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REVIEW

NK-1 Receptor Antagonists and Pruritus: Review of Current Literature

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ABSTRACT

The discovery of the first neurokinin 1 (NK-1) receptor antagonist was a turning point in the prevention of chemotherapy-induced nausea and vomiting. The NK-1 antagonists are a novel class of drugs that possess antidepressant, anxiolytic, and antiemetic properties. Recently, clinicians have also described an anti-itch activity of NK-1 antagonists. We present herein results from currently available data on use of NK-1R antagonists in dermatology. For this purpose, a systemic electronic literature search of the PubMed and CINAHL databases, Cochrane Library, and clinicaltrials.gov website was performed. Based on currently available data, it can be concluded that NK-1 inhibitors show significant antipruritic potential for treatment of chronic pruritus in different dermatological conditions, but further studies are needed to establish the best indications and dosage of these drugs.

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INTRODUCTION

The NK-1 antagonists are a novel class of drugs that possess antidepressant, anxiolytic, and antiemetic properties. Recently, clinicians have also described their antipruritic activity. Aprepitant, the commercially available NK-1 inhibitor, is registered for treatment of emesis associated with anticancer chemotherapy [1]. In 2009 for the first time, it was first reported that orally given aprepitant effectively reduced pruritus in three patients with Sézary syndrome [2]. Subsequent case reports documented its potential antipruritic effect in prurigo nodularis [1], brachioradial pruritus [3], paraneoplastic pruritus [4], drug-induced pruritus [5], and cutaneous T-cell lymphoma [6]. Interestingly, aprepitant was also shown to exert antitumoral activity on a human melanoma cell line, suggesting other possible treatment indications [7, 8]. These findings led to the development of new substances and the initiation of numerous randomized controlled clinical trials for various indications, including also chronic pruritus. We present herein a review of currently available data on use of NK-1R antagonists in dermatology, with special emphasis on their potential antipruritic activity.

METHODS

Data Sources and Study Selection

A systematic electronic literature search of the PubMed database, CINAHL database, Cochrane Library, and clinicaltrials.gov was performed. The PICO criteria for the literature search are presented in Table 1. Index words included combinations of the following terms: NK-1 antagonists, NK-1 inhibitors, aprepitant, serlopitant, tradipitant, orvepitant, and NK-1 blockers coupled with dermatology, skin, cutaneous, and pruritus. All results were checked for relevance. The references of included studies were searched for additional articles.

Our search yielded a total of 389 results (with redundancy) containing the mentioned keywords. Ultimately, 18 clinical articles were included in this review (Fig. 1). Nonhuman studies or articles published in languages other than English were excluded. Case reports and review articles were also eliminated.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Table 1 PICO criteria of included studies

Population	Patients suffering from pruritus of any age
Intervention	Treatment with any NK-1R inhibitor
Comparator	Any comparator, including no treatment or placebo or active treatment
Outcomes	Change in pruritus prevalence
	Change in mean pruritus intensity
	Change in patient-reported outcomes
Time	From the beginning of the database entry until 24 May 2019
Study	Randomized trials, any control or comparison studies, cohort studies, experimental studies (excluded: case reports, review papers)

Substance P and Neurokinin 1 Receptor Antagonist in Relation to Pruritus

Substance P (SP) is a member of the tachykinin family, which also includes neurokinin A (NKA), neurokinin B (NKB), hemokinin 1, neuropeptide-γ (NK-γ), neuropeptide K (NPK), and endokinins. SP has the highest affinity to neurokinin 1 receptor (NK-1R) and lowest to NK-2R and NK-3R [9]. SP is a key mediator in the skin with potent proinflammatory properties and, next to calcitonin gene-related peptide (CGRP), is the most prominent neuropeptide released by peptidergic neurons [1]. NK-1R, also known as tachykinin receptor 1 (TACR-1) or SP receptor, is expressed in the central nervous system (dorsal horn neurons that project to the thalamus or parabrachial nuclei) as well as in peripheral tissues. At the periphery, NK-1R can be found in muscles, gastrointestinal tract, genitourinary tract, pulmonary tissue, thyroid gland, and different types of immune cells, and in the skin on keratinocytes, epithelial cells of hair follicles, mast cells, fibroblasts, epidermal dendritic cells, and endothelial cells [1, 9]. NK-1R is also present on human melanoma cells and can mediate the viability of tumor cells [7]. Many central and peripheral effects of SP are mediated by NK-1R; binding of SP to NK-1R on keratinocytes and fibroblasts stimulates secretion of interferon γ, interleukin (IL)-1β, and IL-8 [9]. Activation of NK-1R on mast cells leads to degranulation and secretion of histamine, leukotriene B4, prostaglandin D2, tumor necrosis factor α, and vascular endothelial growth factor (VEGF), while on vessels it induces vasodilatation and neurogenic inflammation with clinical symptoms including erythema, edema, and pruritus [1].

