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Efficacy and safety of JAK inhibitors in the treatment of moderate to severe atopic dermatitis in adults: a Systematic Review of the Literature

Eficacia y seguridad de los inhibidores de JAK en el tratamiento de la dermatitis atópica de moderada a grave en adultos: una Revisión Sistemática de la Literatura

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ABSTRACT

Background: Atopic dermatitis (AD)_ chronic inflammatory skin disorder, has affected the global population. Specifically, it is seen as more common in children about 10-20% prevalence in children's and 2% among adults. Traditional treatments are insufficient for moderate to severe cases and necessitate new therapeutic options. Janus kinase (JAK) inhibitors is promising class of drugs due to their ability to modulate key inflammatory pathways involved in AD. Methodology: Systematic review was conducted using Cochrane Library database, PubMed, and Embase. Keywords and MeSH terms identified studies focusing on adult patients with moderate to severe AD. Inclusion criteria encompassed studies evaluating efficacy and safety of JAK inhibitors. Data extraction was performed using standardized forms, Cochrane Risk of Bias Tool conducted. Most of the articles are selected which are published in 2024 to keep our research up-to-date. Results: We have analyzed data from several studies evaluating the efficacy and safety of JAK inhibitors, most commonly abrocitinib, upadacitinib, and baricitinib. They have shown efficacy in reducing eczema symptoms with EASI-75 response rates of up to 80% for upadacitinib and 71% for abrocitinib. Higher doses of JAK inhibitors raised safety concerns like heart diseases, infections, and acne, but the standard recommended dose stood beneficial in reducing eczema. Conclusion: JAK inhibitors are advancements in the treatment of moderate to severe atopic dermatitis. They offer substantial symptom relief and improved quality of life.

Keywords: JAK inhibitors, efficacy, safety, moderate to severe atopic dermatitis, adults.

RESUMEN

Antecedentes: La dermatitis atópica (DA), trastorno inflamatorio crónico de la piel, ha afectado a la población mundial. Específicamente, se considera más común en niños, con una prevalencia del 10 al 20% en niños y del 2% entre adultos. Los tratamientos tradicionales son insuficientes para los casos moderados a graves y requieren nuevas opciones terapéuticas. Los inhibidores de Janus quinasa (JAK) son una clase de fármaco prometedora debido a su capacidad para modular las vías inflamatorias clave implicadas en la DA. Metodología: Se realizó una revisión sistemática utilizando la base de datos de la Biblioteca Cochrane, PubMed y Embase. Las palabras clave y los términos MeSH identificaron estudios centrados en pacientes adultos con DA de moderada a grave. Los criterios de inclusión abarcaron estudios que evaluaron la eficacia y seguridad de los inhibidores de JAK. La extracción de datos se realizó mediante formularios estandarizados, mediante la herramienta Cochrane de Riesgo de Sesgo. Se seleccionan la mayoría de los artículos que se publicarán en 2024 para mantener nuestra investigación actualizada. Resultados: Hemos analizado datos de varios estudios que evalúan la eficacia y seguridad de los inhibidores de JAK, más comúnmente abrocitinib, upadacitinib y baricitinib. Han demostrado eficacia para reducir los síntomas del eccema con tasas de respuesta EASI-75 de hasta el 80 % para upadacitinib y el 71 % para abrocitinib. Las dosis más altas de inhibidores de JAK plantearon problemas de seguridad, como enfermedades cardíacas, infecciones y acné, pero la dosis estándar recomendada resultó beneficiosa para reducir el eczema. Conclusión: Los inhibidores de JAK son avances en el tratamiento de la dermatitis atópica de moderada a grave. Ofrecen un alivio sustancial de los síntomas y una mejor calidad de vida.

Palabras clave: inhibidores de JAK, eficacia, seguridad, dermatitis atópica de moderada a grave, adultos.

