Received: 30 March 2023 | Revised: 30 June 2023 | Accepted: 13 August 2023

DOI: 10.1111/exd.14934

Experimental Dermatology WILEY

REVIEW ARTICLE

# Cutaneous findings and treatments in deficiency of interleukin-36 receptor antagonist (DITRA): A review of the literature

Chiamaka L. Okorie[1] | Krithika Nayudu[2] | Vinod E. Nambudiri[3,4]

[1]Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA

[2]Medical College of Georgia, Augusta, Georgia, USA

[3]Harvard Medical School, Boston, Massachusetts, USA

[4]Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts, USA

**Correspondence**
Vinod E. Nambudiri, Department of Dermatology, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, USA.
Email: vnambudiri@bwh.harvard.edu

## Abstract

Deficiency of the interleukin-36 receptor antagonist (DITRA) is a rare autoinflammatory disorder caused by mutations in the *IL36RN* gene. This mutation leads to a lack of functional interleukin-36 receptor antagonists (IL-36Ra), which results in an overactive immune system and chronic inflammation. Despite its rarity, numerous case series and individual reports in the literature emphasize the importance of recognizing and managing DITRA. Early identification of the cutaneous signs of DITRA is crucial for accurate diagnosis and timely administration of appropriate treatment. This review article provides a comprehensive overview of the current understanding of the cutaneous, non-cutaneous and histopathological manifestations of DITRA, with a focus on reported treatments. The disease typically presents in early childhood, although the age of onset can vary. Patients with DITRA exhibit recurrent episodes of skin inflammation, often with a pustular or pustular psoriasis-like appearance. Additionally, non-cutaneous manifestations are common, with recurrent fevers and elevated acute-phase reactants being the most prevalent. The exact prevalence of DITRA is unknown. Some cases of loss-of-function mutations in the *IL36RN* gene, considered a hallmark for diagnosis, have been identified in patients with familial generalized pustular psoriasis (GPP). Biological therapies with inhibition of IL-12/23 and IL-17 are promising treatment options; paediatric patients with DITRA have shown complete response with mild relapses. New and emerging biologic therapeutics targeting the IL-36 pathway are also of interest in the management of this rare autoinflammatory disorder.

**KEYWORDS**
autoinflammation, cutaneous, deficiency of interleukin-36 receptor antagonist (DITRA), generalized pustular psoriasis (GPP), *IL36RN*

Chiamaka L. Okorie and Krithika Nayudu are equal contributors to this work and designated as co-first authors.

## 1 | BACKGROUND

Deficiency of the interleukin-36 receptor antagonist (DITRA) is an extremely rare autosomal recessive autoinflammatory disease caused by mutations in the *IL36RN* gene on chromosome 2.[1,2] DITRA is characterized by recurrent cyclical episodes of eruptive skin inflammations, most notably generalized pustular psoriasis (GPP).[2,3] GPP is a skin disorder characterized by sudden fevers, extensive erythema with pustules and edema, and sometimes life-threatening circulatory and respiratory disturbances.

Mutations in genes including *IL36RN*, *CARD14*, *IL10RA*, *IL10RB* and *IL10* have been identified in non-IL-1-mediated pustular dermatoses.[4] To diagnose DITRA, genetic testing is typically performed to identify mutations in the *IL36RN* gene.[2] Identification of loss-of-function mutations in *IL36RN* is considered a hallmark of DITRA.[1,4–8] The *IL36RN* gene encodes the interleukin-36 receptor antagonist (IL-36Ra), a protein which plays a critical role in regulating the body's immune response. Mutations in the *IL36RN* gene encoding IL-36Ra lead to reduced protein stability and expression. Genetic testing may involve analysing the coding regions and adjacent intronic regions of the *IL36RN* gene to identify various types of mutations, including missense, nonsense, frameshift and splice site mutations. The analysis aims to identify mutations that disrupt the function or expression of IL-36Ra. Once a loss-of-function mutation in the *IL36RN* gene is identified, it helps establish a definitive diagnosis of DITRA, distinguishing DITRA from other forms of autoinflammatory diseases.[2,4]

Normally, IL-36Ra inhibits the signalling of pro-inflammatory cytokines: IL-36α, IL-36β and IL-36γ. Loss of IL-36Ra in DITRA results in unopposed signalling by these cytokines and activation of the nuclear factor-kB and mitogen-activated protein (MAP) kinase pathways (Figure 1). This constitutive activation leads to the overexpression of pro-inflammatory cytokines and the production of IL-8, which is responsible for neutrophil invasion.[9] This immune dysregulation of DITRA thus leads to a range of clinical features, including disseminated dermatitis, pustular psoriasis, systemic inflammation and multi-organ dysfunction.[5,6]

It is important to note that while the presence of an *IL36RN* mutation strongly supports the diagnosis of DITRA, it may not be the sole criterion for diagnosis. Clinical features, including the presence of recurrent pustular skin lesions and a family history consistent with autosomal recessive inheritance, are also considered in conjunction with genetic testing results.

Since the initial description of DITRA, which included 16 patients from nine families,[2,7,10–12] only occasional cases of the disease in various age groups have been reported.[1,8,10–29] Unfortunately, treatment options for DITRA are limited, especially in children.[30] However, there have been some more recent reports of success in managing disease symptoms with various biologics targeted at specific elements of the autoinflammatory cascade.[5,11–13,16–20,27,28,30–32] Here, we review the cutaneous manifestations reported in DITRA to improve our understanding and management of this rare autoinflammatory disorder. In addition, we summarize the existing literature on the presentation, genetics and treatment of skin inflammation in individuals with DITRA.

## 2 | CUTANEOUS MANIFESTATIONS OF DITRA

Reports of cutaneous manifestations of DITRA are crucial in understanding the clinical features of this rare autoinflammatory disease. DITRA leads to systemic inflammation and recurrent GPP episodes. The hallmark of DITRA is recurrent episodes of pustular and scaly skin lesions, either generalized or localized, especially on the trunk and limbs, with or without psoriasis vulgaris, that are resistant to standard topical and systemic therapies for pustular dermatoses. Several case reports in the literature have outlined the cutaneous manifestations of DITRA in detail (Table 1). Each case has had unique cutaneous manifestations, but is typically marked by a striking pustular morphology, reflecting the autoinflammatory nature of the condition.

