with tumor necrosis factor (TNF) or IL-12/23 inhibitors (14). In a controlled trial, treatment with an IL-17A inhibitor resulted in improved endothelial function at one year (15). Registry data also indicate a lowering of mortality by suitable systemic therapy (16).

Inflammation of musculoskeletal structures in psoriatic disease

Modern imaging, especially MRI and high-resolution ultrasonography with power Doppler, has shown that people with cutaneous psoriasis and no joint symptoms already have inflammation at the points of attachment of tendons and ligaments to the bones (entheses), which can be detected regardless of the severity of the psoriatic disease (MRI [e6]; ultrasonography [e7]). Beyond the highly typical inflammation of the Achilles tendon insertion, which is sometimes misidentified as a "heel spur," any of the well over a thousand tendon insertions on the limbs and the spine can be affected. Enthesitis apparently arises because of initial microtraumata due to mechanical stress reactions, in turn favoring the invasion of the above-mentioned cell populations along with inflammatory cytokines (17). In contrast to synovitis, which arises relatively late in the disease course, enthesitis can be a very early sign of musculoskeletal involvement. If peripheral arthritis is present, it is usually an asymmetric oligoarthritis (2–5 joints), unlike in rheumatoid arthritis, where a symmetric polyarthritis of the small joints of the fingers and in the feet is typical (e8). In dactylitis, there is marked tenosynovitis with inflammation of the subcutaneous fat, although synovitis is not necessarily present. Moreover, periosteitis is typical of, and pathognomonic for, dactylitis. This is well

seen on both MRI and ultrasonography, which impressively show the massive inflammation *(Illustration)* (18). 25–70% of cases also show axial involvement i.e., involvement of the spine (e9). Along with inflammation of the vertebral bodies themselves (spondylitis), enthesitis is typically seen, e.g., at the insertions of the erector spinae muscles (19).

Comorbidity in psoriatic disease

As early as 1992, a large-scale association study showed that hypertension, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases are important accompanying diseases of psoriasis (20). Obesity, which used to be considered a comorbidity, is now held to be an independent risk factor for psoriatic disease (e10). Other comorbidities are chronic inflammatory bowel diseases, especially Crohn's disease (21), metabolic fatty liver disease (22), and uveitis (e11).

Depression and anxiety disorders were once thought psychological responses to the stigmatizing skin disease but are now known to have a neuroinflammatory component (especially for depression) (3). All conditions associated with psoriasis can already occur in children (23).

The relationship between these conditions and psoriatic disease follows a similar inflammatory pattern. This is also true of inflammatory changes in the central nervous system, perhaps explaining why, in one study, 21.1% of women with psoriatic disease suffered from chronic depression (compared to 14.2% in the general population) (e12). Yet hypertension can also activate IL-17 cytokines and, in turn, be exacerbated by them (24). In Crohn's disease, a central role is played by IL-23, and there are genetic associations as well. An imbalance of adipokines is known to be present in psoriasis (e13).

The authors of this review assume that the comorbidities of psoriatic disease are associated with its particular inflammatory pattern and should therefore be alleviated by treatments directed against elements of the inflammatory response. Targeted therapies with inhibitors of TNF, IL-17, or IL-23 alleviate depression as well when they alleviate psoriasis (e14).

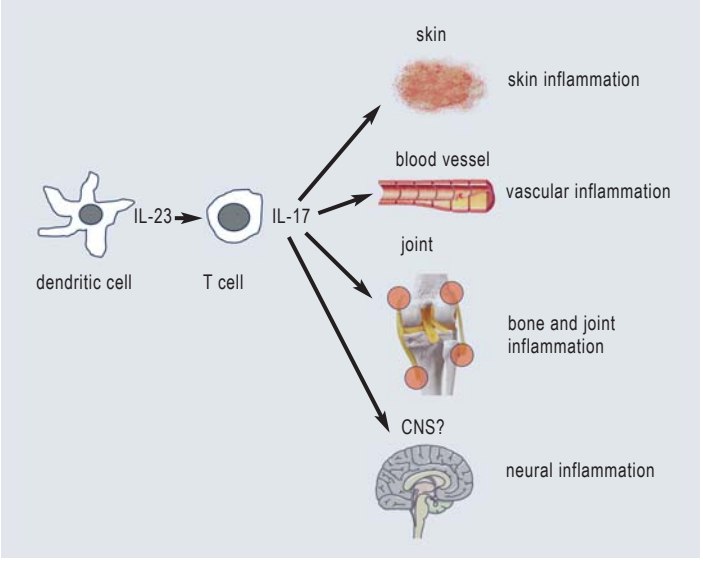
The evidence from clinical studies suggests that the alleviation of severe depression comes about not only as a secondary effect of the alleviation of the skin condition, but also through an anti-inflammatory effect in the central nervous system (25).

