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The today and tomorrow of (almost) each itch

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ABSTRACT

Itch is an unpleasant sensation on the skin that causes the desire to scratch. Its aetiology can be defined by various categories such as cause, period of occurrence, location, and the presence or absence of skin disease in a given area. This burdensome symptom experience can even be compared to chronic pain in terms of quality-of-life-impairment and is particularly common among older people. This article discusses the neural pathways that cause itch, the important but clinically challenging role of histamine, and some of the mechanisms involved in the itch-scratch cycle, such as some quite novel discoveries regarding the contributions of the gastrin-releasing peptide (GRP)/gastrin-releasing peptide receptor (GRPR) axis, transient receptor potential (TRP) channels, and Janus kinase. Pruritus may be associated with various types of diseases affecting the maternal-foetal relationship, skin, cholestasis, renal system or mental health. Some new therapeutic options include drugs that affect opioid receptors, neurokinin 1 receptor (NK-1R) antagonists, Janus kinase inhibitors, and biologics made by combining antibodies against different types of interleukins associated with the itch sensation. Nevertheless, finding an effective form of therapy for patients with various underlying conditions remains a challenge and is the subject of ongoing clinical research.

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Keywords: itch, pruritus, itch-scratch cycle, prurireceptor, neuropathic itch, GRP/GRPR axis, TRP channels

INTRODUCTION

Itching, clinically known as pruritus, is defined as "an unpleasant sensation that produces the desire to scratch" (Samuel Hafenreffer, 1660) [1–3]. It can be grouped into four categories according to 1) cause, 2) duration, 3) location on the skin, and 4) presence or absence of skin disease in the area affected by itching.

1. The itch may be caused by dermatological, systemic, neuropathic/neurogenic or physiogenic diseases, and may be of multifactorial or unknown origin [4–6]. Genetic [2] and pharmacological [4] factors are also believed to elicit itch.
2. Pruritus is described as "acute" — when it lasts less than 6 weeks, or "chronic" — when it lasts longer than 6 weeks [7]. Chronic itch is associated with significant deterioration in quality of life, *e.g.*, sleep difficulties, psychological disorders and antisocial attitudes [2].
3. Pruritus is classified as "generalised pruritus" when the itching sensation affects a large area of the skin and is not limited to a specific part of the body, and as "localised pruritus", when the itching occurs in a specific location. Generalised pruritus may be caused by dry skin, medications, and may be associated with an underlying disease (mainly of internal organs) [4].
4. According to the International Forum for the Study of Itch (IFSI), pruritus can be divided into 3 categories: I — when itch affects diseased skin, II — when it occurs on healthy skin and III — when it refers to chronic skin lesions associated with scratching [8].

The causes of the itch are presented in Table 1 [4, 6, 7, 9, 10].

EPIDEMIOLOGY

Itch is very common among older people (especially those over 85 years of age) [2]. However, it may also occur specifically during pregnancy as a pregnancy-related pruritic disease or coincidentally comorbid with pregnancy [11]. Both of these cases will be discussed in the following

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Table 1. Causes of the itch

Dermatological	Xerosis, psoriasis, atopic dermatitis, prurigo, echema, scabies, urticaria
Systemic	Renal diseases, hepatobiliary diseases, endocrine diseases, rheumatologic diseases, haematologic diseases, mental disorders, cardiogenic diseases, AIDS
Neuropathic	Inflammation, postherpetic neuralgia, fibromyalgia, tumours of the central or peripheral nervous systems, stroke
Physiogenic	Depression, anxiety, delusional parasitosis, tactile hallucinations, obsessive-compulsive disorder, mania, delusional disorders such as parasitophobia, substance abuse
Genetic	Darier disease, Hailey–Hailey disease, epidermolysis bullosa pruriginosa, Sjögren–Larsson syndrome
Drugs	Opioids, diuretics, anti-inflammatory analgesics, cardiovascular drugs (captopril, enalapril, clonidine, amiodarone, dopamine, quinidine, digitalis preparations), antibiotics (β-lactams, rifampicin, polymyxin B), benzodiazepines, carbamazepine, barbital, chloroquine

AIDS (*acquired immune deficiency syndrome*) — zespół nabytego niedoboru odporności

sections. The 2010 Global Burden of Disease (GBD) Study estimated that GBD could be attributed to 15 categories of skin diseases with 261 conditions in 187 countries, by age group every 20 years, by sex, from 1990 to 2010. One of them was pruritus, which ranked among the 50 most common causes of the disease in the world, with a global prevalence of 1/4279,889,120. The highest prevalence rates of pruritus were observed in Western Europe. Moreover, the study presented as a key problem an increased number of cases of age-related pruritus and pruritus in older people, over 70 years of age [12]. Based on a cross-sectional study in 13 European countries, in which 3,530 patients were examined (including 1,094 control subjects), the authors concluded that "the prevalence of itch in prurigo was 88.9%, in atopic dermatitis — 86.0 %, in hand eczema — 82.3%, in other types of eczema — 77.7%, in urticaria — 75.9% and in psoriasis — 70.4%" [13].