The age of onset varies widely, but flares tend to begin in infancy or early childhood. DITRA has been suggested to occur in younger cases with no pre-existing psoriasis vulgaris. However, there have been reports of cases in older individuals with prior history of psoriasis vulgaris.[24] Most patients have some degree of cutaneous involvement at the time of presentation. Cutaneous manifestations of DITRA include acute flares of GPP, which may occur spontaneously or be triggered by other factors such as infection or medications. These eruptions are usually widespread and involve scaly, erythematous and edematous plaques studded with pustules, often accompanied by fever and elevated levels of acute phase reactants. In DITRA, the individual pustules tend to converge, forming pustular 'lakes' or agglomerations. Scalp and nail involvement is common and may occur later in the disease course. The Woronoff ring is an underrecognized clinical sign of DITRA characterized by a halo of non-erythematous skin surrounding psoriatic plaques.[22] Its pathogenesis is not fully understood, but a relative deficiency of prostaglandins and endoglin has been reported. Woronoff rings can occur after various treatments or even in untreated psoriatic lesions.[22] The severity and duration of symptoms in patients with DITRA vary widely, with many patients demonstrating complete remission with appropriate treatment.

## 3 | HISTOPATHOLOGIC MANIFESTATIONS OF CUTANEOUS DISEASE IN DITRA

Cutaneous disease in DITRA is characterized via histopathology by the presence of neutrophilic infiltrates in the dermis and epidermis, as well as spongiform pustules of Kogoj and acantholysis, with elongation of rete ridges, and parakeratosis in the stratum corneum.[2,24] Histologic findings in DITRA lesions may show the presence of intraepidermal pustules or subcorneal pustules that can coalesce into larger pustules. These subcorneal pustules are usually formed by aggregates of neutrophils between degenerated keratinocytes in the upper malphigian layer of the epidermis.[7] Additional reported histopathologic findings include epidermal hyperplasia with acanthosis and lack of granular layer, irregular papillomatosis and compact orthokeratosis.[7] In these cases, IgA pemphigus, in which intercellular IgA deposition in the epidermis is demonstrated, is an important differential diagnosis.

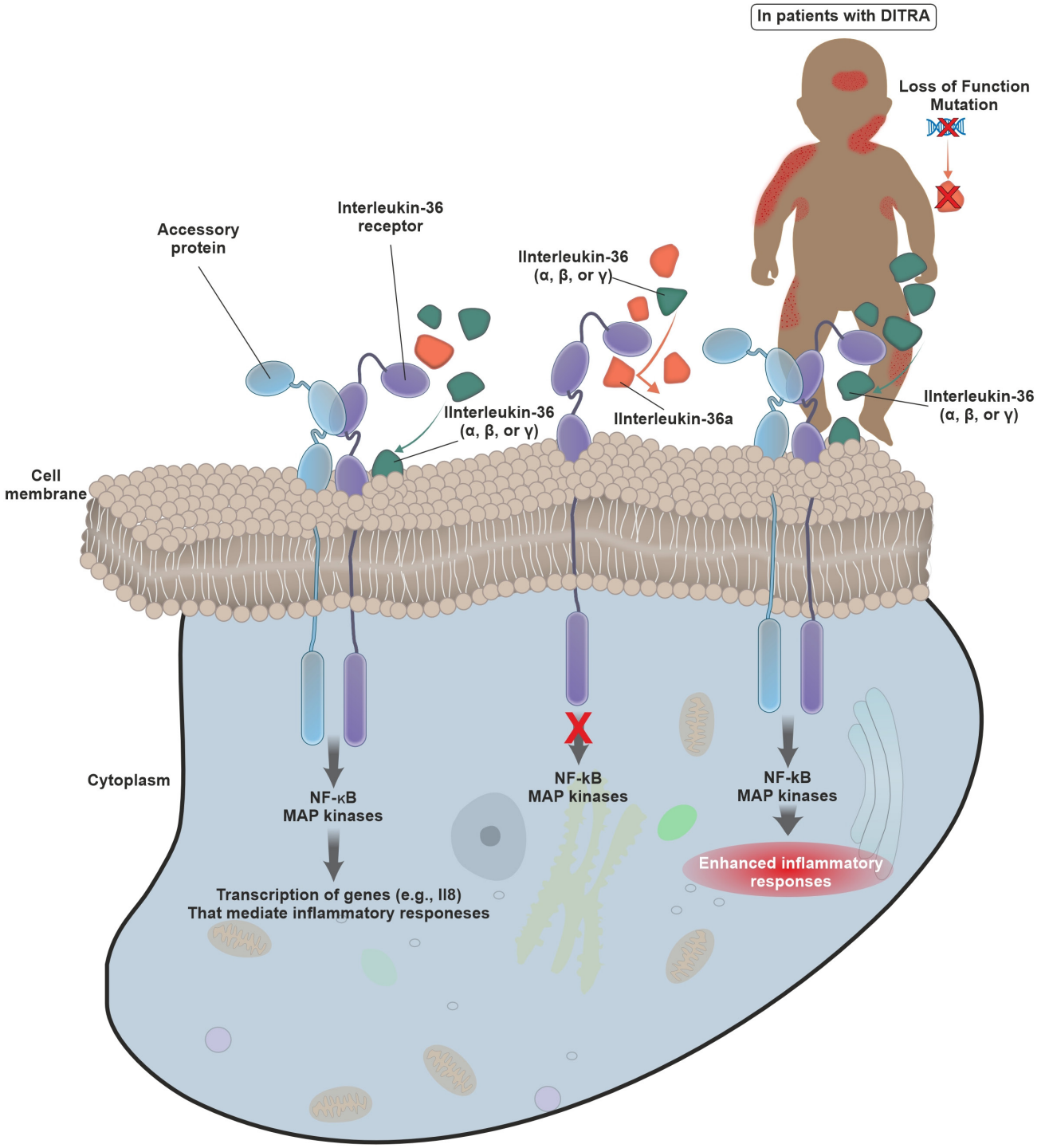


FIGURE 1 Disinhibition of the interleukin-36 signalling pathway. Interleukin-36α, interleukin-36β and interleukin-36γ attach to the interleukin-36 receptor, triggering the recruitment of the interleukin-1–receptor accessory protein, activating nuclear factor-κB (NF-κB) and mitogen-activated protein (MAP) kinases, leading to cellular signalling. Interleukin-36Ra, an inhibitor of the interleukin-36 receptor, counteracts the effects of the agonist ligands. Deficiency of interleukin-36 receptor antagonist (DITRA) denotes impairment in this regulatory mechanism.