Triggers of psoriatic disease

Many patients with psoriatic disease state that certain situations make it worse or were the initial trigger for it. Streptococcal tonsillitis is a known trigger factor In childhood and adolescence. Infections that can be triggers in later life include periodontitis (usually associated with smoking) and HIV infection.

In adulthood, stress, particularly at work, is the most important trigger factor; it is cited by more than 90% of people with psoriasis surveyed (26). Hormonal factors may also play a role in the onset and progression of psoriasis (e15). Although drugs are no longer held to be major trigger factors (26), drug-induced psoriasis certainly does exist. Some of the drugs that can cause it are beta-blockers, ACE inhibitors, hydroxychloroquine, lithium salts, and immune checkpoint inhibitors.

Figure 2



Key cell types, cytokines, and target tissues in psoriatic disease

Risk factors for psoriatic disease

The most important risk factor for psoriatic disease is obesity. This rule applies not only to the three major domains (skin, blood vessels, bones/joints), but also to the comorbidities. Studies on large populations have shown that obesity is still a risk factor even after all confounders have been accounted for; in other words, it is an independent risk factor for psoriatic disease. Large cohort studies of bariatric surgery from Denmark and Sweden have shown that a veer high body mass index (BMI) (above 30 and above 40, respectively) nearly doubles the risk of developing psoriasis (27, 28). Vascular inflammation is also exacerbated by obesity. Obesity has long been recognized as an important risk factor for PsA (29). All of the diseases that are associated with psoriasis are also worsened by obesity.

The pathophysiological link between obesity and psoriatic disease has been well known for many years (30). When body weight increases due to uncontrolled calorie intake, a marked inflammatory reaction occurs in the adipose tissue, mainly (but not only) in the abdomen, which alters the adipokine profile toward a metabolic phenotype (with an increase in leptin, and resistin, among others, and a decrease in adiponectin). There is also a greater release of IL-6 and TNF, in turn contributing to systemic inflammation. Aside from the influence of obesity on cytokines, cellular changes have recently been shown as well, particularly in the important Treg system, which has anti-inflammatory and regulatory properties. A diet rich in calories and long-chain fatty acids lowers number of Tregs and stimulates the formation of IL-17-producing gamma/delta T cells (31).

Beyond the well-documented effect of weight loss on all components of psoriatic disease and comorbidity, an initial report of a single case has shown that the new glucagon-like-peptide-1 (GLP-1) agonist semaglutide can alleviate cutaneous and vascular inflammation in -