It has been suggested that SP plays a significant role in the pathogenesis of pruritus in several disorders such as psoriasis [10–12], atopic dermatitis [13], and cholestatic pruritus [14]. Increased NK-1R expression was reported on keratinocytes along with increased SP serum level in patients with chronic pruritus [15]. Moreover, increased density of dermal SP-positive nerve fibers was identified within the skin of patients suffering from atopic dermatitis and prurigo nodularis and in the skin of chronic

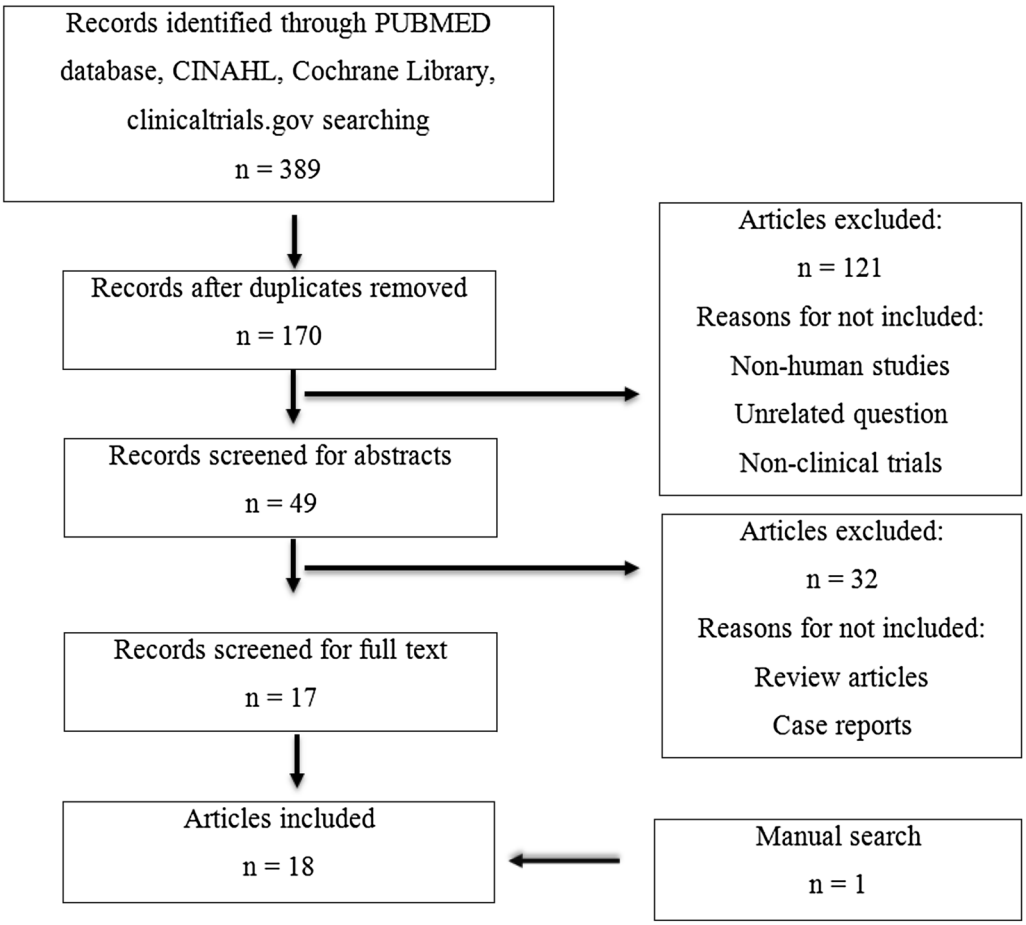

Fig. 1 Selection of publications for the analysis

pruritus patients [15–20]. Interestingly, SP plasma levels did not correlate with pruritus related to psoriasis, and even a significant negative correlation between pruritus severity and levels of SP was reported [21]. Ablation of NK-1-expressing spinal neurons in rats inhibited acute and chronic itch, suggesting that spinothalamic and spinoparabrachial neurons play an important role in itch transmission. One may speculate that a similar situation also occurs in humans.

