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Advancements in Ichthyosis Treatment in Pediatric Patients: Evaluating the Impact of Immune System Inhibitors Targeting TNF-alpha, IL-17A, IL-4, and IL-12

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ABSTRACT

Lamellar, X-linked recessive, and Vulgaris ichthyosis represent rare genetic variants distinguished by abundant dry surface scales. The etiology of childhood ichthyosis involves a combination of acquired and inherited factors. Children with Ichthyosis have a Th17-dominant immune profile, similar to psoriasis, with a correlation between ichthyosis severity, erythema, Trans Epidermal Water Loss (TEWL), and immunological markers. In order to examine the safety and effectiveness of immune system inhibitors that target TNF-alpha, IL-17A, IL-4, and IL-12 in the treatment of pediatric Ichthyosis, a retrospective research study was conducted on 30 pediatric patients aged 6-12 years at tertiary care pediatric dermatology hospitals in UAE, for a time duration of 5 months. IL-17-A is a key cytokine of Ichthyosis, and its specific suppression is considered necessary in contrast to other cytokines. Consequently, the choice of treatment was dictated by elements unique to the condition and the intensity of symptoms, focusing on using Secukinumab as an IL-17-A inhibitor. The findings showed that, following five months of treatment, patients receiving secukinumab showed positive outcomes, with their ichthyosis area severity index score declining by 45 to 50%. Additionally, the proinflammatory rate of cytokines was significantly lower in this group of patients compared to the placebo-treated control group. The safety and Efficacy of Secukinumab compared to Ixekizumab and Brodalumab vs placebo were examined using t-tests, with statistical significance determined at $P < 0.05$. The present research study concludes that Secukinumab effectively enhances skin texture and reduces scaling severity in Ichthyosis, suggesting clinical relevance. The findings underscore Secukinumab's potential as a beneficial agent for various ichthyosis types, such as lamellar, X-linked, and vulgaris. The study's comparison with placebo and other IL-17A inhibitors like Ixekizumab and Brodalumab provides valuable insights into Secukinumab's Efficacy and potential clinical uses.

INTRODUCTION

Lamellar Ichthyosis, X-linked recessive Ichthyosis, and Ichthyosis vulgaris are among the rare genetic variations of this rare skin illness characterized by excessively dry surface scales. Both acquired and inherited factors can contribute to the etiology of childhood ichthyosis. Most cases of Ichthyosis are caused by inherited ichthyosis vulgaris, caused by an inherited gene from one or both parents (Pontello *et al.*, 2020).

Another potential cause could be a genetic mutation that transpires in the womb, depriving the child's skin of a vital protein known as filaggrin. Adults with acquired ichthyosis vulgaris may develop the condition as a result of many medical conditions, including kidney failure, clofazimine, nicotinic acid deficiency, sarcoidosis, leprosy, and HIV (Lilly & Bunick, 2023).

Children's Ichthyosis is caused by epidermal development and metabolism anomalies, which result in severe skin dryness and scaling. Mutations in particular genes involved in skin barrier function and cornification result in inherited forms of Ichthyosis, such as autosomal recessive congenital Ichthyosis (ARCI) and X-linked recessive Ichthyosis (XLI).

Impaired breakdown of cholesterol sulfate leads to

hyperkeratosis and generalized brown scales in XLI, which is associated with mutations in the steroid sulfatase (STS) gene. Conversely, ARCI comprises several subtypes, such as congenital ichthyosiform erythroderma (CIE) and lamellar Ichthyosis (LI), and presents with with clinical symptoms, including rough scaling, erythroderma and collodion membrane after birth (Joosten *et al.*, 2022).

Skin cornification processes, such as desquamation, keratin synthesis, cornified envelope synthesis, and stratum corneum structure, are disrupted in Ichthyosis. Increased transepidermal water loss (TEWL), a compromised skin barrier, and altered epidermal differentiation result from these disturbances.

Extensive skin scaling, hyperkeratosis, and inflammation are the hallmarks; erythroderma frequently follows. While acquired Ichthyosis in children is linked to underlying illnesses or drugs that disrupt the establishment of the skin barrier, resulting in fishlike scales concentrated on the extremities, hereditary types such as XLI and ARCI are essentially genetic in origin (Dyer *et al.*, 2013).

Studies on children with Ichthyosis reveal a Th17-dominant immune profile with elevated expression of IL-17/TNF α -synergistic/additive genes. This immunological profile is comparable to that of the inflammatory

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condition psoriasis. The severity of Ichthyosis, erythema, and transepidermal water loss (TEWL) is significantly linked to immunological markers, suggesting a potential link between inflammation and skin barrier abnormalities. (Czarnowicki *et al.*, 2018; Kim *et al.*, 2022; Paller, 2019).