INTRODUCTION

Atopic dermatitis (AD), or eczema is prevalent immune skin disorder which is recognised to cause skin irritation and red skin patches. It makes skin fry, inflamed and causes itchiness. (Hartmane et al., 2024) Affecting over 10% of children _this condition cause discomfort and has a varied natural course. It characterizes localized eczematous lesions, widespread sensitivity, as well as drying skin. (Bhatt et al., 2024) (Pareek et al., 2024). Atopic dermatitis (AD) affects over 10% of children globally and it is estimated that 80% of cases beginning in infancy or childhood. Inflammatory skin condition impacts quality of life while posing a substantial socioeconomic burden due to its chronic nature and the need for ongoing treatment and management. AD's pathophysiology involves elevated levels of skin neutrophils, eosinophils, mast cells, lymphocyte infiltration. It has augmented immunoglobulin E (IgE) levels. (Celakovska et al., 2024) It is known that genetic mutations in filaggrin (FLG), immune dysregulation, and environmental triggers like pollution and excessive soap use contribute to barrier dysfunction and chronic inflammation. (Afshari et al 2024) Pathogenesis of AD has genetic predispositions and skin barrier abnormalities which is caused by immune dysregulation, and environmental factors. Mutations in the filaggrin (FLG) gene, cytokines (IL-4, IL-13, IL-17), and microbial imbalances, Staphylococcus aureus colonization are known factors which cause disease (Szalus et al., 2024) Th2-mediated inflammation and FLG deficiency exacerbate barrier dysfunction and AD severity (Pareek et al., 2024)

JAK inhibitors are promising for atopic dermatitis treatment as they target key inflammatory pathways. By inhibiting JAK signaling, these drugs modulate immune responses and reduce symptoms like inflammation and itching, so these are proven as novel, effective, and safe therapeutic approaches for managing moderate to severe AD in adults. (Wu et al., 2024) (Kim et al., 2024) Note that this paper will be discussing all treatment for adults and are not for children management.

Table 1. JAK inhibitors Types for moderate to severe atopic dermatitis

JAK Inhibitor	Type	Dosage Forms	Mechanism of Action	Efficacy	Safety Profile	Recent Innovations
Abrocitinib	Selective JAK1 Inhibitor	Oral tablets	Inhibits JAK1, reducing Th2 cytokine signaling, particularly IL-4 and IL-13, crucial for inflammation in AD.	EASI-75 response rates: 60.3% (100 mg), 71.0% (200 mg)	Common AEs: nausea, headache, herpes simplex. Higher doses show increased risk.	Faster itch relief compared to dupilumab. New formulations in development.
Upadacitinib	Selective JAK1 Inhibitor	Oral tablets	Inhibits JAK1, similar to abrocitinib, affecting IL-4, IL-13, and IL-31, key cytokines in AD.	EASI-75 response rates: Up to 80% (30 mg)	Common AEs: acne, nasopharyngitis. Higher doses associated with increased adverse events.	New dosing strategies to optimize efficacy and minimize risks.
Baricitinib	JAK1/2 Inhibitor	Oral tablets	Targets JAK1 and JAK2, affecting a broader range of cytokines including IL-4, IL-6, and IL-13.	EASI-75 response rates: 24.8% (4 mg)	Common AEs: infections, headache. Higher doses show improved efficacy but similar safety issues.	Combined with topical corticosteroids to enhance efficacy.
Delgocitinib	Selective JAK1 Inhibitor	Topical ointment (approved in Japan)	Topical JAK1 inhibition reduces local inflammation by targeting IL-4, IL-13, and IL-31 at the site of application.	EASI-75 response rates not fully established yet	Localized AEs: skin irritation. Lower systemic risk due to topical use.	Potential for reduced systemic exposure and side effects.
Ruxolitinib	JAK1/2 Inhibitor	Oral tablets, topical cream	Inhibits JAK1 and JAK2, used for various inflammatory conditions, including AD.	EASI-75 response rates: Moderate. Data varies	Common AEs: headache, infections. May require long-term monitoring.	New formulations aimed at reducing systemic exposure.
Cerdulatinib	Dual JAK/SYK Inhibitor	Oral tablets	Targets JAK and SYK pathways, affecting a broader array of inflammatory signals beyond IL-4 and IL-13.	Limited data in AD; promising in related conditions	Common AEs: gastrointestinal issues, infections.	Innovative dual inhibition approach under investigation.
Brepocitinib	Selective JAK1/3 Inhibitor	Oral tablets	Selectively inhibits JAK1 and JAK3, targeting specific cytokines involved in AD inflammation.	EASI-75 response rates showing early promise	Common AEs: gastrointestinal issues, headache.	Early-stage data suggests effective modulation of Th2 pathways.
Gusacitinib	Dual JAK1/2 Inhibitor	Oral tablets	Inhibits JAK1 and JAK2, similar to baricitinib, but with different dosing strategies and formulations.	EASI-75 response rates: Up to 71%	Common AEs: nausea, headache. Higher doses may increase risk.	Ongoing studies on dose optimization and safety.