Nevertheless, better understanding of the role of SP in the pathomechanism of pruritus and a number of case series in which NK-1R inhibitors were successfully used to treat pruritus suggest that NK-1R antagonists might be a promising therapeutic option for acute and chronic itch. However, among the number of newly discovered NK-1R inhibitors, only a few (aprepitant, serlopitant, tradipitant, and orvepitant) have been investigated for pruritus-associated conditions. To the best of the authors' knowledge, the current review is the first to summarize data about the activity and efficacy of NK-1R inhibitors in dermatology.

NK-1R INHIBITORS AND SKIN DISEASES

Aprepitant

Aprepitant is a relatively old, selective, high-affinity antagonist of human NK-1R. Aprepitant has little or no affinity to serotonin (5-HT3), dopamine, and corticosteroid receptors.

Aprepitant is able to cross the blood–brain barrier in humans. It was originally developed as an antidepressant, but clinical trials failed to demonstrate an antidepression effect at non-toxic dosing [22]. In animal studies, aprepitant was shown to centrally inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin. The currently approved indications include chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV) [23–25]. The standard dosage for the approved indications is 125 mg on the first day, and 80 mg/day on the following 2 days. Aprepitant is metabolized by cytochrome P450 3A4 isoform (CYP3A4) and thus requires caution and careful monitoring during coadministration with other CYP3A4 substrates such as erlotinib, as it was shown to significantly decrease erlotinib clearance and increase its plasma concentration [26]. Some studies have documented its beneficial effects against pruritus in various conditions. Trials testing the antipruritic activity of aprepitant are summarized in Table 2. To date, the data on aprepitant in pruritus therapy remain conflicting.

Based on the description of two patients with metastatic non-small-cell lung cancer receiving erlotinib and successfully cured of pruritus after treatment with aprepitant [5], a single-center pilot study was designed to assess the efficacy of aprepitant for management of severe pruritus induced by biological anticancer drugs [27]. Forty-five outpatients with metastatic solid tumors treated with cetuximab, erlotinib, gefitinib, imatinib, or sunitinib were enrolled and treated with a short course of aprepitant. The study showed that aprepitant significantly decreased the severity of pruritus induced by biological anticancer treatments and could be a useful antipruritic agent both as the first-choice treatment or after failure of standard antipruritic therapy (Table 2) [27].

In another retrospective, analytical study, promising antipruritic activity of aprepitant was observed in 17 patients with cutaneous T-cell lymphoma. The authors claimed that the best antipruritic response was observed in lymphoma limited to skin (stages IB-IIB) and non-erythrodermic cutaneous lesions [28]. However, in a randomized, double-blind, placebo-controlled, crossover study on five patients with Sézary syndrome (NCT01625455), in which placebo or aprepitant was ingested daily for 7 days (125 mg on day 1, followed by 80 mg on days 2–7) followed by a 1-week washout, aprepitant even increased pruritus over the 7-day period [29]. These observations are contradictory to the significant antipruritic activity of aprepitant described in multiple case series of patients with Sézary syndrome or mycosis fungoides [2, 3, 30–33]. However, authors underlined that their study had several limitations, including small sample size (only five patients were enrolled) due to the rarity of the studied entity. Other reasons which might have an impact on the scoring of pruritus by visual analog scale (VAS) were different disease activity at baseline and external factors such as temperature and humidity [29].

In another open-label randomized trial, a total of 19 patients received 80 mg/day aprepitant orally for 7 days in addition to topical treatment with hydrocortisone butyrate and a moisturizer; the control group received only topical treatment. Both study groups reported a highly significant improvement of atopic dermatitis severity according to SCORing of Atopic Dermatitis (SCORAD) and pruritus (according to VAS and scratching movement count), but no additional effect of oral aprepitant was found [34]. The authors linked the very good therapy result to a high level of compliance with the treatment regimen and suggested that the lack of a beneficial effect of aprepitant was due to rather mild to moderate pruritus in studied patients [34].