## 4 | NON-CUTANEOUS MANIFESTATIONS OF DITRA

In addition to the characteristic cutaneous manifestations, individuals with DITRA can also experience non-cutaneous manifestations. These can include joint pain, swelling and stiffness, which can mimic symptoms of rheumatoid arthritis or other autoimmune disorders. DITRA can also lead to systemic inflammation, affecting various organs and tissues, including severe liver dysfunction with neutrophilic or sclerosing cholangitis, uveitis, iritis, conjunctivitis, renal dysfunction with

**TABLE 1** Cutaneous manifestations reported in the literature.

| Citation | Study design | Age and sex | Cutaneous manifestations | *IL36RN* mutation | Previous treatments | Effective treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Abbas et al., 2013[14] | Case report | 32 years M | • Well demarcated edematous erythema with overlying pustules and nail dystrophy<br>• Recurrent episodes of pain and purulent discharge on all fingers except right thumb and index finger<br>• Well demarcated erythematous scaly plaques on axillary and genital areas | c.338C>T (p.S113L) | Oral antibiotics, topical steroids, topical antibiotics, antifungals | – | – |
| Rossi-Semerano et al., 2013[11] | Case report | 4 months M | • Erythematous and scaly eruption w/ rapid evolution towards generalized pustular psoriasis<br>• Flares of diffuse erythematous rash and pustules involving the whole body | p.L27P | High potency topical corticosteroids and acitretin (retinoid acid) | Anakinra at 2 mg/kg/day; increased to 4 mg/kg/day | No skin improvement at anakinra 2 mg/kg/day; skin improvement noticed in ~1 week w/anakinra at 5 mg/kg/day and no new flares at 2 months' follow-up |
| Renert-Yuval et al., 2014[10] | Case report | 6 years M | • Widespread scaly erythematous plaques with pinhead pustules involving the scalp, face, extremities, torso and buttocks<br>• Palm and sole involvement<br>• Nail pitting | c.28C>T (p.R10X) | Topical and systemic steroids in combination with cyclosporine | Methotrexate at 3.75 mg 1x/ week | Good general condition and partial improvement of skin |
| Cordoro et al., 2017[12] | Case report | (Adolescent) M | • Erythroderma and pustules covering 70% of body surface | c.115+6T>C | Acitretin, infliximab, cyclosporine, phototherapy, adalimumab, prednisone, ustekinumab, apremilast, anakinra | Secukinumab at 150 mg sq, methotrexate 5 mg/week | Rapid and robust clinical and laboratory response, cessation of new pustule formation within 24 h, and discharge after 48 h; skin was nearly clear at 3-day follow-up and no recurrence at 1 year follow-up |
| Bonekamp et al., 2017[27] | Case series | 4 years M | • Diffuse pustular lesions | p.P76L/p.S113L | Acitretin, high dose ciclosporin, anakinra, thalidomide and dapsone | Ustekinumab at 0.75 mg/kg every 2 months increased (1.5 mg/kg every 2 months) | Complete remission, persisting for a total follow-up of 15 months despite discontinuation of steroids |
| | | 5 years F | • Erythroderma and pustular lesions, covering more than 85% of her body surface | p.L27P | Topical steroids, acitretin, ciclosporin, methotrexate, anakinra, etanercept and adalimumab were ineffective | Ustekinumab (0.75 mg/kg every 12 weeks) was started in combination with methotrexate 7.5 mg/week | Within weeks, pustular lesions disappeared and only a few erythematous patches remained, which could be controlled with topical steroids. Methotrexate was slowly reduced and ultimately discontinued. Due to a disease flare after 5 months, dosing interval of ustekinumab was shortened to every 8 weeks and dosage was increased to 1 mg/kg, with a good disease control and discontinuation of steroids |

TABLE 1 (Continued)

| Citation | Study design | Age and sex | Cutaneous manifestations | *IL36RN* mutation | Previous treatments | Effective treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Koike et al., 2017[15] | Case report | 3 months M | • Mild scaly erythema on cheek subsequently spreading to entire body<br>• Well circumscribed scaly erythema on face, trunk and extremities<br>• Few pustules on edematous rash at 13 years<br>• Annular rash on neck that spread centrifugally with numerous pustules at boundaries<br>• Irregularly located milia-sized pustules and a local lake of pus | c.115+6T>C (p.Arg10Argfs*1) | Topical steroids, vitamin D3 ointment, clarithromycin, ciclosporin A | Weekly granulocyte and monocyte apheresis with leukapheresis | Intractable severe pustulous erythema improved dramatically after a single course (5 weeks) of GMA; no recurrence of psoriatic eruptions for 10 months |
| Kostner et al., 2017[18] | Case report | 4 years M | Generalized, scaly and pustulous exanthema with open sores | — | — | Corticosteroids, methotrexate, tumour necrosis factor and IL-1 antagonists | Secukinumab |
| Bal et al., 2017[1] | Case series | 8 years - | • Recurrent flares of cutaneous disseminated erythematous pustules with superficial scaling and yellow crusts | c.4G>T, p.V2F | — | — | — |
| | | 4 m - | • Recurrent flares of cutaneous disseminated erythematous pustules with superficial scaling and yellow crusts | c.4G>T, p.V2F | — | — | — |
| | | – | • Fissured tongue<br>• Facial plaque psoriasis | c.4G>T, p.V2F | — | — | — |
| Cuperus et al., 2018[13] | Case report | 2 months F | • Multiple pustules in perioral and diaper area at first week postpartum<br>• Erythroderma with macerations in the folds at 7 weeks<br>• Palmoplantar confluent pustules<br>• Generalized pustules on scalp, palms and soles at 17 months | c.80T>C (p.L27P) | Topical steroids, coal tar 5% in vaseline-lanette cream and mometasone ointment 2-3x/ week, cyclosporin, anakinra | Acitretin varying between 0.4 mg/kg/day and 1 mg/kg/day w/ later addition of etanercept at 12.5 mg/week | Good initial response to acitretin at 1 mg/kg/day followed by relapses and remissions: good response to etanercept at 12.5 mg/week + acitretin at 15 mg/day after 6 months |
| Clemente et al., 2018[21] | Case report | 5 years M | • Plaque psoriasis, with an erythematous scaly dermatitis that extended throughout the trunk.<br>• Generalized erythroderma with pustules covering almost every part of his body, including palms and soles | pSer113Leu | Intravenous methylprednisolone 2 mg/kg/day and subcutaneous anakinra 2 mg/kg/day | Adalimumab and methotrexate | Patient ended treatment with corticoids without evidence of activity of the disease |
| Babic et al., 2018[17] | Case report | 23 years M | • Pustular psoriasis of left thigh<br>• Abdominal pustular psoriasis | c.115+6T>C | Phototherapy, acitretin, methotrexate, topical corticosteroids | Etanercept | Complete remission within 2 weeks and at 3-year follow-up |

(Continues)