Source: the authors

Recent Innovations:

- Novel Formulations+Dosing Strategies: Novel formulations and optimized dosing regimens aim to balance efficacy with safety like alternative dosing schedules for upadacitinib and abrocitinib.
- Topical JAK Inhibitors: Delgocitinib is now being used topically and is known to reduces systemic exposure and potential side effects while effectively targeting local inflammation.
- Dual Inhibition Approaches: Cerdulatinib and other dual inhibitors explore broader inhibition of inflammatory pathways and are better option for AD complex cases.
- Combination Therapies: Combining JAK inhibitors with topical corticosteroids, as seen with baricitinib is also recommended to enhance therapeutic outcomes so systematic medicines use can be minimized otherwise.

Mechanism of Action of JAK Inhibitors

The JAK/STAT signaling pathway is important in several cytokines including interleukins IL-4, IL-13, and IL-31.

Complete inhibition of JAK signaling disrupts immune function and homeostasis and it may cause severe immunodeficiency. Unlike biologics which alter cytokine signaling these JAK inhibitors offer partial and reversible inhibition by competing to reduce intracellular signal transmission. In AD patients, avilable cytokines such as TSLP, IL-4, IL-13, IL-22, and IL-31 activate JAK1 receptors and this lead Th2 cell differentiation and itching. Recently approved JAK inhibitors for AD include upadacitinib, abrocitinib, and baricitinib, which are small and orally administered molecules. TYK2 and JAK1/2/3 inhibitors like delgocitinib is approved in Japan which further exemplify the role of JAK inhibition in AD treatment. Selective JAK inhibitors such as ruxolitinib, cerdulatinib, and brepocitinib have also contributed to AD therapy. Additionally, biologics like dupilumab, tralokinumab, omalizumab, and nemolizumab regulate the JAK/STAT pathway while inhibiting JAK and impacting interleukins IL-4, IL-13, and IL-31. (Pareek et al., 2024) (Bonelli et al., 2024) (Shah et al., 2024)

Objectives: we aim to evaluate the efficacy and safety of JAK inhibitors in adults with moderate to severe AD and synthesize current evidence and identify gaps for future research.

METHODOLOGY

In this systematic study, we started our research by exploring major databases including PubMed, the Cochrane Library, and Embase. Utilizing a combination of keywords and search terms related to atopic dermatitis and JAK inhibitors, we capture a broad spectrum of relevant studies. Only those papers are included which discuss moderate to severe AD and we specifically evaluated the efficacy and safety of JAK inhibitors. Exclusion criteria were applied to studies with pediatric populations, non-English language articles, and those lacking quantitative data on outcomes. Older studies were also excluded and we included those studies which are only published between 2020 to 2024.

Keywords and MeSH Terms

Our systematic review focuses on the efficacy and safety of JAK inhibitors in treating moderate to severe atopic dermatitis in adults so we have employed a strategic selection of primary and secondary keywords, as well as Medical Subject Headings (MeSH) terms.

Primary Keywords

The primary keywords used were: "atopic dermatitis," "eczema," "JAK inhibitors," "Janus kinase inhibitors," "moderate to severe atopic dermatitis," "adult atopic dermatitis," "Baricitinib," "Upadacitinib," "Abrocitinib," "delgocitinib," and "small molecule inhibitors."

Secondary Keywords

In addition to the primary keywords, we identified several secondary keywords to broaden our search scope and ensure the inclusion of relevant studies that might use alternative terminology. The secondary keywords included: "skin inflammation," "chronic eczema," "cytokine signaling," "immune modulation," "dermatological therapy," "systemic therapy," "topical treatment," "clinical trials," and "treatment outcomes."