The next pilot study showed significant relief of pruritus in 20 randomly selected patients suffering from refractory chronic itch [35]. Aprepitant (80 mg) was given once daily for 3–13 days. The mean pruritus intensity reduced from 8.4 ± 1.7 points to 4.9 ± 3.2 points after treatment. Altogether, 16 (80%) patients responded to short-term aprepitant monotherapy, and subjects with dermatological diseases such as atopic eczema and prurigo nodularis showed the best improvement [35]. Adverse events occurred in three patients (nausea, vertigo, and drowsiness in one each) and were mild [35]. However, these favorable effects have not

Table 2 Summary of studies with aprepitant in patients with pruritus

Study	Indication	No. of patients	Dosing regimen of aprepitant	Results	Comments
Lönndahl et al. [34]	Moderate–severe atopic dermatitis	39 patients	Active treatment group (n = 19): 80 mg/day aprepitant orally for 7 days + topical treatment with hydrocortisone butyrate and moisturizer Control group (n = 20): placebo + topical treatment	Both study groups showed a highly significant improvement in extent of atopic dermatitis and pruritus Extent of disease measured by objective SCORAD decreased in aprepitant-treated group from 40.5 ± 12.0 to 32 ± 11.2 and in control group from 37.0 ± 11.3 to 26.7 ± 14.7 points. Subjective SCORAD decreased in aprepitant group from 49.0 ± 14.1 to 38.1 ± 12.6 and in control group from 47.7 ± 13.7 to 33.0 ± 18.9 points Pruritus measured by VAS reduced from 5.5 ± 2.1 to 3.8 ± 2.2 in aprepitant group compared with reduction from 6.7 ± 2.2 to 4.1 ± 3.0 points in control group No additive effect with oral aprepitant compared with standard topical treatment alone was found	Short-term treatment design might limit the significance of achieved results Thirteen patients reported adverse events: headache, fatigue, dizziness, elevated liver enzymes, palpitations, dyspnea, obstipation, stomachache, periocular dermatitis, altered ability to react, erectile dysfunction Two male patients in the treatment group interrupted their participation in the study due to dizziness, impotence, and headache (one case), and lack of reactivity, dyspnea, and palpitations (second case) Scratching movements showed a high level of deviation from the mean, leading to difficulties in comparing the treatment and control groups
Maroñas-Jiménez et al. [28]	Pruritus in primary cutaneous T-cell lymphoma	17 patients	125 mg on day 1, 80 mg on days 2–3 in a weekly or biweekly repetition regimen	PtGA (Patient's Global Assessment) evaluations demonstrated overall response rate of 84% NRS scores reduced from 10 points at baseline for stages IB–IIB to 1 point and from 9.3 points for stages III–IV to 5.7 points after 1 week of treatment The best antipruritic response was observed in lymphomas limited to skin (stages IB–IIB) and nonerythrodermic cutaneous lesions	This study has serious limitations, due to retrospective design, limited sample size, and concomitant administration of other antipruritics AEs: grade 1 self-limited headache and a transitory mild drowsiness
Ohanyan et al. [20] (NCT01963793)	Chronic prurigo	19 patients	Topical aprepitant 1% gel on one side of the body and placebo vehicle (gel) on the other side, applied twice daily for 28 days	Efficacy was not significantly different between aprepitant gel and the placebo gel vehicle, as both groups showed large (more than expected) improvement in pruritus intensity, with over 50% reduction, as measured by VAS	17 patients (89%) experienced mild and moderate local AEs: most commonly pain and irritation at the site of administration (75% versus 55% in aprepitant versus vehicle group, respectively)