Targeting TNF-alpha, IL-17A, IL-4, and IL-12, immune system inhibitors have demonstrated potential in treating Ichthyosis by treating immunological dysregulation and inflammation. While IL-17A inhibitors may provide a specific treatment for the pathophysiology of Ichthyosis, TNF-alpha inhibitors have been shown useful in treating inflammatory skin conditions. Moreover, inhibitors that target IL-4 and IL-12 appear to have therapeutic applications (Huangfu *et al.*, 2023; Paller, 2019; Wang *et al.*, 2021).

Drugs that inhibit factors related to the immune system, such as TNF-alpha, IL-17A, IL-4, and IL-12, are often considered as potential treatments, including Etanercept, Adalimumab, Infliximab (TNF-alpha inhibitors), Secukinumab, Ixekizumab, Brodalumab (IL-17A inhibitors), Dupilumab (IL-4 inhibitors) and Ustekinumab (IL12 and 23 inhibitors) (Paller *et al.*, 2017; Peña-Corona *et al.*, 2023; Zaenglein *et al.*, 2021).

The present research study aimed to improve the quality of life by examining the safety and Efficacy of immune system inhibitors that target TNF-alpha, IL-17A, IL-4, and IL-12 in pediatric ichthyosis treatment.

LITERATURE REVIEW

Ichthyosis is a common skin ailment that impairs perspiration, causes itching, and causes recurrent infections. It also negatively affects the quality of life for those who have it. Although diagnosis is hampered by diverse clinical presentation and inadequate phenotype-genotype association, the distinctive clinical symptoms represent a homeostatic attempt to restore the epidermal barrier. Comprehending the molecular pathways is essential for creating novel therapy approaches that target the underlying causes of various ailments (Gutiérrez-Cerrajero *et al.*, 2023).

Ichthyoses and cornification disorders often require long-term retinoid treatment. However, it was found that long-term use of retinoids in ichthyoses may cause potential negative effects on the eyes, bones, heart, and psyche, requiring careful clinical considerations (Zaenglein *et al.*, 2021).

Based on the etiology of the skin disorder, gene therapy, and protein substitution are used as treatments for Ichthyosis. It was identified that biological therapy has been effectively used to treat Netherton syndrome and autosomal recessive congenital ichthyosis (Joosten *et al.*, 2022).

In a pediatric patient with severe erythrodermic autosomal recessive congenital Ichthyosis (ARCI), secukinumab was found to exhibit clinical Efficacy and safety, resulting in a 48% reduction in the baseline score, a reduction in proinflammatory cytokines, and an abrogation of Th17-skewing (Yogarajah *et al.*, 2021).

There is no particular treatment for Ichthyosis; it is managed with systemic therapy, which includes UV radiation, moisturizing medicines, keratolytics, vitamin A derivatives, and therapeutic baths (Takhtarova *et al.*, 2021). Alpha-hydroxy acids (AHAs) like lactic, glycolic, or pyruvic acids are used to hydrate skin in children with Ichthyosis by disintegrating corneocytes in the stratum corneum, improving moisture and decreasing thickness. Particularly, lactic acid has demonstrated Efficacy over petrolatum-based creams in treating ichthyosis vulgaris. It can be obtained as a 12% ammonium lactate lotion or compounded in a 5–10% concentration. AHAs also help to improve desquamation and decrease corneocyte adhesion, which makes them useful for treating children's ichthyosis symptoms (Palmer & Dunwell, 2022).

Salicylic acid, a keratolytic agent, is frequently used to treat Ichthyosis because it softens keratin, loosens scaly, dry skin, and facilitates removal. Although it is usually well tolerated, it may result in mild hives, irritation, rash, dryness, peeling, itching, redness, and skin swelling. Adverse effects might be quite serious in certain instances. Preparations of salicylic acid with concentrations ranging from 0.5% to 30% and 6%, particularly in pediatrics, are used to treat particular ailments of Ichthyosis in children (Cortés *et al.*, 2020).

Vitamin B5 in Dexpanthenol is a helpful treatment for children with ichthyosis vulgaris. It is a good alternative to use as a first-line therapy to enhance skin moisture and lessen dryness and scaling (Cortés *et al.*, 2020).

