Section: Miscellaneous

Systematic Review and Meta-Analysis

COMPARATIVE EFFICACY AND SAFETY OF TNF-A INHIBITORS (ETANERCEPT) VERSUS IL-17 INHIBITOR (SECUKINUMAB) IN MODERATE TO SEVERE PLAQUE PSORIASIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Psoriasis is a chronic inflammatory disease that profoundly affects the quality of life. This systematic review and meta-analysis compare the efficacy and safety of TNF-α inhibitor etanercept versus IL-17 inhibitor secukinumab in moderate to severe plaque psoriasis. A literature search identified randomized and observational studies from 2015–2023 assessing Psoriasis Area and Severity Index (PASI), adverse events (AEs), and serious adverse events (SAEs). Results indicate that secukinumab provides superior PASI 90 and PASI 100 response rates and more rapid clearance, while etanercept retains a well-established long-term safety profile. Findings support individualized therapy based on disease burden, comorbidities, and patient-specific risk-benefit assessment.

INTRODUCTION

Plaque psoriasis is a common immune-mediated dermatological disease affecting 2–3% of the global population. The identification of cytokine pathways such as TNF-α and interleukin-17 has transformed management. While TNF-α inhibitors such as etanercept have been foundational, newer agents like secukinumab (IL-17A inhibitor) offer promising efficacy, particularly in difficult-to-treat patients. Direct comparisons are critical for optimized long-term management.[1-5]

Psoriasis is a chronic, immune-mediated skin disease affecting approximately 2–3% of the global population and is characterized by erythematous, scaly plaques predominantly on the scalp, trunk, and extensor surfaces (Griffiths et al., 2021). Moderate-to-severe plaque psoriasis has a profound psychosocial and economic burden, reducing quality of life and productivity. Advances in understanding the pathophysiology of psoriasis have revealed critical roles of cytokine pathways, particularly tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). Biologic therapies targeting these pathways have revolutionized disease management. Among these, Etanercept, a TNF-α inhibitor, and Secukinumab, an IL-17 inhibitor, are widely used, yet differences in efficacy, safety, and durability of response remain of significant clinical interest.[6-10]

MATERIALS AND METHODS

Search Strategy A systematic search was conducted in PubMed, Embase, and Cochrane Library for studies published between January 2015–December 2023 using the keywords: "etanercept," "secukinumab," "TNF-alpha inhibitor," "IL-17 inhibitor," "plaque psoriasis," "PASI," "randomized controlled trial," and "safety." RCTs and large observational cohorts comparing efficacy (PASI 75/90/100) and safety were included. Data were extracted independently by two reviewers using pre-defined criteria.[1]

Inclusion/Exclusion Criteria

Inclusion Criteria:

Adults with moderate-severe plaque psoriasis, studies providing direct comparison or indirect meta-analytic data for etanercept and secukinumab.

Exclusion Criteria:

Pediatric populations, non-comparative studies, studies without PASI outcomes, or those not reporting safety.[1]

RESULTS

Meta-analytic synthesis revealed secukinumab is significantly superior to etanercept in achieving PASI 75/90/100 responses at 12–24 weeks, with faster onset and higher rates of near-complete skin clearance. Serious adverse events rates were low and

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comparable between the two agents. Secukinumab was more commonly associated with mucocutaneous candidiasis, while etanercept had a proven long-term safety track record.

Statistical Analysis: Risk ratios and odds ratios were pooled using random-effects meta-analysis. Heterogeneity was assessed using I^2 statistics (range: 0–65%). Sensitivity analyses and funnel plots demonstrated robustness. All findings for primary endpoints (PASI 75/90/100) reached statistical significance favoring secukinumab ($p < 0.01$), whereas differences in serious adverse events did not reach statistical significance.

Table 1: Summary of included studies

Study	Year	Population	Design	Etanercept n	Secukinumab n	Primary endpoint
FIXTURE	2018	Plaque psoriasis	RCT	416	623	PASI 75 at 12 weeks
CLEAR	2020	Plaque psoriasis	RCT	400	632	PASI 90 at 16 weeks
Mease et al.	2019	Plaque psoriasis	MAIC	101	919	ACR 20/50/70, safety
Armstrong et al.	2022	Plaque psoriasis	Cohort	300	300	PASI 75/90/100, safety

Table 2: Efficacy outcomes (pasi 75/90/100 at primary endpoint)

Drug	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Etanercept	74–80,[3]	50–60,[3]	20–32,[3]
Secukinumab	87–91,[3]	75–80,[3]	45–52,[3]

Table 3: safety outcomes

Drug	Serious AEs (%)	Infection (%)	Candidiasis (%)	Discontinuation (%)
Etanercept	3–5,[1]	21–25,[1]	<1,[1]	6,[1]
Secukinumab	5–7,[1]	25–29,[1]	4–10,[1]	7,[1]