Table 2 continued

Study	Indication	No. of patients	Dosing regimen of aprepitant	Results	Comments
Santini et al. [27] (NCT01683552)	Severe pruritus induced by biological anticancer drugs	45 patients	125 mg on day 1, 80 mg on day 3, 80 mg on day 5	Severity of pruritus measured by VAS decreased in refractory group (patients refractory to antipruritic drugs in the past) from 8.0 points at baseline to 1.0 point after 1 week of treatment, and in naive group (patients naive to antipruritic therapy) from 8.0 points at baseline to 0 points after 1 week of treatment	No toxic effects potentially related to aprepitant treatment occurred
				41 out of 45 (91%) patients responded to aprepitant	
Ständer et al. [35]	Refractory chronic pruritus	20 patients	80 mg once daily for 3–13 days	Severity of pruritus measured by VAS reduced from 8.4 points (SD ±1.7) at baseline to 4.9 points (SD ±3.2) after treatment with aprepitant	Patients with dermatological diseases and patients aged between 36 and 60 years showed the best benefit from the treatment
				16 out of 20 (80%) patients responded to the therapy	Men tended to respond better than women
					AEs occurred in three patients and were mild: nausea, vertigo, drowsiness
Tsanakas et al. [36] (EudraCT no. 2013-001601-85)	Antihistamine-refractory chronic nodular prurigo	58 patients	80 mg/day versus placebo (crossover design)	No significant differences found between aprepitant treatment and placebo for any of the parameters investigated: mean itch intensity, worst itch, prurigo lesions, patients' global assessment, quality of life, patient benefit index, anxiety and depression scoring	To date, the best designed trial conducted on aprepitant for treatment of pruritus
Wallengren [39]	Pruritus in chronic skin disease volunteers	13 patients with various skin diseases	5% topical aprepitant or vehicle applied in a right–left study design	Mean VAS scores for pruritus were 4.5 ± 2.0 prior to treatment with aprepitant, 4.1 ± 2.2 after 30 min, and 2.8 ± 1.6 after 2 h. The corresponding values on the vehicle-treated side were 5.1 ± 2.2, 3.4 ± 1.9, and 2.8 ± 1.9	A single topical application of 5% aprepitant failed to inhibit pruritus in 13 enrolled patients, despite satisfactory absorption of the drug
Wallengren [39]	Pruritus and erythema induced by prick-test reaction to histamine in nonatopic healthy volunteers	7 healthy nonatopic volunteers	5% topical aprepitant/vehicle was applied to the volar surface on the left and right forearm, and left on for 30 min; thereafter cream was wiped, and both forearms were pricked with histamine	Mean VAS scores for pruritus induced by prick-test reactions to histamine were 4.3 ± 3.4 on aprepitant-treated side and 4.8 ± 2.4 on vehicle-treated side	A single topical application of 5% aprepitant failed to inhibit clinical pruritus when histamine was pricked into the skin, despite satisfactory absorption of the drug
Wallengren and Edvinsson [38]	Pruritus associated with prick-test reactions	13 healthy nonatopic volunteers	5% aprepitant gel, 1% telcagepant hydrogel, and their respective vehicles were applied to an area of 4 cm × 4 cm on the volar surface of the forearms (blinded right–left protocol), then histamine was pricked on the pretreated areas and on control areas of the skin	The flare and weal as well as pruritus induced by histamine prick tests were not significantly affected by any of the pretreatments	Study limited by small sample size

Table 2 continued

Study	Indication	No. of patients	Dosing regimen of aprepitant	Results	Comments
Wallengren and Edvinsson [38]	Pruritus associated with patch test reactions	11 patients	Patch tests with 5% nickel sulfate in petrolatum were performed on five locations on the dorsal part of the upper arms. After 48 h, the patch tests were removed and evaluated. Four test areas were then covered with 5% aprepitant gel, 1% telcagepant hydrogel, or respective vehicles and removed after another 24 h	None of the treatments influenced the nickel patch test-induced pruritus Treatment with aprepitant and its vehicle alone resulted in potentiation of the infiltration of nickel reactions compared with test reactions obtained after no treatment	Study limited by small sample size
Zic et al. [4] (NCT01625455)	Pruritus in Sézary syndrome	5 patients	Aprepitant: 125 mg on day 1, 80 mg on days 2–7 versus placebo given orally for 7 days	Significant increase of pruritus according to VAS during aprepitant treatment No change over 7 days of treatment in placebo group No change in quality of life in either group	Limitations due to difficulty in patient recruitment and small sample size

AE adverse event, *NRS* numerical rating scale, *VAS* visual analog scale

been confirmed by the recently published results of a double-blind, placebo-controlled phase II study on patients with chronic nodular prurigo [36]. Fifty-eight patients were randomized to receive either oral aprepitant 80 mg/day or placebo for 4 weeks. Next, following a 2-week washout phase, patients were crossed over to receive the other treatment for 4 weeks. At the end of the trial, no significant differences were found between the aprepitant and placebo arm for any of the analyzed parameters (Table 2) [36].