THE PATHOMECHANISM

The physiopathology of itch may have various sources, depending on the underlying clinical entity responsible for this phenomenon (Fig. 1). Although histamine has been widely used as first-line therapy for most cases of pruritus, in recent years targeted treatment is being explored as a promising form of future clinical management with superior efficacy [14]. The full mechanism of the itch-scratch cycle remains unknown. However, there are several pathways responsible for this cycle, some of which are understood but still under investigation for their true therapeutic potential [15]. Initially, the understanding of itch was limited to its role solely as a scratching stimulus, which is a natural skin response designed to inhibit toxins, microorganisms, and harmful environmental substances that have the potential to damage the skin barrier. However, the itching sensation may also be pathological, resulting from underlying clinical changes related to specific diseases; it also significantly affects the deterioration of the quality of life, which is surprisingly comparable to the quality of life of patients experiencing chronic pain (Kini et al.) [16]. Itching can even be described as a skin sensation equivalent to pain [17]. Therefore, it was concluded that itch and pain are closely related but (academically recognised) distinct sensations [18].

THE NEUROBASICS

The sensation of the itch is transmitted by specific slow-conducting C neurons. Prurireceptors (primary afferent neurons), "serving as antennae", transmit neural information evoked by itch mediators to the dorsal root ganglion and spinal cord, where the signals are modified before reaching the brain. The discovery of itch-specific neuronal pathways supports the thesis that itch and pain are distinct [1, 19]. Although more and more different mediators of itch have been discovered, the sensation remains poorly described.

Prurireceptors can vary in their chemical structure. However, itch-signalling pathways, under certain very specific conditions (without the presence of a "conventional pruritogen"; pruritogens are stimuli that directly affect sensory neurons to produce itch), can arise from a mechanical stimulus, *e.g.*, contagious itch. Mainly, there are G protein-coupled receptors (or seven-space receptors) that are specifically associated with causing itch in the periphery [20].

THE FIRST ITCH-SPECIFIC PATHWAY — GASTRIN-RELEASING PEPTIDE

Gastrin-releasing peptide (GRP) is a regulatory human neuropeptide that primarily stimulates gastric G cells (although this cell type is also found in the duodenum and pancreas) to release gastrin [21] and initiates protein binding [22], which enables the transmission of direct non-histaminergic itch stimuli (because their ligands are direct receptors) [1]. The human GRP gene, encoding bombesin-like peptides, is located on chromosome 18q21 [22]. The gastrin-releasing peptide receptor (GRPR) as a member of the bombesin receptor family (GRPR, neuromedin B receptor