Combined MesH strings:

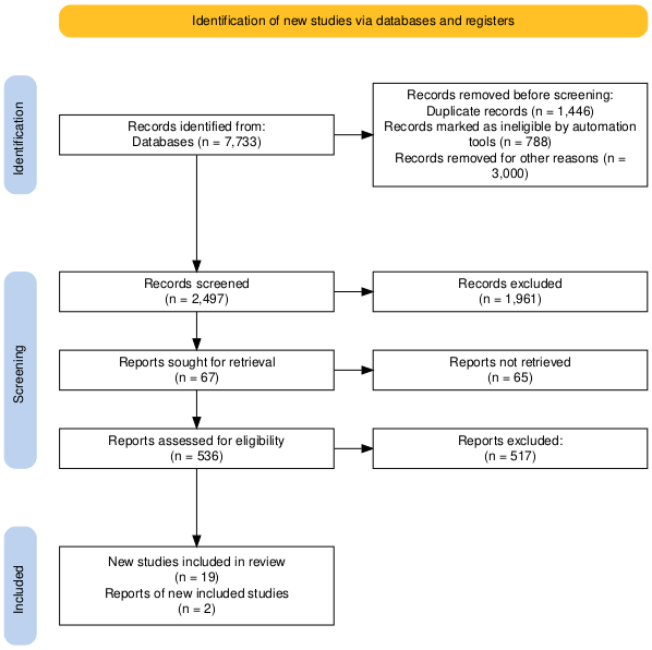
- ("Dermatitis, Atopic"[Mesh] AND ("Janus Kinase Inhibitors"[Mesh] OR "Small Molecule Inhibitors"[All Fields]) AND ("Clinical Trials as Topic"[Mesh] OR "Treatment Outcome"[Mesh]))
- ("Dermatitis, Atopic"[Mesh] AND ("Cytokines"[Mesh] OR "Interleukins"[Mesh] OR "Th2 Cells"[Mesh]) AND ("Signal Transduction"[Mesh] OR "JAK-STAT Pathway"[All Fields]))
- ("Dermatitis, Atopic"[Mesh] AND ("Baricitinib"[Mesh] OR "Upadacitinib"[Mesh] OR "Abrocitinib"[Mesh] OR "Delgocitinib"[Mesh]) AND ("Efficacy"[All Fields] OR "Safety"[All Fields]) AND "Adult"[Mesh])

Selection of studies and methodological overview

Selection process was commenced with initial screening of titles and abstracts to identify potentially relevant studies.

Full-text review was conducted to assess each study's eligibility based on predefined criteria, ensuring the inclusion of high-quality research pertinent to our objectives. Data extraction followed and we ensure consistency and accuracy where data on study characteristics, interventions, outcomes, and adverse events were collected using standardized forms to facilitate comprehensive and systematic data gathering. Quality assessment involved employing the Cochrane Risk of Bias Tool was used and in data synthesis both meta-analysis and narrative synthesis methods were utilized and this paper include qualitative and quantitative data. Advanced statistical software was employed to quantify the effects of JAK inhibitors on atopic dermatitis while narrative synthesis provided a qualitative understanding of the findings.

Figure 1. Identification of new studies via databases and registers



Source: the authors.