Similar results were reported regarding topical application of aprepitant in chronic prurigo, in which a topical formulation of aprepitant (10 mg/g gel) did not show superiority over vehicle in reducing itch intensity [20]. Interestingly, both patient groups showed large (more than expected, over 50% reduction as measured by VAS) improvement in pruritus intensity [20]. The authors suggested that it is highly probable that decrease of pruritus intensity in one arm or leg resulted in perception of an overall reduction in pruritus intensity by the patient, as shown in itch relief through "mirror scratching" trials [37]. Moreover, they reported significant differences observed in scratch artifacts and crusting in aprepitant-treated but not placebo-treated skin, which further supports such a hypothesis [20]. Analyses of patients' blood samples showed that aprepitant effectively penetrated skin and was absorbed into the blood, but the blood levels were too low to have any systemic effects and did not correlate with VAS scores [20]. In another study, the effect of topically applied aprepitant and telcagepant (CGRP antagonist) was examined on immediate and delayed reactivity of the skin as well as on associated pruritus [38]. Neither the flare nor pruritus induced by histamine prick tests were affected by any of the treatments. Also, none of the treatments influenced the nickel patch test-induced pruritus. Treatment with aprepitant and its vehicle alone even resulted in a potentiating effect on the inflammatory infiltration upon nickel exposure compared with test reactions obtained after no treatment [38]. Further results with 5% topical aprepitant application in clinical and experimental pruritus was obtained from a study in which single topical application of 5% aprepitant gel failed to inhibit pruritus in 13 enrolled patients, as well as erythema and itch after histamine [39]. These results contradict the suggestion that aprepitant may prevent mast cell activation in skin [20, 38].

In addition to the above-mentioned anti-itch activity, aprepitant elicits antitumor action by

inducing apoptosis of tumor cells, an effect reported in different in vitro studies carried out in lung cancer, rhabdomyosarcoma, neuroblastoma, and larynx, gastric, and colon carcinoma cell lines [40–44]. NK-1R has also been detected in all analyzed human primary invasive malignant and metastatic melanomas [7]. Aprepitant at 10–60 μM concentrations elicited cell growth inhibition in a concentration-dependent manner in all melanoma cell lines through NK-1R [7]. These data indicate that NK-1R antagonists could also be considered as potential candidate new antitumor drugs for human melanoma.

Serlopitant

Serlopitant was originally developed for treatment of overactive bladder [45]. Based on the role of NK-1R in pruritus [46, 47] and the good safety and tolerability of serlopitant in a phase 2 trial [45], a number of controlled trials testing its antipruritic efficacy have been planned, are ongoing, or have recently been completed with pending results (chronic pruritus—NCT01951274, atopic dermatitis—NCT02975206; chronic prurigo nodularis—NCT03546816 and NCT02196324; plaque psoriasis—NCT03343639; epidermolysis bullosa—NCT02654483). Three of the recent studies (NCT01951274, NCT02196324, and NCT03343639) confirmed a significant antipruritic efficacy of serlopitant. The another one, testing the efficacy of serlopitant in atopic dermatitis (NCT02975206), produced disappointing results.

The first study (NCT01951274) showed significant antipruritic efficacy of serlopitant compared with placebo in patients with chronic refractory pruritus. A total of 222 patients received three different doses of serlopitant (0.25 mg, 1 mg, or 5 mg) daily for 6 weeks. At week 6, the mean percentage change from baseline VAS score was significantly greater in the serlopitant 1 mg ($p = 0.022$) and 5 mg ($p = 0.013$) groups versus placebo. The study affirmed good tolerability of serlopitant; the most common treatment-emergent adverse events were somnolence and mild diarrhea [48].

Another phase 2 trial (NCT 02196324) evaluated the reduction of pruritus in patients with treatment-refractory prurigo nodularis [49]. Patients ($n = 128$) were divided into two groups, receiving 5 mg serlopitant or placebo for 8 weeks. The average itch VAS scores significantly improved with serlopitant versus placebo at week 4 and 8. In the serlopitant group, the mean percentage changes of average itch VAS score were − 22.8%, − 31.2%, and − 48.3% at weeks 2, 4, and 8, respectively, and in the placebo group − 11.2%, − 17.2%, and − 26.3%, respectively. Noteworthy, antipruritic effect was observed as early as 2 weeks after beginning treatment. The most frequent adverse events in the serlopitant group were nasopharyngitis, diarrhea, and fatigue [49].