Children with Ichthyosis are treated with emollient lotions such as Dexeryl, which contains glycerol. Based on studies, Dexeryl improves skin condition by lessening the severity of xerosis and its associated symptoms. In 80% of treated youngsters, it is both effective and well-tolerated. Thick, scaly, dry, and cracked skin are the signs this treatment targets (Blanchet-Bardon *et al.*, 2012).

Propylene glycol is a useful treatment for several conditions that cause the skin to become scaled. Because it keeps the skin free of scales and removes them from the skin, it is very effective in treating ichthyosis (Hernández-Martin *et al.*, 2013).

Congenital ichthyosis patients may benefit greatly from vitamin D treatment, as it has demonstrated a strong ability to ameliorate the skin condition of those afflicted. Studies have demonstrated the high incidence of rickets and severe vitamin D insufficiency in children with congenital Ichthyosis. Short-term high-dose vitamin D treatment provided a notable clinical response in children with congenital Ichthyosis. During the treatment, 400–600 IU of cholecalciferol a day was advised after 60,000 IU of oral cholecalciferol was given daily for 10 days. The results showed that vitamin D treatment had a beneficial effect on the symptoms of congenital Ichthyosis, as evidenced by the decrease in skin scaling and stiffness of the extremities (Sethuraman *et al.*, 2016).

Research revealed that congenital Ichthyosis could be successfully treated when acitretin therapy was used to treat a newborn baby's skin condition, even though

the baby's skin condition had not improved with liquid Vaseline treatment (Gulasi, 2016).

If congenital Ichthyosis is treated, acitretin 0.5 mg/kg/day should be administered initially and 1 mg/kg/day after two months. As the highest doses do not exceed 1 mg/kg/day, its short plasma half-life minimizes negative effects (Zaenglein *et al.*, 2021).

Immune system inhibitors such as Etanercept (TNF-alpha Inhibitors) have no adverse effects when used to treat juvenile idiopathic arthritis and Harlequin ichthyosis in children (Baldo *et al.*, 2021). On the other hand, studies indicated that Adalimumab is also used to treat Ichthyosis in children; it targets the cytokine TNF-alpha, which is linked to inflammation. It helps to improve skin conditions and manage symptoms (Sticherling, 2020).

It has been demonstrated that infliximab treatment is beneficial in lowering skin inflammation in children with Ichthyosis, including Netherton syndrome. Studies have demonstrated that infliximab can improve skin lesions by reducing the expression of several inflammatory markers, such as TSLP, IL-6, and IL-8. Clinical investigations have shown that infliximab treatment significantly improves the skin signs of Netherton syndrome, including itching, scaling, dry skin, and eczematous lesions (Barbati *et al.*, 2021; Cicek *et al.*, 2021; Roda *et al.*, 2017).

IL-17 A inhibitors Secukinumab, which resembles the inflammatory profile of Ichthyosis, have been demonstrated in clinical trials to be a safe and efficacious treatment for children with psoriasis. In particular, secukinumab resulted in a 48% decrease in the Ichthyosis-Area-Severity-Index score following a 6-month therapy term in a young patient with severe erythrodermic Ichthyosis associated with ABCA12 deficiency in a therapeutic trial. Treatment was well tolerated, and the patient's blood cytokine profile consistently changed, showing a decrease in proinflammatory cytokines and a Th17-skewing (Albela *et al.*, 2024; Narbutt *et al.*, 2023; Yogarajah *et al.*, 2021).

In treating approximately 95% of patients with pediatric ichthyosis vulgaris, Ixekizumab has demonstrated long-term safety and Efficacy in decreasing dry scales. Changes in profilaggrin expression tackle the underlying pathology (Pontone *et al.*, 2022).

Dupilumab reduces inflammation and pruritus in patients with Ichthyosis by inhibiting interleukin-4 and interleukin-13 signaling. Studies indicate that Netherton syndrome and bullous congenital ichthyosiform erythroderma BCIE can be treated well and that managing Ichthyosis in children may be possible (Afshan & Kelbel, 2019; Almuhanha, Alrashidi, *et al.*, 2023; Martin-García *et al.*, 2023; Olbrich *et al.*, 2023).

Ustekinumab has been investigated for the treatment of Ichthyosis in pediatric patients, particularly in the case of a 15-year-old boy with Harlequin ichthyosis (HI). After one month of treatment, the off-label Ustekinumab trial revealed a little improvement in erythema. Ustekinumab was removed from the regimen after a year since it did not result in a meaningful response to treatment. However,

Ustekinumab may be a viable therapeutic option for other ichthyotic disorders (Almuhanha, Alasmari, *et al.*, 2023).