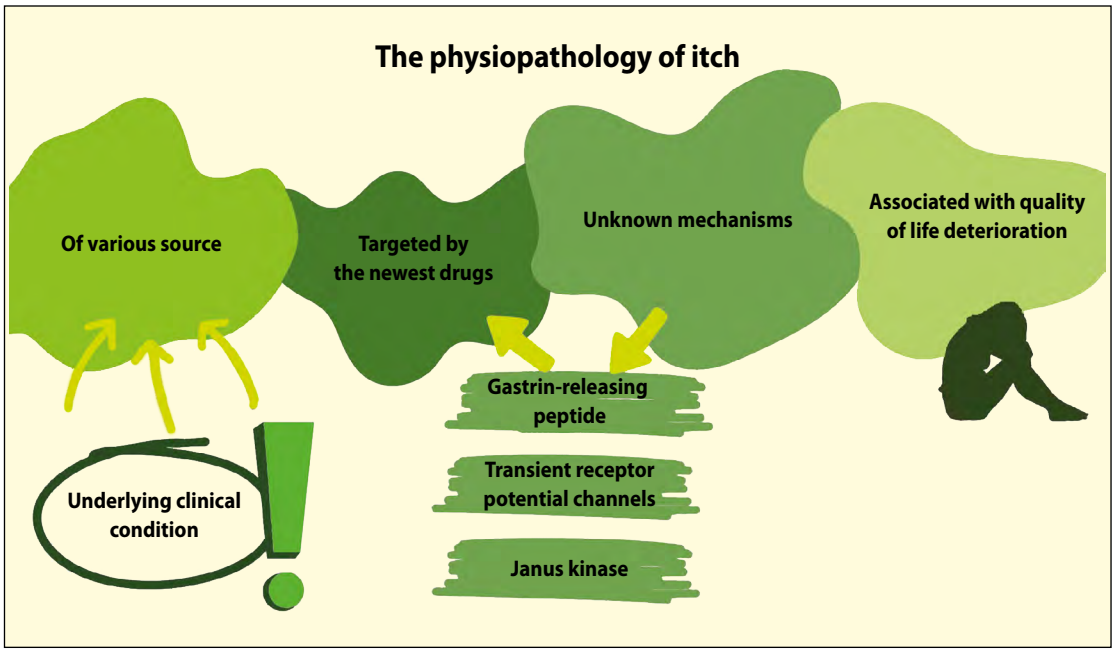

Figure 1. The physiopathology of itch; created by the authors using Canva.com, 2024

and orphan bombesin receptor subtype 3) is widely overexpressed in numerous pathological processes, including prostate, breast, and lung cancer. Therefore, GRPR remains the subject of oncological discussions — mainly in the context of prospective targeted molecular anticancer therapy. Furthermore, increased expression of these receptors, present widely in the central nervous system and peripheral tissues, is commonly associated with central nervous system/neural tumours, including gliomas, neuroblastomas, and medulloblastomas. All these examples seem to reasonably signal a link between neurological pathways and the occurrence of a specific type of itch, namely neuropathic itch; this means that the feeling of itching is characteristic not only of dermatological but also of neurological conditions. Recently, many new approaches have emerged to understand the consequences of GRP/GRPR axis activity in different diseases. In the future, they will likely be able to provide even deeper insight into the occurrence of GRP/GRPR axis-induced itch in certain medical conditions [23]. Elementally, itching can be divided into histaminergic, when histamine is released, and non-histaminergic when histamine is not involved in the process [19].

THE HISTAMINE ESSENTIAL ROLE AND ITS CLINICAL UNDERPERFORMANCE

Histamine injection was shown to induce the urge to scratch in most strains of mice (Inagaki et al. [24]). Yet, only one (H1R) of four different histamine G-protein-coupled receptors is known to be distinctly expressed by both human and mouse itch sensory neurons and prurireceptors. The elicitation of H1R histaminergic pruritus may only be enabled by opening the transient receptor potential (TRP) channel — transient receptor potential vanilloid 1 (TRPV1). Paradoxically, antihistamine H1R blockers were insufficiently effective in most cases associated with chronic pruritus (with the exception of urticaria or urticaria). The importance of histamine receptors is likely to be further investigated in the future; however, with the apparent insufficient clinical results of antihistamine performance, a recent shift in the focus of pruritus research toward pathways mediating nonhistaminergic pruritus can be seen [17].

TRANSIENT RECEPTOR POTENTIAL CHANNELS

Two types of itch-transmitting receptors have been discovered — GRPR and TRP channels. The latter are widespread in various human organs, including the heart, lungs, liver, kidneys, gastrointestinal tract, nerves and skin tissues. TRP channels are ion cations permeable channels located on the cell surface, whose main function is to sense (enabled through the process of their activation) various stimuli and trigger appropriate sensory reactions/responses. Although TRP channels have been studied since their discovery in 1969, our understanding of their biological and pathophysiological function still remains incomplete. However, the involvement of TRP channels and their potential malfunction may be observed in various diseases, such as inflammatory bowel disease and its complications [*e.g.* non-alcoholic fatty liver disease (NAFLD)], psoriasis, coronavirus disease 2019 (COVID-19), chronic obstructive pulmonary disease (COPD) and asthma, as well as in many

neurological diseases (*e.g.* epilepsy, stroke, anxiety, depression) and cardiovascular diseases (*e.g.* heart hypertrophy, heart failure, high blood pressure, atherosclerosis) [25, 26].