TABLE 1 (Continued)

| Citation | Study design | Age and sex | Cutaneous manifestations | *IL36RN* mutation | Previous treatments | Effective treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Ho et al., 2018[19] | Case report | 6 years M | • Erythematous pustular lesions on trunk at 40 days, developing into generalized pustules with episodic flares after vaccinations | c.115+6T>C | Methotrexate, cyclosporin A, etanercept and adalimumab | 2 doses of secukinumab 150 mg in 1 week then 7 doses monthly; acitretin 20 mg daily, topical calcipotriol and betamethasone | Rapid reduction of pain and >50% reduction of areas of erythema and pustules 1 week after first dose and completely cleared skin 2 weeks after second dose; Plaque-type psoriasis lesions developed on scalp and limbs 4 months after last injection of secukinumab which was managed with acitretin, topical calcipotriol and betamethasone |
| Espindola et al., 2019[29] | Case report | 23 years F | • Widespread small pustules which coalesce forming large plaques, erythema, and peeling, involving 85% of the skin, geographic tongue | c.338C>T (p.Ser113Leu) | Cyclosporin, acitretin and methotrexate | Methotrexate 25 mg per week, acitretin 20 mg per day, prednisone 50 mg per day and subcutaneous adalimumab 40 mg every 15 days | Symptoms gradually improved and the patient was discharged after being 2 months at the hospital |
| Zea-Vera et al., 2019[23] | Case report | 19 years F | • Scaly plaques in the trunk and extremities with severe pruritus for 6 weeks<br>• Confluent small pustules forming plaques on pre-existing lesions as well as face without palms, plants, or nail involvement<br>• Hyperkeratotic erythematous lesions with pustules which coalesce forming large plaques affecting scalp, trunk, extremities, and face involving 90% of total body surface | c.200G>T (p.C67F) | Wet dressings with emollient and desonide 0.1% cream 2 h per day, shampoo with salicylic acid 3%, foam mometasone 0.1% on scalp nightly, desonide 0.05% emulsion on face nightly, methotrexate 12.5 mg/week | Adalimumab 80 g followed by 40 g every other week | Improvement of erythroderma after 4 weeks of adalimumab with only mild compromise in the scalp remaining |
| Morgado-Carrasco et al., 2019[22] | Case report | 54 years M | • Halo of non-reddened skin circumscribing an erythematous pustular plaque | — | — | Anakinra and topical corticoids | Complete clinical response in following weeks |
| Stephenson et al., 2020[38] | Case report | 4 years M | • Scalp plaque psoriasis at age 2 transforming into pustular psoriasis | p.S113L | Prednisone, methotrexate, cyclosporine, colchicine | Etanercept, ustekinumab | Complete remission within 2 weeks; switched etanercept to ustekinumab due to recurrent infection. Sustained remission on ustekinumab. |
| Bozonnat et al., 2021[33] | Case report | 16 years M | • Pustular eruption with superficial scaling and yellow crusts<br>• Presence of pustular lakes | p.V2F | Acitretin, cyclosporine | Adalimumab for earlier flare up; topical steroid treatment w/ betamethasone once daily | Complete remission of earlier flareup for several months after withdrawal from adalimumab; skin rash partially resolved with betamethasone |

TABLE 1 (Continued)

| Citation | Study design | Age and sex | Cutaneous manifestations | *IL36RN* mutation | Previous treatments | Effective treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Jing et al., 2021[16] | Case report | 5 years F | • Erythematous scaly plaques with painful pustules on trunk w/ rapidly progressive scalp and nail involvement | c.227C>T; c.115+6T>C | Desonide cream | Secukinumab at 8.3 mg/kg sq at Weeks 0, 2, 6 | Almost complete clearing on skin within 2 weeks; almost complete hair regrowth and almost clear nails at 14 weeks; no relapse in 3 months after secukinumab withdrawal |
| Almutairi et al., 2022[26] | Case report | 4 years F | • Developed diffuse erythematous, scaly and pustular skin lesions within first few weeks of life<br>• Worsened skin lesions complicated by abscesses at 2 years | c.39C>G (p.D13E) | Topical cyclosporin | — | — |
| Tong et al., 2022[25] | Case report | 5 months F | • Widespread erythema and pustules on scalp and hairline<br>• Scaly erythema and circumjacent pustules subsequently integrated into pus lakes and spread to entire body<br>• Extremities covered with thick yellowish-white scales | c.115+6T>C; c.227C>T (p.P76L) | Oral antihistaminic and topical corticosteroid ointment | — | — |
| Huffmieir et al., 2023[20] | Case report | 47 years F | • Skin lesions had started with scaly erythema on the elbows.<br>• Later, more widespread erythema with multiple pustules developed, particularly on her hands and feet.<br>• Over the years, the involved body surface area and the frequency of flares increased.<br>• Erythroderma with disseminated massive exudative crusts | c.142C>T/p.Arg48Trp and c.338C>T/p.Ser113Leu | Etanercept (50 mg subcutaneously twice weekly) for 4 months | Tumour necrosis factor blocker to adalimumab (40 mg subcutaneously every other week), and subcutaneous anakinra 100 mg daily | Skin had been almost clear for 6 weeks, except for erythema, nail dystrophy, hyperkeratosis and multiple vesicles of about 1 mm in diameter on her hands and feet |

oliguria and renal failure, neutrophilic pneumonitis, acute respiratory distress syndrome and electrolyte imbalance, which can ultimately result in death.[3,7] DITRA can also result in life-threatening complications such as sepsis or organ failure in severe cases.[3] Other non-cutaneous manifestations reported include recurrent fevers, weight loss, glossitis, neutrophilic cholangitis, headache, abdominal pain, nausea and fatigue. The symptoms can be triggered as episodic flares by various factors such as infections, medication, pregnancy, trauma or exposure to cold.[2,3] The severity and frequency of these non-cutaneous manifestations can vary widely among individuals with DITRA, and management typically involves using immunosuppressive medications to control the underlying inflammation.[7]

## 5 | TREATMENTS FOR DITRA

### 5.1 | Topical

Topical treatments can be useful in managing the cutaneous manifestations of DITRA by reducing inflammation and controlling symptoms such as itching, scaling and erythema. Some topical treatments used in DITRA with various efficacy include topical corticosteroids, topical calcineurin inhibitors (such as tacrolimus and pimecrolimus), topical retinoids (such as tazarotene and adapalene) and emollients and moisturizers for symptomatic relief.[22,23,33] Overall, topical treatments can be a useful adjunct to systemic therapies in managing the cutaneous manifestations of DITRA.[10,27] However, their effectiveness may vary depending on the severity and extent of skin involvement, and individual responses to treatment may vary. As highlighted in Table 1, no cases in the literature to date have reported resolution using a topical strategy alone as an effective treatment.