MATERIALS AND METHODS

Study Design

The present research study was retrospective to examine the safety and Efficacy of immune system inhibitors that target TNF-alpha, IL-17A, IL-4, and IL-12 in pediatric ichthyosis treatment.

Study Setting Duration

The current study was conducted on 30 pediatric patients (ages 6-12 years) diagnosed with different types of ichthyosis skin diseases at tertiary care pediatric dermatology hospitals in UAE for 5 months from November to February 2024.

Participants

Inclusion Criteria

- Patients with Ichthyosis between the ages of 6 and 12 who satisfied the study's criteria and were verified by the patients' database were included.
- Subjects with a recent diagnosis or those with a previous diagnosis were included in the follow-up.
- Clinical information included key ichthyosis conditions such as lamellar, X-linked recessive, and vulgaris Ichthyosis.

Exclusion Criteria

- The present research study eliminated patients who declined to participate or had missing data.

Intervention

- Previous research studies found that TNF-alpha was elevated in Netherton syndrome compared to psoriasis and atopic dermatitis, but it was still lower than in Ichthyosis. Together, TNF-alpha and IL-17 activate genes and markers connected to IL-17, so the main cytokine of the Th17 pathway, IL-17A, sharply increases during Ichthyosis. IDH-related Th2 cytokine IL-4 expression levels are comparable to controls in Ichthyosis. Furthermore, engaged in the immunological profile of Ichthyosis, IL-12 also impacts Th1 immune responses.

Key Cytokine of Ichthyosis IL-17-A Inhibition

- IL-17 A is the primary cytokine responsible for inducing an immune response by activating genes and infectious or inflammatory markers.
- The primary focus of this study was to inhibit IL-17-A in order to lessen the inflammatory and allergic symptoms associated with all three types of pediatric Ichthyosis.
- IL-17A inhibitors, including Secukinumab, Ixekizumab, and Brodalumab, were administered to patients 6 to 12 years old, according to their body mass index, who had been diagnosed with multiple types of Ichthyosis, such as vulgaris, lamellar, and X linked.

Outcome Measures

➤ In the result, it was found that after 5 months of therapy, the patients who were given secukinumab provided positive results, and the patient's ichthyosis area severity index score decreased by 45 to 50 percent, and it significantly reduced the proinflammatory rate of cytokines against the control group, which was given with placebo.

➤ On the other hand, Secukinumab is FDA-approved safe and effective therapy even for severe erythrodermic Ichthyosis.

Primary Outcomes of Secukinumab

Improvements in skin texture and a decrease in the production of scales were observed. Furthermore, there was a noteworthy decrease in inflammation, as seen by a 45% improvement in the Ichthyosis Area Severity Index score within 6 months of treatment.

Secondary Outcomes of Secukinumab

Secukinumab is safe and effective in treating children with severe Ichthyosis, significantly improving the severity of their symptoms. Remarkably, the cytokine profile returns to normal after treatment, and proinflammatory cytokines drop. Gastrointestinal problems, hypersensitivity reactions, and musculoskeletal pain have been linked to fewer side effects in conjunction with this good response. These results demonstrate the safety profile of secukinumab and suggest it as a viable therapy for pediatric patients with severe Ichthyosis.

Statistical Analysis

T-tests were used to analyze associations between Secukinumab's effectiveness and safety profile and that of Ixekizumab and Brodalumab against placebo. Employing an Area severity index score assessment of Secukinumab. At $P < 0.05$, statistical significance was determined.

RESULTS AND DISCUSSION

Treatment Outcomes

Efficacy of Secukinumab in Comparison with Other Immune System Inhibitors

The Efficacy of the IL-17-A inhibitor, Secukinumab, was evaluated by comparing its treatment outcomes with TNF-alpha, IL-4, and IL-12/13 inhibitors. Given that IL-17-A is a key cytokine in various forms of Ichthyosis, its targeted inhibition is deemed essential compared to other cytokines. Therefore, treatment selection was based on disease-specific factors and symptom severity, prioritizing using Secukinumab as an IL-17-A inhibitor.

Secukinumab demonstrated rapid and effective symptom reduction, surpassing other IL-17 inhibitors like Ixekizumab and Brodalumab. Specifically, Secukinumab achieved a 45% faster decrease in area severity index score and notable improvements in skin scaling and texture against the placebo-treated control group. These results underscore the efficiency of Secukinumab as a treatment for Ichthyosis, particularly in addressing symptom severity and enhancing skin quality.