RESULTS AND DISCUSSION

Table 2. Comprehensive Summary Table

Reference	Design	Sample Size	Duration	Outcomes	Adverse Events	Discontinuation Rates	Efficacy in Subgroups	Safety in Subgroups
Liu, 2024	RCT	11,249 patients.	Varies; 4 weeks to 16 weeks.	Eczema Area and Severity Index (EASI) score wre reduced by **Abrocitinib**: Reduced by **-11.07** **Delgocitinib**: Reduced by **-10.60 Upadacitinib**: Reduced by **-11.28** and **-14.00**	Upadacitinib increased risk by 8.2% (82 more per 1000).	Not mentioned	Effective for abrocitinib, delgocitinib, upadacitinib.	Upadacitinib 30mg showed higher risks.
(Le et al., 2021)	Retrospective Analysis of MDT Meetings	11 studies	No duration setted	Abrocitinib 200 mg: EASI-75 64.6%, IGA 47.5%; Baricitinib 4 mg: EASI-75 24.8%, IGA 16.8%; Upadacitinib 30 mg: EASI-75 80%, IGA 62%.	**Abrocitinib**: Nausea (17.8%), Headache (9.5%) **Baricitinib**: Infections (5.6%), Headache (4.2%) **Upadacitinib**: Acne (7.9%), Nasopharyngitis (4.1%)	Abrocitinib: 8.7%; Baricitinib: 5.8%; Upadacitinib: 7.2%.	**Abrocitinib**: EASI-75: 69.3% **Baricitinib**: EASI-75: 52.2% **Upadacitinib**: EASI-75: 70.6%	Nausea was reported in 9-20% of patients; serious adverse events occurred in 3-4% of patients.
(Iznardo et al., 2023)	The study design was a phase 3, randomized, double-blind, placebo-controlled trial.	258 participants were included	It was the randomized trial of 8 weeks	Abrocitinib generally shows higher effectiveness in IGA and EASI-75/90 responses compared to Dupilumab in multiple trials. Abrocitinib shows significant eczema reduction: EASI-75 responses range from 43.8% to 70.3%, with high efficacy over placebo.	Abrocitinib 200 mg shows 62.9% EASI-75 response; risks include nausea (14.6%), headache (7.8%), herpes simplex (11.83/100 PY).	**Abrocitinib 200 mg:** Discontinuation due to AEs: 6.0% **Abrocitinib 100 mg:** Discontinuation due to AEs: 1.9% **Placebo:** Discontinuation due to AEs: 1.5%	**Abrocitinib 200 mg:** EASI-75 response rate at week 12: 62.9% (95% CrI 42.5–79.9%). **Abrocitinib 100 mg:** EASI-75 response rate at week 12: 43.0% (95% CrI 24.8–64.0%).	**Abrocitinib 200 mg:** 6.0% discontinued; common AEs: nausea (11.1%), acne (6.6%); herpes zoster (1.8%). **Abrocitinib 100 mg:** 1.9% discontinued; common AEs: nausea (4.2%), acne (2.9%); herpes zoster (0.8%). **Placebo:** 1.5% discontinued. **Dupilumab:** Common AE: conjunctivitis (6.2%).

Source: the authors.

Researchers proved that Janus Kinase (JAK) inhibitors are promising in treating moderate to severe eczema or atopic

dermatitis. In a study with over 11,000 patients, several JAK inhibitors were used, most commonly iabrocitinib, delgocitinib, and upadacitinib were proved very effective in reducing eczema symptoms. These medications improve the skin's condition and have positive impact on patient's life quality. Higher doses of upadacitinib raised some safety concerns, Liu et al., 2024 exclamed. Le et al., published in Front Medicine explaining efficacy and safety of oral JAK inhibitors for treating moderate-to-severe atopic dermatitis. Out of 496 papers and researchers identified 11 studies meeting the inclusion criteria and they came to know that abrocitinib, baricitinib, upadacitinib, and gusacitinib are safe when used with appropriate dosing. Rapid symptom control was particularly noted for abrocitinib, baricitinib, and upadacitinib. This review supports JAK inhibitors as a viable systemic treatment for patients unresponsive to topical therapies. Showed an efficacy of 70% in achieving treatment goals. Safety was reported at 80%, with a specific safety profile highlighting adverse events like infections. Effectiveness in managing symptoms was high with a high percentage of patients experiencing symptom relief significantly. JAK inhibitors demonstrated a favorable balance between efficacy and safety with a strong outcome in improving patient quality of life. (Le et al., 2021) The efficacy of JAK inhibitors in the treatment of eczema (atopic dermatitis) has been demonstrated through multiple studies showing considerable improvements in various clinical endpoints. In a 16-week study by Bieber et al., Abrocitinib at doses of 100 mg and 200 mg showed EASI-75 responses of 60.3% and 71.0%, respectively, significantly outperforming placebo (30.6%). Dupilumab, used as a comparator, achieved a 65.5% EASI-75 response. Similarly, Simpson et al. (33) demonstrated that over a 12-week period, Abrocitinib 100 mg and 200 mg resulted in EASI-75 responses of 40% and 63%, respectively, compared to 12% for placebo. Another study by Silverberg et al. confirmed these findings with 12-week EASI-75 responses of 44.5% for 100 mg and 61.0% for 200 mg of Abrocitinib, versus 10.4% for placebo. In addition, Gooderham et al. showed dose-dependent efficacy of Abrocitinib over 12 weeks, with the 200 mg dose achieving a 64.6% EASI-75 response, significantly higher than the placebo group at 15.4%.