### 5.2 | Systemic

Systemic treatments are often necessary to manage the systemic and cutaneous manifestations of DITRA. Systemic therapies aim to suppress the immune system and reduce inflammation, thus improving the overall disease activity and quality of life of individuals with DITRA.

Some of the systemic treatments that have been used in DITRA include:

- Systemic corticosteroids: These potent immunosuppressants can rapidly reduce inflammation and control disease activity in individuals with DITRA. However, long-term use of systemic corticosteroids can lead to significant side effects and complications, so they are generally reserved as adjunctive therapy for severe or refractory cases.[12] The dose of systemic corticosteroids given for DITRA depends on the severity and nature of the skin reaction.
- Methotrexate is a systemic immunosuppressant medication commonly used to treat psoriasis and other autoimmune diseases. It works by inhibiting the growth and division of rapidly dividing cells, including immune cells contributing to inflammation.[10] Case reports of successful management of DITRA using methotrexate as both rescue and maintenance with prolonged response, have been reported in the literature.[12]
- Cyclosporine is another immunosuppressant medication used to treat psoriasis and other inflammatory skin conditions.[13,19] It works by inhibiting T-cell activation and the production of inflammatory cytokines, and similarly has been highlighted to have efficacy in the management of DITRA (Table 1). It has been used as a maintenance therapy, with reports of a prolonged response to treatment followed by breakthrough flares.[12]
- Apremilast: This oral medication is in the phosphodiesterase-4 (PDE-4) inhibitor class. It works by blocking the activity of PDE-4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP), which regulates various cellular functions, including inflammation. By inhibiting PDE-4, apremilast increases cAMP levels and reduces the production of pro-inflammatory cytokines. Apremilast has been used as a rescue medication in the management of DITRA, but with limited response.[12]

### 5.3 | Granulocyte and monocyte apheresis (GMA)

There is some research on the efficacy of GMA in patients with DITRA published in the literatre. GMA was indicated for GPP in Japan in 2012, and it has been suggested as an alternative or adjuvant therapy to other medications for DITRA treatment. One study reported the successful treatment using GMA of a 78-year-old, the oldest reported case of DITRA.[24] This patient had erythroderma with widespread generalized pustules. They had failed prednisolone and the erythrodema persisted after treatment with cyclosporin and etretinate. GMA once weekly was effective with a decrease of IL-6 and IL-8 serum levels. Another study showed 10 patients with maintained clinical response for 10 weeks after the last GMA session.[34] Given these reports, the use of GMA warrants further exploration.

### 5.4 | Acitretin

Acitretin is a vitamin A-derived retinoid with reported efficacy in inducing temporary remission in patients with acute cutaneous flares of DITRA.[13,31] However, relapses are common,[12] and therapy for patients with refractory courses remains a clinical challenge. Additionally, acitretin can cause various side effects, such as dry skin, itching, hair loss, elevated liver enzymes and congenital disabilities, requiring careful monitoring, as well as an extremely long half-life that limits its use due to teratogenicity concerns. Therefore, while acitretin may provide some benefit for DITRA patients, its use needs to be carefully considered.[13,31]

### 5.5 | Biologic agents

Biologic medications that target specific molecules involved in the inflammatory response offer a particularly compelling class of

agents for the treatment of DITRA and similar autoinflammatory conditions. A recent review found that of 29 flares in 14 patients, biological agents targeting IL-1R, IL-17, IL-12/23 and tumour necrosis factor (TNF)-α were used.

### 5.5.1 | Spesolimab

Spesolimab binds to IL-36 receptor and inhibits ligand binding. Spesolimab secured FDA approval in 2022 as the first agent specifically approved for generalized pustular psoriasis. Clinical trials of spesolimab have shown promising results in the treatment of DITRA. In a Phase 2 clinical trial, spesolimab significantly reduced disease activity and improved the quality of life in individuals with DITRA. In addition, the drug was well-tolerated, with no serious adverse events reported.[32,35,36]

### 5.5.2 | Secukinumab

Secukinumab is a fully human monoclonal antibody that selectively binds to and neutralizes IL-17A, a cytokine involved in the inflammatory processes of various autoimmune diseases, including psoriasis.[14,16,18] Reports show high response rates and rapid improvement in the erythema and pustules in adult patients with GPP.[37] However, its safety and efficacy in treating children with DITRA has yet to be extensively studied. Few non-adult cases have described the potential effectiveness of secukinumab in treating DITRA.[12] These reports describe rapid and complete clearance with and without combination therapy, after failed systemic therapies.[2,19,37] One described a 5-year-old girl with severe scalp and nail involvement who responded well to secukinumab after failing multiple other treatments.[16] The optimal paediatric doses of secukinumab are currently unknown. The clearance and volume of secukinumab have been shown to vary allometrically with body weight and is a clinically relevant consideration in paediatric patients.[37] Despite these promising reports, further studies are needed to evaluate the efficacy and safety of secukinumab in treating DITRA.

### 5.5.3 | Adalimumab

Adalimumab is a TNF-α inhibitor used to treat various inflammatory diseases, including psoriasis. Emerging case reports suggest adalimumab may benefit DITRA patients, particularly in combination with other immunosuppressive agents like methotrexate or cyclosporine.[12,21,23,31,33] A case report describes an adolescent male with DITRA who was treated with subcutaneous secukinumab and methotrexate, significantly improving his skin lesions and systemic symptoms.[12] Another case report described a 5-year-old girl with DITRA who was treated with adalimumab and cyclosporine.[21] This led to the complete remission of her skin lesions and the normalization of her laboratory parameters. Given the data are limited to use in case reports, more studies are warranted to evaluate the efficacy and safety of adalimumab in patients with DITRA.

### 5.5.4 | Infliximab

Infliximab is a monoclonal antibody that targets TNF-α. Infliximab's ability to suppress TNF-α can indirectly reduce the effects of IL-36 signalling and provide symptomatic relief in DITRA patients during acute flares.[12] It is also essential to consider that TNF-α inhibitors, including adalimumab, have been associated with rare but serious adverse effects, including infections and malignancies, and should be used cautiously in patients with underlying conditions.

### 5.5.5 | Ustekinumab

Ustekinumab is a monoclonal antibody that targets the IL-12 and IL-23 cytokines and has been shown to be effective in treating psoriasis, including psoriasis with pustular manifestations. Some reports have also shown its efficacy in treating DITRA.[12,18,27,38] A case reported that patients with DITRA treated with ustekinumab experienced significant improvement in skin lesions and reduced systemic inflammation.[27] Another case report described a patient with DITRA who was treated with ustekinumab and achieved complete remission of skin lesions within 2 weeks of treatment.[38] However, more studies are needed to confirm its effectiveness and safety in treating DITRA and determine the optimal dosing and duration of treatment.