Of the twenty-seven TRP channels that have been discovered to date, at least six have been proven to be involved in the perception of itch. There is a good chance that there are more TRP channels responsible for the sensation of itching; this assumption is based on the relationship between itch and pain and the already-made discoveries about the role of TRP channels in pain perception. Nevertheless, the functional role of transient receptor potential melastatin 2 (TRPM2) and transient receptor potential canonical 5 (TRPC5) (both studied in the context of the relationship between pain and pruritus) remains unknown [27].

JANUS KINASE AND THE IMMUNE RESPONSE

Protein kinases are a group of enzymes that facilitate the transfer of a phosphate group from adenosine triphosphate (ATP) to amino acid residues, specifically serine, threonine or tyrosine. Depending on the amino acid phosphorylated, they are classified as serine/threonine kinases, tyrosine kinases, or dual-specificity kinases. This phosphorylation process initiates a signalling cascade that activates pathways that regulate gene expression.

Janus kinases (JAKs) are a family of cytoplasmic tyrosine kinases, with four family members in humans: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). These enzymes are widely expressed, with the exception of JAK3, which is found mainly in haematological cell types. Their role is to couple signals from cell membrane receptors with signal transducer and activator of transcription (STAT) transcription factors, actively participating in the JAK/STAT signalling paradigm. The relationship between JAKs and pruritus will be discussed in the following sections.

The JAK/STAT cascade is a simple and evolutionarily conserved signalling pathway. It begins with the binding of a ligand (*e.g.* growth factors, cytokines) to JAK bound to a receptor on the cell membrane, leading to activation of the receptor through autophosphorylation and transphosphorylation. JAKi then phosphorylate tyrosine residues on the cytoplasmic tails, creating docking sites for cytoplasmic STATs. Phosphorylated STATs form a dimer, enter the nucleus and bind to DNA, activating gene expression. This pathway allows direct communication between cell membrane receptors and the cell nucleus [15].

THE RELATIONSHIP BETWEEN ITCHING AND VARIOUS DISEASES AND CONDITIONS

Pruritus is usually associated with skin disorders, but its impact may also occur in systemic diseases (*e.g.* kidney disease, liver disease or cancer) [28].

Uraemic pruritus

Pruritus is the most common skin symptom in patients with chronic kidney disease (CKD), called "uraemic pruritus" or "chronic kidney disease-related pruritus" (CKD-P), and affects up to 42–57% of people on dialysis [28–30]. Increased levels of urea, creatinine, calcium, phosphorus, parathyroid hormone (PTH) or vitamin A, or decreased levels of vitamin D, are believed to be involved in the occurrence of pruritus. In a cohort study of 471 patients, 8.1% reported severe itching, 37% described it as moderate, and 40% described it as mild. Generalised pruritus was reported by 26.6% of patients, while 38% of them described itch as well localized [28]. In another study (Wojtowicz-Prus et al. [29]) involving 103 children, researchers assessed the frequency and severity of pruritus and dry skin and estimated that approximately 20% of children with CKD suffer from pruritus. A 2020 meta-analysis (Hercz et al. [31]) based on 92 studies involving 4,466 people indicates gabapentin and pregabalin (GABA) analogues as the most effective drugs in reducing itch in patients with CKD.

Hepatic pruritus

Hepatic pruritus is a common symptom of liver diseases such as cholestasis and non-alcoholic liver disease. Bile acid, bilirubin, lysophosphatidic acid (LPA), endogenous opioids, serotonin and histamine are considered to be responsible for the occurrence of pruritus [30]. The new bile acid receptor — MRGPRX4 — is a receptor for bile acids and bilirubin. Moreover, based on the high probability that autotaxin/LPA plays a major role in the pathogenesis of cholestatic pruritus, this receptor is considered to represent new therapeutic opportunities [32, 33].

Interestingly, recent findings also point to lysophosphatidic acid and autotaxin as key elements in the pathophysiology of cholestatic pruritus [34]. The first-line therapy for cholestatic pruritus is cholestyramine, which is generally well-tolerated and effective in most cases. For those for whom cholestyramine fails to reduce persistent symptoms, alternative medications, including rifampicin and μ-opioid receptor antagonists, may be considered [35].

Pruritus in pregnancy

Many changes can be observed during pregnancy (*e.g.* immunological, metabolic and vascular), which can potentially significantly affect the entire body of a pregnant woman. The activity of the endocrine system, which is largely responsible for skin symptoms, also has a significant impact. During pregnancy, the activity of sweat and sebaceous glands increases, while the activity of apocrine glands decreases; this may be associated with causing itching in pregnant patients. Therefore, itching may even

be the first symptom of pruritic disease characteristic of pregnancy [11].