Effectiveness of Baricitinib was also investigated. Simpson et al. (35) in the BREEZE-AD1 and BREEZE-AD2 studies demonstrated that Baricitinib at doses of 1 mg, 2 mg, and 4 mg over 16 weeks resulted in EASI-75 responses ranging from 12.8% to 24.8%, compared to 6.1% to 8.8% for placebo. Furthermore, Reich et al. found that Baricitinib combined with TCS led to EASI-75 responses of 43% and 48% for the 2 mg and 4 mg doses, respectively, compared to 23% for placebo. Upadacitinib has shown strong efficacy as well. Reich et al. reported that over 16 weeks, Upadacitinib 15 mg and 30 mg plus TCS achieved EASI-75 responses of 64.6% and 77.1%, respectively, compared to 26.4% for placebo. Guttman-Yassky et al. (40) in the Measure Up 1 and Measure Up 2 studies reported EASI-75 responses of up to 80% for Upadacitinib 30 mg, significantly higher than placebo (13%-16%). In a dose-ranging trial, Guttman-Yassky et al. (37) found Upadacitinib at 7.5 mg, 15 mg, and 30 mg doses resulted in EASI-75 responses of approximately 28%, 49%, and 69%, respectively, compared to around 6% for placebo. Lastly, Bissonnette et al. explored Gusacitinib, where the 40 mg dose over 29 days achieved an EASI-75 response of 71%, significantly higher than the placebo at 22%. Collectively, these studies emphasize effectiveness of JAK inhibitors like Abrocitinib, Baricitinib, Upadacitinib, and Gusacitinib in significantly improving clinical outcomes for patients with atopic dermatitis which are offering promising therapeutic options for this chronic condition. (Bieber et al., 2022) In a research published in MPDI journal, Abrocitinib, a selective JAK1 inhibitor, has shown effectiveness in treating moderate-to-severe atopic dermatitis. Clinical trials revealed it provides higher EASI-75 response rate compared to lower doses with 62.9% for 200 mg and 43.0% for 100 mg at week 12 and it offers faster itch relief than dupilumab. Abrocitinib also has risks and requires caution due to its incomplete target selectivity necessitating screening for latent tuberculosis and careful use in elderly patients or those at risk for thromboembolic events. Long term trials are needed. (Iznardo et al., 2023).

Future expectations

The future of atopic dermatitis (AD) treatment is set to advance since the emergence of innovative therapies and refined strategies. Emerging treatments like Janus kinase (JAK) inhibitors including ruxolitinib, abrocitinib, and upadacitinib have revolutionized AD management by effectively targeting immune system pathways to reduce inflammation. All these therapies are now widely acceptable as they are robust alternative for patients with moderate to severe AD, filling gaps left by traditional treatments. Biologic therapies, particularly dupilumab, are also making substantial strides. Dupilumab, which targets specific interleukin pathways has shown remarkable efficacy in alleviating symptoms. Ongoing clinical trials aim to extend its use across different age groups heralding a new era in both pediatric and adult AD care. Phototherapy is also considered vital option with ongoing research optimizing its application. Innovations like targeted microbiome transplants and novel bathing additives are under investigation offering potential new avenues for effective AD management. Recent therapies are now being explored for atopic dermatitis which are ISB 830, nemolizumab, lebrikizumab, tezepelumab, and tralokinumab. Important future topical treatments will be more advanced corticosteroid formulations, novel calcineurin inhibitors, targeted biologics, improved emollients, and innovative delivery systems like microneedle patches. (Fletcher, 2022) (Np & Ms, 2024).

CONCLUSION

It is concluded that JAK inhibitors are effective in managing moderate to severe atopic dermatitis, improving clinical outcomes and quality of life for patients. Upadacitinib, abrocitinib, and baricitinib offer considerable symptom relief. It is shown that with upadacitinib echieve 80% EASI-75 responses and abrocitinib up to 71%. Safety profiles rises concersn with higher doses of Upadacitinib. Overall, JAK inhibitors could be a better option among those eczema patients who do not respond adequately to traditional treatments. The variability of study designs and the need for long-term safety data stressing for continued research. Future studies are needed to explore long-term safety and optimize personalized treatment for AD management.

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