### 5.5.6 | Anakinra and canakinumab

Anakinra is a recombinant IL-1RA that competes with IL-1R agonists for its receptor. Canakinumab is a human anti-IL-1β monoclonal antibody that binds to IL-1β and prevents it from activating the IL-1 receptor. In a series of nine patients with DITRA who received anakinra and canakinumab, 77.8% experienced a good initial clinical response. Of these, 33.3% maintained the response in the short term (12 weeks), and 22.2% continued the treatment in the medium/long term (>24 weeks).[31] Other cases show excellent results with anakinra when used in adjunct with other therapies[19,20] while some show no response.[12] Some studies suggest that canakinumab may also effectively treat DITRA-like diseases.[39] IL-1 blockade has been associated with systemic infection, renal and hepatic laboratory abnormalities, rising white blood cell count, and deteriorating clinical status, raising caution when using such agents.[11,31]

Overall, systemic treatments can effectively manage the symptoms and improve the quality of life of individuals with DITRA. However, the treatment choice will depend on various factors, such as disease severity, comorbidities and individual response to treatment. There is currently no uniformly effective treatment identified for DITRA. Due to the lack of specific treatment guidelines for

DITRA, additional information regarding efficacies of current therapies is required. In our review, topical treatments demonstrated limited efficacy as a monotherapy. In terms of systemic treatments, methotrexate has been shown to be efficient as an adjunct to biologic therapy, while acitretin and cyclosporine demonstrated greater potential for disease recurrence. Biologics such as TNF-α, IL-17 and IL-12/23 inhibitors were shown to drastically improve symptoms in patients with DITRA, while IL-1 inhibitors demonstrated lower success with symptom resolution (Table 1). Newer biologics that act specifically on the IL-36 pathway may offer the best targeted approaches to date for this condition.[30] Close monitoring and regular follow-up with a healthcare provider are essential to ensure optimal disease management and minimize potential side effects.

### 5.5.7 | Paediatrics

In paediatric patients with systemic inflammation and GPP, it is recommended to consider monogenic diseases such as DITRA, but also others like deficiency of IL-1 receptor antagonist (DIRA) and caspase activation and recruitment domain 14-mediated psoriasis (CAMPS). According to a recent study, there was a significant delay of 47 months between the onset of symptoms and a confirmed diagnosis in paediatric cases of such autoinflammatory diseases.[30] Findings from a study of the clinical epidemiology of DITRA suggest that there is a male predominance to the disease, the median age of symptom onset is 7 months, and the most commonly reported mutation in the *IL36RN* gene is p.Leu27Pro. The response to IL-1 blocking agents was found to be lower in children with DITRA compared to adults with DITRA in a review of treatment responses.[11,30] However, IL-12/23 and IL-17 inhibition were effective treatment options for paediatric patients with DITRA, showing complete responses with mild relapses.[18,30,31] Inhibition of TNF-alpha and IL-1 has shown variable responses.[30] While the efficacy of IL-36 receptor inhibitors has been previously shown in adults, substantial data on these drugs in paediatric populations is yet to be published. Additional studies regarding these biologics are needed. Phototherapy has also been shown to cause temporary response when initiated for greater than 6 months in late childhood.[12]

## 6 | DISCUSSION

This review highlights the various cutaneous manifestations seen in DITRA, including pustular psoriasis-like lesions, erythematous plaques and other skin eruptions that can occur in response to triggers such as infections or trauma. The article also explores other autoinflammatory disorders as a possible differential diagnosis for these cutaneous manifestations that may mimic DITRA. Identification of *IL36RN* gene loss-of-function mutations plays a vital role in diagnosing DITRA. Genetic testing helps confirm the presence of a mutation, allowing for accurate diagnosis and distinguishing DITRA from other similar conditions. Due to the marked delay in genetically confirming this disease, dermatologists and other physicians must be clinically aware of this disease presentation and should initiate genetic testing when suspected.[30] The results of genetic testing, along with clinical features, aid in the appropriate management and genetic counselling for affected individuals and their families.

The various treatment options available for the cutaneous manifestations of DITRA, including topical or systemic therapies such as corticosteroids, immunosuppressants and biologic agents, as well as newer targeted therapies that are emerging, are also highlighted. By summarizing the existing literature on the cutaneous manifestations of DITRA, this review article helps dermatologists recognize and manage this rare and complex condition more effectively. It is important to note that DITRA can significantly impact the quality of life, and management strategies should be tailored to individual needs and preferences. Patient-centered care that prioritizes affected individuals' perspectives and preferences can help improve treatment outcomes and quality of life.

## 7 | FUTURE DIRECTIONS

Research and clinical practice development in managing DITRA should include working towards an improved understanding of disease pathogenesis, as, despite the known genetic cause of DITRA, the precise mechanisms underlying the disease are not fully understood. In addition, current systemic treatments for DITRA are not specific and can have significant side effects. Therefore, emerging targeted therapies that block the IL-36 pathway or other vital molecules involved in disease pathogenesis may offer the most effective and best-tolerated treatment options for individuals with DITRA. As such, results of underway clinical trials are highly anticipated.

DITRA is a chronic and lifelong disease with little known about the long-term outcomes and optimal management strategies for affected individuals. Longitudinal studies and registries that track disease progression, treatment responses and complications can help to improve understanding and guide clinical practice. Also, as DITRA is a rare disease that may be underdiagnosed or misdiagnosed, increased awareness and screening efforts can improve early detection and timely initiation of appropriate treatments.

Overall, efforts are needed to improve the understanding, diagnosis, and management of DITRA. Advances in these areas can lead to more effective and better-tolerated treatments for DITRA, improved early detection and diagnosis, better disease progression and complications tracking, individualized management strategies that prioritize patient needs and preferences, and ultimately a better understanding of autoinflammatory conditions. Continued research and clinical efforts in these areas can ultimately lead to better outcomes and quality of life for individuals affected by DITRA and other similar conditions.