In a study evaluating the efficacy and safety of serlopitant in treatment of pruritus associated with plaque psoriasis (NCT03343639), 206 patients with the diagnosis of plaque psoriasis covering ≤ 10% of body surface area, lasting for at least 6 months prior to randomization and suffering from severe pruritus, received serlopitant 5 mg or placebo orally once daily. Patients were not allowed to use any other antipsoriatic therapy except bland emollients for the duration of the trial. A statistically significant reduction of pruritus based on a 4-point improvement responder analysis was observed: 33% of patients treated with serlopitant 5 mg daily achieved a 4-point or greater improvement on the worst-itch numeric rating scale (WI-NRS) at week 8 compared with baseline (primary efficacy endpoint) versus 21% of patients treated with placebo ($p = 0.028$). Serlopitant was well tolerated, and no serious adverse events were reported related to the drug [50].

In contrast, a trial assessing two doses of serlopitant (1 mg/day and 5 mg/day versus placebo) in 484 patients with atopic dermatitis (NCT02975206) did not meet its primary endpoint (WI-NRS score reduction) [51]. In addition, the secondary endpoint was not statistically different between the serlopitant-treated group and placebo. However, this study confirmed the good tolerability and safety profile of serlopitant in patients with severe pruritus (Table 3) [51].

Table 3 Summary of studies with serlopitant, tradipitant, and orvepitant in pruritus patients

Reference	Drug/ indication	No. of patients	Dosing regimen	Results	Comments
Yosipovitch et al. (NCT01951274) [48]	Serlopitant/ chronic refractory pruritus	222 patients	3 different doses of serlopitant: 0.25 mg, 1 mg, 5 mg versus placebo once daily for 6 weeks	At week 6, 43%, 38%, and 53% of patients in the serlopitant 0.25 mg, 1 mg, and 5 mg dose groups, respectively, reported at least 4-point decrease in average VAS pruritus score versus 26% of placebo-treated patients ($p < 0.05$ for 1 mg/day and 5 mg/day serlopitant group versus placebo)	The most common adverse events in the active treatment group were somnolence and diarrhea
Ständer et al. (NCT02196324) [49]	Serlopitant/ treatment-refractory prurigo nodularis	128 patients	5 mg/day serlopitant versus placebo for 8 weeks	Mean percentage changes from baseline in mean average itch VAS score at week 2, 4, and 8 were − 22.8%, − 31.2%, and − 48.3%, respectively, in the serlopitant group versus − 11.2%, − 17.2%, and − 26.3%, respectively, in the placebo group (difference significant at week 4 and 8)	Antipruritic effect was observed as early as 2 weeks after beginning treatment The most frequent adverse events were nasopharyngitis, diarrhea, and fatigue
NCT03343639 [50]	Serlopitant/ pruritus associated with plaque psoriasis	206 patients	5 mg/day serlopitant versus placebo for 8 weeks	Response of 4-point or greater improvement of WI-NRS at week 8 achieved in 33% of patients treated with serlopitant and 21% of patients treated with placebo ($p < 0.05$)	No serious AEs reported

Table 3 continued

Reference	Drug/ indication	No. of patients	Dosing regimen	Results	Comments
NCT02975206 [51]	Serlopitant/ atopic dermatitis	484 patients	2 different doses of serlopitant: 1 mg/day and 5 mg/day versus placebo	Mean change of WI-NRS from baseline to week 6 was -2.25 ± 2.2 in serlopitant 5 mg/day and -2.32 ± 2.42 in serlopitant 1 mg/day versus -2.01 ± 2.21 in placebo group (p NS) Responder rate of 4-point or greater improvement of WI-NRS at week 6 was 20.6% in patients treated with 5 mg/day serlopitant and 22.4% in patients treated with 1 mg/day serlopitant versus 16.5% in patients treated with placebo (p NS)	No serious AEs were reported
NCT02004041 [56]	Tradipitant/ atopic dermatitis	69 patients	50 mg of tradipitant versus placebo given orally for 4 weeks	Tradipitant was not superior to placebo in reducing itch intensity in patients with atopic dermatitis	
Heitman et al. (NCT02651714) [57]	Tradipitant/ atopic dermatitis	168 patients	85 mg tradipitant versus placebo administered orally twice a day	Subjects receiving tradipitant showed improvements on: the Worst Itch VAS scale compared with placebo (44.2 versus 30.6; $p = 0.019$) The total SCORAD index compared with placebo (21.3 versus 13.6; $p = 0.008$) Objective SCORAD compared with placebo (13.3 versus 7.2; $p = 0.005$)	No full report available