In a Szczęch et al. [36] study involving 292 pregnant women, itching occurred in as many as 38% of them. On average, this began at 27.2 ± 7.6 weeks of gestation, while approximately 22 of these women suffered from this bothersome sensation before pregnancy. Interestingly, the abdomen was indicated as the most common place of itching (by almost 90% of women), while hands, feet and calves were mentioned less often.

Skin diseases characteristic of pregnancy include dermatoses coinciding with pregnancy or recurrent during pregnancy (*e.g.* psoriasis, atopic dermatitis, dyshidrosis and dyshydrotic dermatitis, dermatomyositis HIV/AIDS, urticaria, mastocytosis, lichen planus, neurofibromatosis, Gibert's lichen rosea) [37]. Another pathophysiological process associated with pruritus that may be associated with pregnancy is specifically four dermatoses: atopic eruption of pregnancy (AEP), polymorphic eruption of pregnancy (PEP), pemphigoid pregnancy (PG) and intrahepatic cholestasis of pregnancy (ICP) [11].

Atopic eruption of pregnancy

Atopic eruption of pregnancy is one of the most common dermatoses occurring during pregnancy. It includes patients diagnosed with eczema of pregnancy, prurigo of pregnancy and pruritus follicles of pregnancy [38]. Lesions may appear throughout pregnancy and may be localised on the trunk, limbs or atopic eczema in flexures-atopic sites [39].

Polymorphic eruptions of pregnancy

Polymorphic eruptions of pregnancy, also known as pruritic urticarial papules and plaques of pregnancy (PUPPP) are benign, self-limited inflammatory disorders characterized by a polymorphic clinical presentation [40]. Patients most often receive a diagnosis of PEP in the third trimester, when pruritic plaques appear on the abdomen and combine into papules [41].

It is estimated that the incidence of PEP is 1:120–1:160 pregnancies and may be associated with multiple pregnancies and excessive maternal weight gain [40, 42]. Fortunately, the disease spontaneously disappears within 4–6 weeks after delivery, so the only recommended treatment is symptomatic (*e.g.* emollients, antihistamines, topical glucocorticosteroids) [11].

Pemphigoid of pregnancy

According to a study conducted in Saudi Arabia between 1990 and 2014 involving 32 patients with pemphigoid of pregnancy, symptoms of the disease occurred in the second or third trimester in 84% of cases. All patients participating in the study suffered from pruritus, which in most cases (94%) was the first symptom of gestational pemphigoid. This condition most often intensifies during labour (during or just after) and improves spontaneously after delivery; the pemphigoid of pregnancy regresses spontaneously within 4 weeks. Typically, symptoms include pruritus associated with erythematous plaques and a vesicular eruption that characteristically affects the umbilicus area on the abdomen; however, it can spread to the trunk, lower (mainly thighs), and upper limbs. It is estimated that the incidence of gestational pemphigoid is approximately 1:2000–1:60,000 pregnancies. Unfortunately, the recurrence rate is high, with up to 50% of subsequent pregnancies in previously affected patients [11, 43]. Due to the risk of premature birth and intrauterine growth retardation, patients should be monitored throughout pregnancy. Gestational pemphigoid may also be associated with a higher likelihood of developing other autoimmune diseases in pregnant women (*e.g.* Graves' disease) [11].

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy is a reversible condition described as the inability to excrete bile salts from the liver, leading to an increase in bile acid levels, which can be a potential trigger for pruritus. The disease manifests itself with a characteristic triad of symptoms, including pruritus, jaundice (appearing 2–4 weeks after the onset of pruritus), and high levels of bile acids. Additionally, several other conditions may be associated with ICP, namely gallstones, hepatitis C virus infection, preeclampsia, and gestational diabetes [11].

The prevalence of ICP is estimated to be 0.3–5.6% and depends on existing ethnic, geographic and seasonal shifts [44]. It usually appears in the second or third trimester and spontaneously resolves within 6 weeks after delivery. Nevertheless, ICP is associated with a higher risk of foetal complications, low birth weight, perinatal necrosis and death [11].

Stress

Psychological stress, due to its high prevalence, is a challenge of the utmost importance for today's society. It can affect the immune system, leading to increased skin inflammation and worsening of itching. Moreover, itching has been proven to be an important factor in worsening the quality of life (sleep problems, chronic stress). Therefore, this situation can create a vicious cycle in which stress increases the number of itch sensations and vice versa (the itch-scratch cycle contributes to stress) [45].