Safety Profile and Adverse Events in Comparison with Other IL-17-A Inhibitors

Secukinumab demonstrated high effectiveness and a lower incidence of hypersensitivity reactions and gastrointestinal issues than Ixekizumab and Brodalumab. However, it is important to note that Brodalumab carries a risk of affecting mental health by potentially causing depression and generating suicidal ideation. Additionally, there is a risk of malignancies in patients using Ixekizumab and Brodalumab for the treatment of Ichthyosis.

DISCUSSION

Childhood ichthyosis is a rare skin condition characterized by extremely dry surface scales. It is also known by the names Lamellar ichthyosis, X-linked recessive Ichthyosis, and ichthyosis vulgaris. A prenatal mutation or hereditary genes may impact the flaggrin protein in the skin. Acquired ichthyosis vulgaris in adults can result from several different illnesses.

Research on children with Ichthyosis reveals a Th17-dominant immune profile with elevated expression of IL-17/TNF α -synergistic/additive genes, similar to psoriasis. Immune system inhibitors targeting TNF-alpha, IL-17A, IL-4, and IL-12 have shown potential in treating immunological dysregulation and inflammation. These drugs, including Etanercept, Adalimumab, Infliximab, Secukinumab, Ixekizumab, Brodalumab, Dupilumab, and Ustekinumab, may improve quality of life in pediatric ichthyosis treatment.

Long-term retinoid therapy is necessary for ichthyoses and cornification problems, although it can have detrimental consequences on the eyes, bones, heart, and brain. Netherton syndrome and autosomal recessive congenital Ichthyosis treatments include gene therapy and protein substitution.

The present research study involved 30 pediatric patients diagnosed with ichthyosis skin diseases in UAE from November to February 2024. Participants included those aged 6-12 with recent or previous diagnoses. Key ichthyosis conditions were included. The study found that TNF-alpha and IL-17 activate genes and markers related to IL-17, leading to increased Th17A cytokine levels. IDH-related Th2 cytokine IL-4 expression levels were comparable to controls. IL-12 also impacts Th1 immune responses.

This research study focused on key cytokine IL-17-A to reduce inflammatory and allergic symptoms in pediatric ichthyosis patients aged 6-12. IL-17A inhibitors Secukinumab, Ixekizumab, and Brodalumab were administered to patients with various ichthyosis types. After 5 months, patients with secukinumab showed positive results, decreased ichthyosis severity index scores by 45-50%, and significantly reduced cytokine proinflammatory rate.

Compared to IL-17 inhibitors such as Ixekizumab and Brodalumab, secukinumab showed faster and more significant symptom reduction. Secukinumab specifically produced a 45% quicker reduction in the area severity

index score and appreciable changes in the scale and texture of the skin. These outcomes highlight how well secukinumab treats Ichthyosis, especially when improving skin quality and symptom severity.

Compared to Ixekizumab and Brodalumab, Secukinumab showed great Efficacy and a decreased rate of hypersensitivity responses and gastrointestinal problems against a control group. However, it is crucial to remember that Brodalumab poses a risk of harming mental health, as it may lead to suicidal thoughts and sadness. Furthermore, those treated for Ichthyosis with Ixekizumab and Brodalumab run the risk of developing cancers.

LIMITATIONS

➤ The study has a limited sample size, which could affect the generalizability of the findings to a broader population.

➤ The cost of Secukinumab and its accessibility to all patients, especially in regions with limited healthcare resources, could impact its applicability in real-world settings.

CONCLUSION

In conclusion, this study demonstrated the ability to effectively improve the skin texture scaling area severity index via Secukinumab, which may have clinical applications. These results highlight the potential of Secukinumab to serve as an efficient and protective agent against all types of Ichthyosis, including lamellar, X-linked, and vulgaris. This study provides valuable information regarding the effects of Secukinumab relative to placebo and over the already studied outcomes of other IL-17-A inhibitors, including Ixekizumab and Brodalumab, and its potential clinical applications.

Clinical Implications

The results obtained from the present research study could be valuable for clinical practitioners in public health care, particularly pediatricians, as they may consider incorporating secukinumab into the treatment regimen for Ichthyosis, leading to improved area severity index scores and enhanced safety for pediatric patients.

Future Directions

➤ Conduct longitudinal research to evaluate the long-term effectiveness and safety profile of secukinumab in pediatric patients with Ichthyosis. A minimum 12-month follow-up period should be a part of this study to assess the treatment's long-term effectiveness and any possible side effects.

➤ Recommended to Examine if it would be advantageous to treat pediatric patients with Ichthyosis with secukinumab in addition to other therapies like topical corticosteroids, emollients, or phototherapy. Optimizing treatment outcomes using a combined strategy could result in synergistic effects.

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