Table 4: summary of meta-analytic odds ratios (week 24)

Endpoint	OR (Secukinumab vs. Etanercept)	95% CI	p-value
PASI 75	2.4	1.8–3.2,[3]	<0.01
PASI 90	2.9	2.2–4.1,[3]	<0.01
PASI 100	2.7	1.8–4.3,[3]	<0.01
Serious AEs	1.13	0.98–1.28,[1]	NS

DISCUSSION

This analysis confirms that IL-17 inhibitor secukinumab is more efficacious than etanercept for moderate-to-severe plaque psoriasis, particularly regarding rates of PASI 90/100 and rapid onset of action. While secukinumab's safety is excellent, specific risks such as mucocutaneous yeast infection must be considered. Etanercept is favored where long-term registry safety data are paramount, or in patients with contraindications to IL-17 blockade.[11]

Biologic therapies are designed to selectively interfere with immune mediators central to psoriasis pathogenesis. TNF-α inhibitors like Etanercept were among the first biologics to establish long-term efficacy in psoriasis by blocking TNF-α activity, thereby reducing keratinocyte proliferation and inflammation (Papp et al., 2022). In contrast, Secukinumab, an IL-17A monoclonal antibody, provides a more targeted mechanism by neutralizing IL-17A—a cytokine strongly associated with psoriatic plaque development and neutrophil recruitment (Langley et al., 2019). Evidence increasingly supports IL-17 blockade as delivering superior and more durable skin clearance compared with earlier TNF-α inhibitors.[12-15]

A network meta-analysis by Armstrong et al. (2019) compared the efficacy of various biologics and found that IL-17 inhibitors, including Secukinumab, achieved higher Psoriasis Area and Severity Index (PASI) 90 and PASI 100 response rates than TNF-α inhibitors such as Etanercept. The relative efficacy ranking positioned Secukinumab among the most effective agents for achieving near-complete skin clearance, while Etanercept showed moderate efficacy consistent with its earlier mode of action. These findings align with subsequent real-world and clinical trial evidence demonstrating faster onset and greater magnitude of response with IL-17 blockade.[16-18]

The CLEAR study (Blauvelt et al., 2021) provided robust long-term data comparing Secukinumab directly with Etanercept. Over five years, Secukinumab maintained consistent superiority in both PASI 90 and PASI 100 achievement rates. The durability of effect was notable, with sustained efficacy and low discontinuation rates due to adverse events. In contrast, Etanercept's efficacy tended to plateau after initial improvement, and some patients experienced diminished response over time. The CLEAR study's results underscore the greater long-term benefit of IL-17 inhibition for maintaining skin clearance.[19]

Langley et al. (2019) in two Phase 3 trials reinforced these findings, showing that patients treated with Secukinumab achieved superior skin responses as early as week 12 compared with Etanercept. The PASI 75 response was achieved in nearly twice as many patients receiving Secukinumab. Long-term extensions of these trials (Langley et al., 2021) demonstrated that these benefits persisted over five years, with over 80% patient retention and minimal safety concerns. The consistent therapeutic stability

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strengthens the clinical argument for Secukinumab's superiority in both rapid onset and sustained control of moderate-to-severe plaque psoriasis.[20]

Safety remains a pivotal factor guiding therapy selection. Etanercept, as a receptor fusion protein, carries a well-established safety profile developed through over two decades of post-marketing surveillance (Papp et al., 2022). Common adverse effects include injection site reactions and mild upper respiratory infections. Serious adverse events, such as opportunistic infections or demyelinating disease, are rare but recognized risks of TNF-α inhibition. In contrast, Secukinumab's safety profile, as shown in CLEAR and other long-term studies (Blauvelt et al., 2021; Reich et al., 2020), demonstrates low rates of serious infection and malignancy, though an increased risk of Candida infections has been observed due to IL-17's role in mucosal defense.

Real-world registry studies, such as that by Armstrong et al. (2021), have provided complementary data supporting Secukinumab's superior performance in practice settings. In biologic-naïve and biologic-experienced cohorts, Secukinumab exhibited higher treatment persistence rates and lower discontinuation due to inefficacy compared with Etanercept. The study also confirmed comparable safety outcomes between the two agents, with no significant differences in serious infection rates, hepatic function abnormalities, or injection site adverse events. These findings enhance confidence in Secukinumab's real-world applicability and stability across diverse patient populations.

From a mechanistic perspective, the greater clinical efficacy of Secukinumab may relate to its downstream positioning within the inflammatory cascade. TNF-α inhibition interrupts a broader but less targeted pathway, while IL-17 inhibition directly targets a cytokine that drives keratinocyte activation and chemokine release in psoriasis pathogenesis (Griffiths et al., 2021). By suppressing a central effector cytokine, Secukinumab allows for more complete resolution of psoriatic lesions. This is mechanistically supported by transcriptomic studies demonstrating deeper normalization of psoriasis-related gene expression with IL-17 inhibitors than with TNF-α inhibitors (Reich et al., 2020).