A study conducted in Germany among 876 students showed that highly stressed students were more likely to

experience itching (approximately 56.5%). Respondents also reported other skin problems (*e.g.*, flaky skin, itchy rashes on hands, dry/painful rashes, pimples, and warts). Interestingly, these conditions were also more frequently reported by students with high levels of stress [46]. A very similar study was conducted among Australian university students. In a study involving 541 people, respondents were divided into three groups — with low, medium and high levels of stress. Comparing the results, it can be concluded that highly stressed students complained of itching, dry painful rashes and other skin problems more often than less stressed students. Additionally, it has been proven that increased psychological stress can influence many different skin problems and feelings [47].

Depression

Based on research, approximately 20–30% of depressed patients may experience itching during depressive episodes. A Polish pilot study involving 40 patients with depression showed that 7 of them (17.5%) reported itching during depressive episodes. Six patients with recurrent episodes of depression reported itching sensations, usually in the same place on the skin, with each episode. After treatment with antidepressants, pruritus disappeared in these patients. Antidepressants have also been observed to relieve itching [48]. According to a study conducted in 13 European countries, the prevalence of depression in pruritus patients was approximately 14.1% and anxiety 21.4%. However, the incidence of suicidal thoughts was 15.7%. A strong association has been demonstrated between depression, suicidal thoughts and the experience of itch, which may lead to the conclusion that mental states are significantly associated with itch [13].

Emerging options for chronic itch treatment

Finding effective therapeutic options for chronic itch presents many challenges that may be related to the extremely complex pathogenesis of itch. Chronic itch in its most common form can be seen in atopic dermatitis and is described as a "result of crosstalk between the nervous system, cutaneous immune system and keratinocyte populations" [49].

Interestingly, anti-exudative effects were observed with several drugs acting on opioid receptors, which was probably an expected result since pruritus is a common side effect of clinical opioid use. The ability to induce the itch-scratch cycle has been noted as a function of not only mu-opioid receptor agonists but also mu-opioid receptor antagonists or kappa-opioid receptor agonists. "Classic antiexudatives" (with predominant mu-opioid receptor antagonist activity) include naloxone, naltrexone, and nalmefene. Slightly more complex options (created by combining mu-opioid receptor antagonism and kappa-opioid receptor agonism) with promising clinical antiexudative efficacy include butorphanol and nalbuphine [49, 50].

The neurokinin-1 receptor (NK-1R) has a strong basis in causing the itch response in humans, as it leads to vascular response, mast cell degranulation, expression of nerve growth factor (NGF) in keratinocytes, and stimulation of neurogenic inflammation. Therefore, NK-R1 antagonists may also provide moderate effectiveness in relieving pruritus. Aprepitant is an oral NK-1R antagonist that is commonly used to counteract the nausea and vomiting that may occur after surgery or be caused by chemotherapy. However, the anti-exudative effect of this drug has been demonstrated in patients with Sézary syndrome, solid tumours and in people receiving anticancer drugs such as epidermal growth factor receptor inhibitors (EGFRIs) and tyrosine kinase inhibitors. Ongoing clinical trials are also testing the itch-inhibiting ability of other NK-1R antagonists (*e.g.*, serlopitant, tradipitant, and orvepitant) [49, 51].

JAKs are a family of enzymes involved in inflammatory conditions such as rheumatoid arthritis and inflammatory bowel diseases. However, JAKs inhibition may also be beneficial for certain dermatological conditions. Increasing evidence supports the safety and effectiveness of JAK inhibitors in the treatment of psoriasis, atopic dermatitis (AD), alopecia areata, and vitiligo [49, 52].

Recently, much more evidence has emerged supporting the involvement of cytokines in pruritus and supporting the use of targeted therapies with biologics (antibodies against IL-4, IL-13, IL-17, Il-23 or IL-31) in various chronic inflammatory conditions skin [49].

CONCLUSIONS

Itch remains a clinical mystery for all specialists — not only because of its particularly complex pathophysiology but also because it is a troublesome symptom for many patients. Therefore, pruritus is continually researched in the hope of finding an effective treatment option. Nevertheless, it can be assumed that obtaining a cure for all types of itching will be extremely difficult because we are constantly discovering new factors influencing this condition. Moreover, it is one of the few symptoms that may be familiar not only to patients with various disorders but to each and every one of us.

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