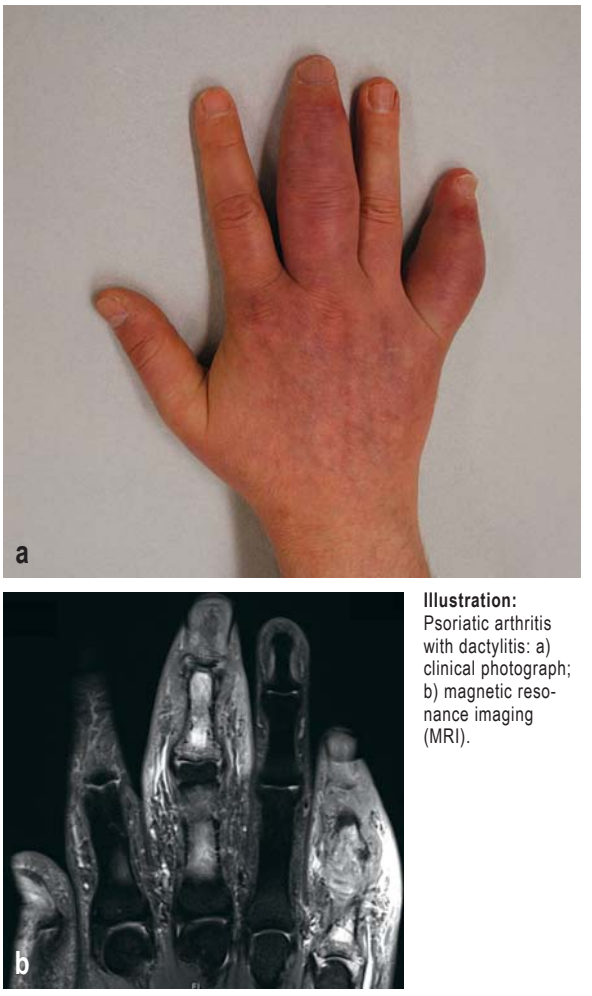


Illustration: Psoriatic arthritis with dactylitis: a) clinical photograph; b) magnetic resonance imaging (MRI).

addition to counteracting diabetes and promoting body weight loss (32).

Psychosocial aspects of psoriatic disease

The health-related quality of life and well-being, as defined by the World Health Organization, are impaired in psoriatic disease of any severity to an extent resembling that seen in other serious diseases, including cancer (e16, e17). Stigmatization and self-stigmatization contribute to marked impairment in patients who are already suffering from depression (33). The cumulative burden of psoriatic disease can have a lasting effect, which has been called cumulative life course impairment (34). Physicians caring for patients with chronic psoriatic disease must be aware of these major psychosocial effects.

The treatment of psoriatic disease

The complexity of psoriatic disease requires an individually tailored approach, with, as a rule, long-term drug treatment to achieve as much improvement as possible in all three major domains, as well as in the comorbidities (35). Unfortunately, in Germany at present, the drugs that can bring about an asymptomatic state, or nearly so, and that can exert a broad anti-inflammatory effect are prescribed only reluctantly to most patients with psoriatic disease, and often only after the failure of so-called conventional treatment.

There is no longer any justification for the old strategy of saving the best drugs for last. According to the current guideline, biologic agents can be used for first-line therapy, particularly for severely affected patients, if conventional drugs are not expected to yield adequate relief (36). It was recently shown that patients who have had psoriasis for less than two years can be effectively treated with the IL-23p19 inhibitor guselkumab, so that they experience a longer-lasting remission (37). The current "hit hard, hit early" strategy is also based on analogous beneficial results in rheumatology and gastroenterology. Early and highly effective treatment for rheumatoid arthritis prevents irreversible joint destruction more effectively than step treatment, which begins with the mildest form of treatment and is then escalated as necessary. Especially for PsA, rapid, disease-arresting treatment is needed regardless of the severity of skin involvement. The ability to arrest the course of PsA has been shown for modern biologic agents (e18; e19), but not for conventional agents such as methotrexate or leflunomide. Moreover, methotrexate is ineffective in some PsA subtypes, such as axial or nail involvement, but continues to be prescribed for these conditions despite the contrary recommendation in the rheumatology guidelines (38). Early evidence suggests that the probability of developing PsA over the course of psoriatic disease can be lessened with biologic agents (39).

Optimal treatment adherence can only be achieved when the appropriate treatment has been chosen in a shared decision-making process (40). This involves evaluating the psoriatic disease in all of its individually relevant dimensions and identifying the patient's goals for treatment. As a wide variety of approved treatments are available, there is room for the patient's preferences to be taken into account. There is also an increasing amount of room for adjusting the dosage or dose intervals of biologic agents within the parameters of their approval, on the basis of the patient's body weight, thereby improving the treatment of overweight patients and others. The overriding goal of treatment is to restore these patients' well-being and quality of life to normal levels as far as possible. The treatment of comorbidities requires close interdisciplinary cooperation among dermatologists, primary care physicians, rheumatologists, and psychologists. Awareness of the dimensions of psoriatic disease beyond the skin lesions is essential so that physicians of multiple specialties can cooperate optimally to help their patients.