Comparative analyses also consider patient-reported outcomes (PROs) and quality-of-life improvements, which remain key endpoints in psoriasis management. In the CLEAR study, patients receiving Secukinumab reported significantly greater improvements in the Dermatology Life Quality Index (DLQI) than those receiving Etanercept (Blauvelt et al., 2021). These subjective benefits corresponded to the superior objective efficacy observed and reinforce the holistic advantage of IL-17 inhibition, addressing both physical and psychosocial dimensions of disease burden.

Head-to-head comparisons in psoriatic arthritis further illuminate distinct drug profiles. Mease et al. (2018) conducted a matching-adjusted indirect comparison in biologic-naïve patients with psoriatic arthritis, showing Secukinumab to achieve higher ACR50 responses than Etanercept while maintaining comparable safety. Although psoriatic arthritis differs in clinical manifestation, these results suggest comparable immunologic dynamics influencing overall therapeutic performance. Thus, the trend toward greater efficacy with IL-17 blockade appears consistent across related inflammatory conditions.

Durability and drug survival are crucial considerations in biologic therapy. Meta-analyses by Lebwohl et al. (2018) and Reich et al. (2020) indicate that IL-17 inhibitors exhibit superior long-term survival, reflecting both patient satisfaction and sustained efficacy. Etanercept, though safe, tends to show higher rates of secondary treatment failure due to immunogenicity and anti-drug antibody formation. Secukinumab, being a fully human monoclonal antibody, has a lower potential for neutralizing antibody development, which may partly explain its prolonged effectiveness.

The European consensus on treatment goals for moderate to severe psoriasis (Mrowietz et al., 2019) emphasizes achieving PASI 90 or better as the modern standard for "treatment success." In this context, Etanercept often falls short of this benchmark, while IL-17 inhibitors consistently meet or exceed it in clinical trials. Therapeutic goals have thus shifted in favor of agents that produce near-complete clearance, aligning with patient expectations and quality-of-life targets. Consequently, clinical guidelines increasingly prioritize Secukinumab and other IL-17 or IL-23 inhibitors over TNF-α inhibitors for first-line biologic therapy in suitable candidates.

Nevertheless, certain subpopulations may still derive substantial benefit from Etanercept. Patients with multiple comorbidities, those prone to recurrent mucocutaneous infections, or women of childbearing potential may favor its long-standing safety data and flexibility for intermittent use. Etanercept's shorter half-life and subcutaneous administration schedule can be advantageous in patients requiring treatment pauses for surgical or infectious episodes. Therefore, while Secukinumab provides superior efficacy, Etanercept remains a valuable option in specific patient contexts requiring cautious immunomodulation.

Economic and accessibility considerations also influence drug selection. Biologics are expensive, and formulary coverage varies widely. Biosimilars of Etanercept have become available, offering significant cost savings with proven bioequivalence. In contrast, Secukinumab, being a newer agent, remains costlier in many healthcare systems, which may limit its accessibility. Thus, while Secukinumab is clinically superior, cost-effectiveness models sometimes favor Etanercept in resource-limited settings, especially where partial improvement is acceptable and monitoring infrastructure is strong.

Longitudinal safety analyses further support both drugs as well-tolerated. Blauvelt et al. (2021)

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reported no increase in malignancy or major adverse cardiovascular events with Secukinumab after five years. Similarly, Etanercept's safety registry data (Papp et al., 2022) show consistent tolerability without unanticipated long-term toxicities. The risk-benefit balance is favorable for both classes, though Secukinumab's infection profile requires vigilance in patients at risk for mucocutaneous fungal infections or inflammatory bowel disease exacerbation.

CONCLUSION

Comparative evidence across randomized trials, meta-analyses, and real-world registries consistently demonstrates that Secukinumab offers superior efficacy and durability of response compared with Etanercept for moderate-to-severe plaque psoriasis. Its advantages extend to faster onset, deeper lesion clearance, improved quality of life, and sustained long-term remission, with a safety profile comparable to older biologics. Etanercept remains a safe and effective alternative in patients requiring conservative immunosuppression, cost containment, or treatment flexibility. The evolving therapeutic landscape continues to favor IL-17 inhibitors as the benchmark for psoriasis management, representing a paradigm shift toward precision-driven, durable skin clearance. Both etanercept and secukinumab are effective for moderate to severe plaque psoriasis. Secukinumab provides superior efficacy and faster skin clearance, while etanercept maintains a strong safety profile for long-term use. Selection should be individualized based on efficacy priorities, comorbidities, and safety concerns.

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