### AUTHOR CONTRIBUTIONS

*Study concept and design*: Chiamaka L. Okorie, Krithika Nayudu, Vinod E. Nambudiri. *Drafting of the manuscript*: Chiamaka L. Okorie, Krithika Nayudu. *Critical revision of the manuscript for important*

*intellectual content*: Chiamaka L. Okorie, Krithika Nayudu, Vinod E. Nambudiri. *Figure design*: Chiamaka L. Okorie. *Study supervision*: Vinod E. Nambudiri. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

## ACKNOWLEDGEMENTS

All listed authors (CO, KN and VN) contributed to the drafting and editing of this manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## ORCID

*Chiamaka L. Okorie* https://orcid.org/0000-0003-2233-4557
*Krithika Nayudu* https://orcid.org/0009-0005-0473-3054

## REFERENCES

1. Bal E, Lim AC, Shen M, et al. Mutation in IL36RN impairs the processing and regulatory function of the interleukin-36-receptor antagonist and is associated with DITRA syndrome [Internet]. *Exp Dermatol*. 2019;28:1114-1117. https://onlinelibrary.wiley.com/doi/10.1111/exd.13387
2. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36–receptor antagonist deficiency and generalized pustular psoriasis [Internet]. *N Eng J Med*. 2011;365:620-628. [cited 2023 Mar 26]. http://www.nejm.org/doi/abs/10.1056/NEJMoa1013068
3. Zelickson BD, Muller SA. Generalized pustular psoriasis in childhood. Report of thirteen cases. [Internet]. *J Am Acad Dermatol*. 1991;24:186-194. [cited 2023 Mar 26]. http://www.ncbi.nlm.nih.gov/pubmed/2007662
4. de Jesus A, Goldbach-Mansky R. Genetically defined autoinflammatory diseases. *Oral Dis*. 2016;22:591-604.
5. Cowen EW, Goldbach-Mansky R. DIRA, DITRA, and new insights into pathways of skin inflammation: what's in a name? [Internet]. *Arch Dermatol*. 2012;148:381-384. [cited 2023 Mar 27]. http://www.ncbi.nlm.nih.gov/pubmed/22431779
6. Ganesan R, Raymond EL, Mennerich D, et al. Generation and functional characterization of anti-human and anti-mouse IL-36R antagonist monoclonal antibodies [Internet]. *MAbs*. 2017;9:1143-1154. [cited 2023 Mar 27]. https://www.tandfonline.com/doi/full/10.1080/19420862.2017.1353853
7. Diaz A. Deficiency of the interleukin-36 receptor antagonist (DITRA) and generalized pustular psoriasis [Internet]. In: *Auto-Inflammatory Syndromes Pathophysiology, Diagnosis, and Management*. Springer; 2019;85-94. [cited 2023 Mar 26]. https://link.springer.com/chapter/10.1007/978-3-319-96929-9_7
8. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis [Internet]. *Am J Hum Genet*. 2011;89:432-437. [cited 2023 Mar 26]. https://linkinghub.elsevier.com/retrieve/pii/S0002929711003168
9. Towne JE, Renshaw BR, Douangpanya J, et al. Interleukin-36 (IL-36) ligands require processing for full agonist (IL-36α, IL-36β, and IL-36γ) or antagonist (IL-36Ra) activity [Internet]. *J Biol Chem*. 2011;286:42594-42602. [cited 2023 Mar 27]. https://linkinghub.elsevier.com/retrieve/pii/S0021925820871476
10. Renert-Yuval Y, Horev L, Babay S, et al. IL36RN mutation causing generalized pustular psoriasis in a Palestinian patient [Internet]. *Int J Dermatol*. 2014;53:866-868. [cited 2023 Mar 26]: https://onlinelibrary.wiley.com/doi/10.1111/ijd.12525
11. Rossi-Semerano L, Piram M, Chiaverini C, et al. First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra. [Internet]. *Pediatrics*. 2013;132:e1043-7. [cited 2023 Mar 26]. http://www.ncbi.nlm.nih.gov/pubmed/24019411
12. Cordoro KM, Ucmak D, Hitraya-Low M, Rosenblum MD, Liao W. Response to interleukin (IL)-17 inhibition in an adolescent with severe manifestations of IL-36 receptor antagonist deficiency (DITRA) [Internet]. *JAMA Dermatol*. 2017;153:106. http://archderm.jamanetwork.com/article.aspx?doi=10.1001/jamadermatol.2016.3490
13. Cuperus E, Koevoets R, van der Smagt JJ, et al. Juvenile interleukin-36 receptor antagonist deficiency (DITRA) with c.80T>C (p.Leu27Pro) mutation successfully treated with etanercept and acitretin [Internet]. *JAAD Case Rep*. 2018;4:192-195. https://linkinghub.elsevier.com/retrieve/pii/S2352512617302047
14. Abbas O, Itani S, Ghosn S, et al. Acrodermatitis continua of hallopeau is a clinical phenotype of DITRA: evidence that it is a variant of pustular psoriasis [Internet]. *Dermatology*. 2013;226:28-31. https://www.karger.com/Article/FullText/346572
15. Koike Y, Okubo M, Kiyohara T, et al. Granulocyte and monocyte apheresis can control juvenile generalized pustular psoriasis with mutation of *IL36RN* [Internet]. *British Journal of Dermatology*. 2017;177:1732-1736. https://academic.oup.com/bjd/article/177/6/1732/6697398
16. Jing G, Bin W, Ying ZZ. Rapid response to secukinumab in a 5-year-old with deficiency of the interleukin-36 receptor antagonist (DITRA) with severe scalp and nail involvement [Internet]. *Pediatr Dermatol*. 2021;38:1258-1263. https://onlinelibrary.wiley.com/doi/10.1111/pde.14737
17. Babic V, Moawad S, Bursztejn A-C, Schmutz JL. DITRA syndrome in a Vietnamese patient: efficacy of etanercept [Internet]. *Eur J Dermatol*. 2018;28:244-246. http://www.john-libbey-eurotext.fr/medline.md?doi=10.1684/ejd.2018.3219
18. Köstner K, Prelog M, Almanzar G, et al. Successful use of secukinumab in a 4-year-old patient with deficiency of interleukin-36 antagonist [Internet]. *Rheumatology*. 2018;57:936-938. [cited 2023 Mar 27]. https://academic.oup.com/rheumatology/article/57/5/936/4836312
19. Ho P-H, Tsai T-F. Successful treatment of refractory juvenile generalized pustular psoriasis with secukinumab monotherapy: a case report and review of published work [Internet]. *J Dermatol*. 2018;45:1353-1356. [cited 2023 Mar 28]. https://onlinelibrary.wiley.com/doi/10.1111/1346-8138.14636
20. Hüffmeier U, Wätzold M, Mohr J, et al. Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations [Internet]. *Br J Dermatol*. 2014;170:202-204. [cited 2023 Mar 28]. https://academic.oup.com/bjd/article/170/1/202/6615049
21. Clemente D, López Robledillo JC, Torrelo A, et al. AB1087 prolonged response with tumour necrosis factor alfa inhibition in a 5 year old boy with severe manifestations of il-36 receptor antagonist deficiency (DITRA) [Internet]. *Paediatric Rheumatol*. 2018;77(2):1653.1. [cited 2023 Mar 27]. https://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2018-eular.6532
22. Morgado-Carrasco D, Podlipnik S, Mascaró JM Jr. Woronoff ring in deficiency of interleukin-36 receptor antagonist (DITRA) [Internet]. *Dermatol Pract Concept*. 2019;10:e2020008. [cited 2023 Mar 27]. https://dpcj.org/index.php/dpc/article/view/dermatol-pract-concept-articleid-dp1001a08
23. Zea-Vera AF, Estupiñan-Lopez FE, Cifuentes-Burbano J, Vargas MJ, Bonelo A. Interleukin-36 receptor antagonist deficiency (DITRA) with a novel IL36RN homozygous mutation c.200G>T (P.Cys67Phe) in a young colombian woman [Internet]. *J Clin*