Conflict of interest statement

SG has received research funding from Almirall-Hermal and Amgen. He has served as a paid consultant for AbbVie, Almirall-Hermal, Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen-Cilag, Klinge Pharma, Leo Pharma, Neubourg Skin Care GmbH, Novartis, Pfizer, and UCB. He has received lecture honoraria from AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Eli Lilly, Hexal AG, Janssen-Cilag, Leo Pharma, Medac, Neuborg Skin Care GmbH, Novartis, Pfizer, Sandoz Biopharmaceuticals, and UCB-Pharma, and reimbursement of travel expenses and meeting participation fees from AbbVie, Almirall-Hermal, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Pfizer, and UCB Pharma. He serves on the advisory boards of AbbVie, Almirall-Hermal, Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen-Cilag, Klinge Pharma, Leo Pharma, Neuborg Skin Care GmbH, Novartis, Pfizer, and UCB.

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UM is a paid consultant for AbbVie, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Formycin, Janssen-Cilag, LEO Pharma, Merck, Sharp & Dohme, Novartis, and UCB Pharma. He has received honoraria for continuing medical education events from AbbVie, Almirall, Amgen, Boehringer-Ingelheim, Biogen, Eli Lilly, Janssen-Cilag, Merck, Sharp & Dohme, Novartis, and UCB Pharma. He has received reimbursement of travel expenses and meeting participation fees from AbbVie, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Eli Lilly, Janssen-Cilag, Novartis, and UCB Pharma. He serves on the advisory boards of Almirall, Amgen, Eli Lilly, Formycon, LEO Pharma, Novartis, UCB Pharma, and UNION Therapeutics.

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WS is a paid consultant for AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi Genzyme, and UCB. She has received honoraria for continuing medical education events from AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi Genzyme, and UCB. She has received reimbursement of travel expenses from AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi Genzyme, and UCB. She serves on the advisory boards of AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen, LEO Pharma, Lilly, Novartis, Pfizer, Sanofi Genzyme, and UCB. She receives writing support from Almirall, Boehringer-Ingelheim, LEO Pharma, and medi GmbH Bayreuth.

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Supplementary material:
eReferences, eTable:
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Supplementary material to accompany the article:

Psoriasis as a Systemic Disease

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eTable

Randomized and controlled trials of relevant systemic therapies for psoriasis vulgaris*1

	First author	Year	ClinicalTrials.gov	PASI90 response	Time of observation	Undesired events (UE)
Conventional drugs and small molecules						
Dimethy lfumarat	Mrowietz et al. (e20)	2017	NCT01726933	18.4%	16 weeks	gatrointestional complaints, flush, lymphopenia
MTX s.c.	Warren et al. (e21)	2017	NCT02902861	18%	16 weeks	myelosuppression, hepatic and renal toxicity, nausea
Apremilast	Papp et al. (e22)	2015	NCT01194219	9.8%	16 weeks	gastrointestinal complaints, depression
	Paul et al. (e23)	2015	NCT01232283	8.8%	16 weeks	
Deucravacitinib	Armstrong et al. (e24)	2023	NCT03624127	35.5%	16 weeks	upper respiratory infections
	Strober et al. (e25)	2023	NCT03611751	27%	16 weeks	
Anti-TNF biologic agents						
Adalimumab	Menter et al. (e26)	2018	NCT00237887	37%	12 weeks	elevated risk of infection, reactivation of latent tuberculosis, infusion reactions (only infliximab)
Certolizumab	Gottlieb et al. (e27)	2018	NCT02326298 NCT02326272	45.9%	16 weeks	
Etanercept	Papp et al. (e28)	2005	Nicht angegeben	21%	12 weeks	
Infliximab	Reich et al. (e29)	2005	NCT00106834	57%	10 weeks	
Anti-IL17 biologic agents						
Bimekizumab	Gordon et al. (e30)	2021	NCT03410992	91%	16 weeks	elevated risk of infection, particularly for Candida; induction of chronic inflammatory bowel disease, rarely neutropenia
Brodalumab	Papp et al. (e31)	2016	NCT01708590	70.3%	12 weeks	
Ixekizumab	Gordon et al. (e32)	2016	NCT01474512	70.9%	12 weeks	
Secukinumab	Langley et al. (e33)	2014	NCT01365455 NCT01358578	54.2–59.2%	12 weeks	
Anti-IL12/23 biologic agents						
Ustekinumab	Leonardi et al. (e34)	2008	NCT00267969	36.7–41.6%	12 weeks	low risk of infection
	Papp et al. (e35)	2008	NCT00307437	42,.%–50.9%	12 weeks	
Anti-IL23 biologic agents						
Guselkumab	Blauvelt et al. (e36)	2017	NCT02207231	73.3%	16 weeks	low risk of infection
	Reich et al. (e37)	2017	NCT02207244	70.0%	16 weeks	
Risankizumab	Gordon et al. (e38)	2018	NCT02684370 NCT02684357	74.8–75.3%	16 weeks	
Tildrakizumab*2	Reich et al. (e39)	2017	NCT01722331 NCT01729754	35.0–39.0%	12 weeks	