Table 3 continued

Reference	Drug/ indication	No. of patients	Dosing regimen	Results	Comments
EU-CTR2013 002763-25 [55]	Orvepitant/ EGFRi-induced intense pruritus	27 patients	Orvepitant 10 and 30 mg versus placebo given once daily, orally for 4 weeks	Antipruritic effect of a high-dose (30 mg daily) or low-dose (10 mg daily) regimen was not confirmed	Small numbers of studied patients and technical problems limit the reliability of obtained data Full report of the trial has not been published

AE adverse event, *NS* not significant, *VAS* visual analog scale, *WI-NRS* Worst Itch Numerical Rating Scale

Orvepitant and Tradipitant

Orvepitant and tradipitant are other NK-1R antagonists tested for their antipruritic properties. Initially, orvepitant was developed as an antidepressant drug, but in spite of having some antidepressant properties, its efficacy was not good enough to continue further development [52, 53]. However, data on animals suggested that orvepitant might possess antipruritic properties [54]. Subsequently, a trial was conducted to evaluate orvepitant efficacy in humans (10 and 30 mg given orally once daily for 4 weeks) compared with placebo in reducing the intensity of epidermal growth factor receptor inhibitors (EGFRi)-induced pruritus. Importantly, neither a low-dose regimen (10 mg daily) nor a high-dose regimen (30 mg daily) showed a significant antipruritic effect (EU-CTR2013 002763-25) (Table 3) [55].

Data on tradipitant also remain controversial. The dose of 50 mg of tradipitant given orally for 4 weeks was not superior to placebo in reducing itch intensity in patients with atopic dermatitis (NCT02004041) [56]. However, in a subsequent study, in which a higher dose (85 mg) was administered for 8 weeks, significant antipruritic effect compared with placebo was recorded (NCT02651714) (Table 3) [57]. Another large study is ongoing (NCT03568331) and may provide further important data on the antipruritic efficacy of this drug against atopic itch [58].

DISCUSSION

NK-1R inhibitors have shown significant, albeit not uniform, anti-itch potential in the treatment of chronic pruritus present in different dermatological conditions. Interestingly, aprepitant also elicited in vitro antitumor activity by inducing apoptosis of melanoma cells, suggesting another potential indication of this drug that warrants further investigation. Studies evaluating topical use of aprepitant did not show its superiority versus placebo despite good absorption of the drug, but this may be due to predominant centrally mediated activity in the nervous system [20, 38, 39]. However, currently available studies have several limitations, such as small sample size, improper trial design, or too short therapy period, to draw valid conclusions for the future. Thus, larger, double-blind, placebo-controlled, parallel group designed trials with topical and oral NK-1R antagonists are needed to verify their possible usefulness.

In various trials with oral aprepitant, improvement of pruritus symptoms was observed, but the use of this drug may be limited by potential interactions with other drugs, especially those metabolized by CYP3A4, as strict monitoring and surveillance of drug

plasma concentrations could be necessary [59]. So far, based on reports of almost 3000 people taking up to 300 mg of oral aprepitant for up to 8 weeks, it is generally well tolerated over a long time period with no significant differences in adverse events versus placebo [60, 61]. The trial with serlopitant in patients with pruritus and atopic dermatitis, in which neither the primary nor secondary end point was achieved (NCT02975206), indicates that further exploration of the antiinflammatory effects of NK-1R antagonists is needed. In contrast, serlopitant was effective in other types of pruritus, namely psoriatic itch, chronic refractory itch, and prurigo nodularis. A possible explanation for such discrepancies could be different pathogenesis and mechanisms involved in both inflammation and pruritus. It is possible that, in some conditions, SP is not a principal mediator of pruritus. In addition, the influence of polymorphism of the tachykinin receptor (TacR)-1 gene may be of importance [62].

CONCLUSIONS

In summary, based on studies publish to date, NK-1R inhibitors seem to exhibit significant antipruritic activity and further studies are needed to define optimal dosing regiments to achieve long-term control of pruritus and better understand the pruritic states that will benefit most from NK-1R antagonists, as the pathomechanism may differ between various diseases. Pruritus remains one of the most bothersome subjective symptoms and can have a strong impact on quality of life. Effective therapy for patients suffering from chronic pruritus remains challenging, thus new therapies are urgently needed.

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