*Immunol*. 2019;39:261-263. http://link.springer.com/10.1007/s10875-019-00622-7
24. Tominaga C, Yamamoto M, Imai Y, et al. A case of old age-onset generalized pustular psoriasis with a deficiency of IL-36RN (DITRA) treated by granulocyte and monocyte apheresis. [Internet]. *Case Rep Dermatol*. 2015;7:29-35. [cited 2023 Mar 26]. http://www.ncbi.nlm.nih.gov/pubmed/25848350
25. Tong X, Li Y, Tang X, et al. Case report: infantile generalized pustular psoriasis with IL36RN and CARD14 gene mutations. *Front Genet*. 2023;13:13.
26. Almutairi A, Amin MM, Rashwan MAM, et al. Digenic inheritance of IL-36RA and SEC61A1 mutations underlies generalized pustular psoriasis with hypogammaglobulinemia [Internet]. *Clin Immunol*. 2022;235:108930. https://linkinghub.elsevier.com/retrieve/pii/S1521661622000109
27. Bonekamp N, Caorsi R, Viglizzo GM, et al. High-dose ustekinumab for severe childhood deficiency of interleukin-36 receptor antagonist (DITRA). [Internet]. *Ann Rheum Dis*. 2018;77:1241-1243. [cited 2023 Mar 26]. http://www.ncbi.nlm.nih.gov/pubmed/28866646
28. Pan J, Qiu L, Xiao T, et al. Juvenile generalized pustular psoriasis with IL36RN mutation treated with short-term infliximab [Internet]. *Dermatol Ther*. 2016;29:164-167. [cited 2023 Mar 26]. https://onlinelibrary.wiley.com/doi/10.1111/dth.12325
29. Espíndola A, Casimiro F, Pesquero J, et al. Extensive deep venous thrombosis in a patient with interleukin-36 receptor antagonist deficiency (DITRA): a case report [Internet]. *Arch Clin Med Case Rep*. 2019;3:600-604. [cited 2023 Mar 28]. http://www.fortunejournals.com/articles/extensive-deep-venous-thrombosis-in-a-patient-with-interleukin36-receptor-antagonist-deficiency-ditra-a-case-report.html
30. Hospach T, Glowatzki F, Blankenburg F, et al. Scoping review of biological treatment of deficiency of interleukin-36 receptor antagonist (DITRA) in children and adolescents [Internet]. *Pediatr Rheumatol*. 2019;17:37. [cited 2023 Mar 26]. https://ped-rheum.biomedcentral.com/articles/10.1186/s12969-019-0338-1
31. Gómez-García F, Sanz-Cabanillas JL, Viguera-Guerra I, et al. Scoping review on use of drugs targeting interleukin 1 pathway in DIRA and DITRA [Internet]. *Dermatol Ther (Heidelb)*. 2018;8:539-556. [cited 2023 Mar 27]. http://link.springer.com/10.1007/s13555-018-0269-7
32. Morita A, Tsai T, Yee EYW, et al. Efficacy and safety of spesolimab in Asian patients with a generalized pustular psoriasis flare: results from the randomized, double-blind, placebo-controlled Effisayil™ 1 study [Internet]. *J Dermatol*. 2023;50:183-194. [cited 2023 Mar 27]. https://onlinelibrary.wiley.com/doi/10.1111/1346-8138.16609
33. Bozonnat A, Assan F, LeGoff J, Bourrat E, Bachelez H. SARS-CoV-2 infection inducing severe flare up of deficiency of interleukin thirty-six (IL-36) receptor antagonist (DITRA) resulting from a mutation invalidating the activating cleavage site of the IL-36 receptor antagonist [Internet]. *J Clin Immunol*. 2021;41:1511-1514. https://link.springer.com/10.1007/s10875-021-01076-6
34. Ikeda S, Takahashi H, Suga Y, et al. Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis. *J Am Acad Dermatol*. 2013;68:609-617.
35. Baum P, Visvanathan S, Garcet S, et al. Pustular psoriasis: molecular pathways and effects of spesolimab in generalized pustular psoriasis [Internet]. *J Allergy Clin Immunol*. 2022;149:1402-1412. [cited 2023 Mar 27]. https://linkinghub.elsevier.com/retrieve/pii/S0091674921015542
36. Bissonnette R, Abramovits W, Saint-Cyr Proulx É, et al. Spesolimab, an anti-interleukin-36 receptor antibody, in patients with moderate-to-severe atopic dermatitis: results from a multicentre, randomized, double-blind, placebo-controlled, phase study [Internet]. *J Eur Acad Dermatol Venereol*. 2023;37:549-557. [cited 2023 Mar 27]. https://onlinelibrary.wiley.com/doi/10.1111/jdv.18727
37. Kolbinger F, Di Padova F, Deodhar A, et al. Secukinumab for the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis: physical and pharmacological properties underlie the observed clinical efficacy and safety [Internet]. *Pharmacol Ther*. 2022;229:107925. doi:10.1016/j.pharmthera.2021.107925
38. Stephenson C, Prajapati VH, Hunter C, Miettunen P. Novel use of autoinflammatory diseases activity index (AIDAI) captures skin and extracutaneous features to help manage pediatric DITRA: a case report and a proposal for a modified disease activity index in autoinflammatory keratinization disorders [Internet]. *Pediatr Dermatol*. 2020;37:670-676. https://onlinelibrary.wiley.com/doi/10.1111/pde.14155
39. Ulusoy E, Karaca NE, El-Shanti H, et al. Interleukin-1 receptor antagonist deficiency with a novel mutation; late onset and successful treatment with canakinumab: a case report [Internet]. *J Med Case Rep*. 2015;9:145. [cited 2023 Mar 28]. https://jmedicalcasereports.biomedcentral.com/articles/10.1186/s13256-015-0618-4

**How to cite this article:** Okorie CL, Nayudu K, Nambudiri VE. Cutaneous findings and treatments in deficiency of interleukin-36 receptor antagonist (DITRA): A review of the literature. *Exp Dermatol*. 2023;00:1-12. doi:10.1111/exd.14934