*1 The key approval studies in adult patients with moderate to severe psoriasis vulgaris are listed. The clinical endpoint is the percentage achievement of a 90% reduction in the Psoriasis Area and Severity Index (PASI) after the induction phase. A PASI90 response corresponds to lesion-free or almost lesion-free skin.
*2 Marked discrepancy in the PASI90 response between the RCT and real-world data (50% PASI90 after 16 weeks, e.g. in the Austrian Psoriasis Registry (e40)).
s.c.: subkutan

Questions on the article

CME plus+

Psoriasis as a Systemic Disease

The submission deadline is 11 July 2025. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Approximately what percentage of the German population suffers from psoriasis?

a) 0.1%
b) 2%
c) 10%
d) 20%
e) 35%

Question 2

As described in this article, what areas of the skin are commonly affected by the typical red, raised plaques of psoriasis?

a) the hairy scalp, natal cleft, and nails
b) the upper back, scalp, and palms
c) the dorsal surfaces of the feet, the chest, and the abdomen
d) the face, chest, and soles
e) the nails, soles, and upper back

Question 3

As described in this article, what are the three main domains for inflammation in psoriatic disease?

a) the skin, lungs, and eyes
b) the mucous membranes, blood vessels, and glands
c) the joints, mucous membranes, and glands
d) the skin, blood vessels, and joints
e) the skin, lungs, and glands

Question 4

What interleukins play a central role in the inflammatory reaction that is characteristic of psoriatic disease?

a) IL-18 and IL-11
b) IL-17 and IL-23
c) IL-13 and IL-27
d) IL-9 and IL-7
e) IL-3 and IL-13

Question 5

What does the abbreviation Trm in the article stand for?

a) t-cell relayed memory
b) therapy-resistant memory cells
c) tissue-resident memory cells
d) t-cell regulated memory
e) tissue-relayed memory

Question 6

People with psoriatic disease have a higher risk of developing certain other diseases. Which of the following elevated risks are mentioned in the article?

a) gastric ulcer (double the risk)
b) cystic fibrosis (risk three times as high)
c) polycystic ovarian syndrome (risk five times as high)
d) myocardial infarction (risk as high)
e) blindness (risk five times as high)

Question 7

According to the article, what disease of children is a frequent trigger for the onset or worsening of psoriasis?

a) varicella-zoster infection (chickenpox)
b) influenza infection
c) infectious mononucleosis
d) three-day fever (HHV 6 infection)
e) streptococcal tonsillitis

Question 8

What do 90% of adult patients with psoriatic disease say is the main trigger factor for their disease?

a) stress (mainly at work)
b) sleep deprivation
c) high ambient temperatures (sweating)
d) a high-protein diet
e) contact with chlorinated water, e.g., in swimming pools

Question 9

According to the text, which of the following is an independent risk factor for psoriatic disease?

a) hypertension
b) depression
c) obesity
d) migraine
e) anxiety disorder

Question 10

What treatment is recommended in this article for patients suffering from severe psoriasis, and especially psoriatic arthritis, in accordance with a hit-hard-and-early strategy, in case conventional treatments are not expected to yield adequate relief?

a) step treatment (mildest treatment at first, then escalation if necessary)
b) first-line treatment with biologic agents
c) first-line treatment with methotrexate
d) first-line treatment with leflunomide
e) first-line treatment with corticosteroids